16.1.9 DOCUMENTATION OF STATISTICAL METHODS

STATISTICAL ANALYSIS PLAN

VERSION: *1.1*

DATE OF PLAN: *2-5-2025*

STUDY DRUG: *IFETROBAN*

PROTOCOL NUMBER: *CPI-IFE-007*

STUDY TITLE:

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

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CUMBERLAND PHARMACEUTICALS STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

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2. LIST OF ABBREVIATIONS

Term	Definition
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse Event
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor/neprilysin inhibitor
AUC	Area under the Curve
BMI	Body Mass Index
BSA	Body surface area
CBC	Complete blood count
CFB	Change From Baseline
C_{max}	Maximum Plasma Concentration
CMR	Cardiac Magnetic Resonance
CMP	Comprehensive metabolic panel
CPI	Cumberland Pharmaceuticals Inc.
CRF	Case Report Form
CV	Coefficient of Variation
DB	Double blind
DMD	Duchenne Muscular Dystrophy
ECC	Circumferential strain
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in 1 second
FEV1%p	Forced Expiratory Volume in 1 second percent predicted
FVC	Forced Vital capacity
FVC%p	Forced Vital capacity percent predicted
FWHM	Full-width half-maximum
GI	Gastrointestinal
ICC	Intraclass Correlation
IMP	Investigational Medicinal Product; synonymous with “study drug”
INR	International Normalized Ratio
ITT	Intent-to-Treat
LGE	Late gadolinium enhancement
LOCF	Last Observation Carried Forward
LVEDVi	Indexed left ventricular end diastolic volume
LVEF	Left ventricle ejection fraction
LVESVi	Indexed left ventricular end systolic volume
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
MRI	Magnetic resonance imaging
MVPA	Moderate to Vigorous Physical Activity
NH	Natural history

NMM	Neuromuscular Module
OL	Open label
PedsQL	Pediatric Quality of Life Inventory
PEF	Peak expiratory flow
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PP	Per Protocol
PT	MedDRA Preferred Term
PTT	Partial thromboplastin time
QMT	Quantitative Muscle Testing
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	MedDRA System Organ Class
t1/2	Half-life
TEAE	Treatment-Emergent Adverse Event
Tmax	Time of maximum plasma concentration
VM	Vector Magnitude

3. INTRODUCTION AND OVERVIEW

This statistical analysis plan (SAP) is intended to provide a detailed description of the statistical methods and procedures that will be used to evaluate and report the results of the study outlined in protocol CPI-IFE-007 (Amendment 04a, dated March 10, 2025). This SAP incorporates analyses for both the double-blind treatment period and open-label extension periods as described in the protocol, including the use of natural history study data as a historical comparator and supplemental placebo group.

Data will be analyzed by Symbiance Pvt. Ltd. using Statistical Analysis Software (SAS®, version 9.4).

A separate document contains the table, figure, and listing (TFL) specifications.

3.1 Study Design

This is a double-blind (DB), placebo-controlled, multicenter, dose-ranging study with an open-label extension (OL) to determine the safety, pharmacokinetics, and efficacy of two dose ranges of oral ifetroban in subjects with DMD.

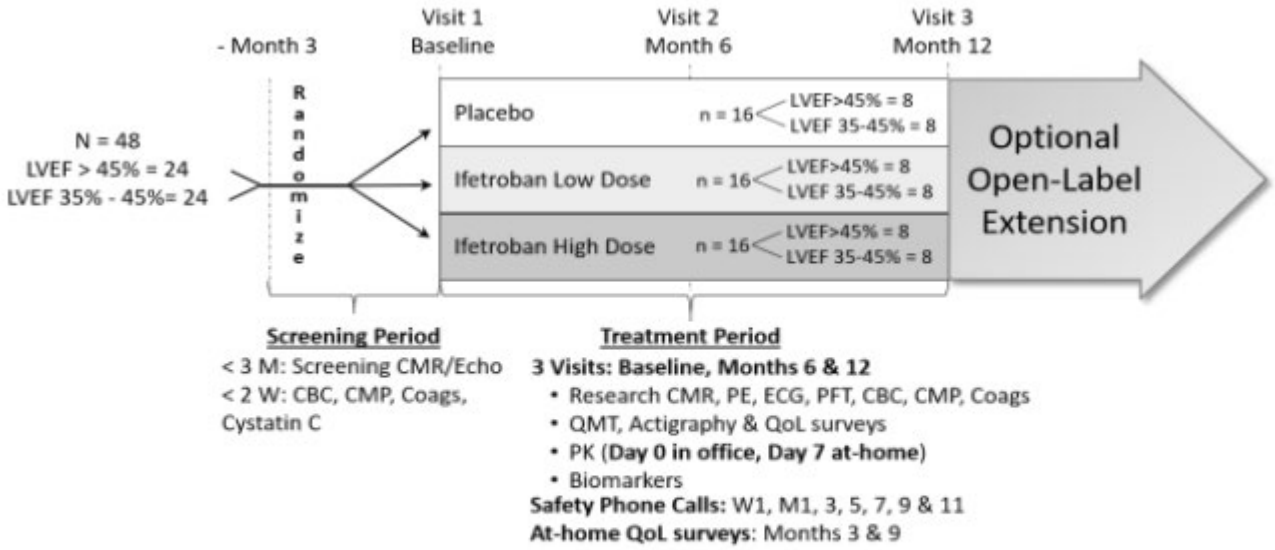
Subjects who meet eligibility criteria will be randomly assigned to one of three treatment groups 1:1:1 ratio, low-dose ifetroban, high-dose ifetroban or placebo, and dosed based on weight. Each treatment group will be evaluated by eight subjects with early stage (LVEF >45%) and eight subjects with advance stage (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 an OL extension (Figure 1).

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 clinical study will be conducted with two periods:

- Screening period of up to 12 weeks.
- Randomized ifetroban/placebo treatment period of 12 months.
- Subjects who complete 12 months of treatment will be eligible to participate in an OL extension.

Figure 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

3.2 Study Objectives

3.2.1 Primary Objectives

The primary objective of the trial is to assess the safety of oral ifetroban in male subjects with Duchenne Muscular Dystrophy (DMD).

3.2.2 Secondary Objectives

To evaluate the pharmacokinetics and efficacy of oral ifetroban.

3.2.3 Exploratory Objectives

- Evaluate novel biomarkers for diagnosis and monitoring of cardiomyopathy in DMD.
- Evaluate changes in daily life activity and quality of life.

3.3 Study Endpoints

Definitions for study endpoints, including baseline values, are specified in Section 4.4.1. Unless otherwise noted, all data, including baseline up to, and including week 52 will be analyzed.

Subjects who discontinue the study treatment before week 52 will have their data imputed last observation carried forward (LOCF).

Section 4.2 describes how to handle missing data points.

3.3.1 Primary Endpoints

Safety Endpoints:

Safety assessment will be based on treatment emergent adverse events (TEAEs), laboratory abnormalities, ECG, vital signs, and physical examination.

- Percentage of subjects with one or more TEAE
- Change from baseline in laboratory variables and incidence of markedly abnormal laboratory values and shifts from baseline of laboratory values.
- Change from baseline in ECG parameters and incidence of abnormal ECG findings.
- Change from baseline in vital signs.

3.3.2 Secondary Endpoints

Key secondary efficacy endpoints of the study are as follows:

PK:

- 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:

- 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).

3.3.3 Exploratory Endpoints

Exploratory endpoints of the study are as follows:

Exploratory Biomarkers:

- 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.

Exploratory Efficacy:

- 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.

3.4 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 (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 (LVEF 35-45%). Assuming a dropout rate of 10%, 54 subjects will be recruited to meet the target sample size of 48 subjects.

3.5 Randomization

Subjects will be randomly assigned to one of three treatment groups: low-dose ifetroban 100 mg/day, high-dose ifetroban 300 mg/day or matching placebo, using a 1:1:1 randomization ratio. All subjects will be treated with IMP daily for a minimum of six months and a maximum of 12 months. Approximately 48 subjects shall be randomized to ensure at least 16 subjects per group will be analyzed for efficacy.

3.6 Analysis Sets

3.6.1 Intention-To-Treat (ITT) Population

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

3.6.2 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 visits.

3.6.3 Safety Population

All subjects who receive at least one dose of treatment will be included in the Safety Population. The Safety population will be used in the statistical analyses for safety.

3.6.4 Pharmacokinetic Analysis (PK) Set

The PK Analysis Set is the group of subjects who received at least 1 dose of test drug and had sufficient PK data to derive the plasma PK parameter.

3.7 Study Period Definition

The following definitions for the study periods are as follows: Double-blind period for efficacy or safety endpoints is defined as the time from randomization or first dose date, respectively, to:

- the last dose of double-blind study drug if the subject continues to the OL period or,
- the last study visit if the subject does not continue to the OL period.

3.8 Open-Label Period

Open-label period is defined as the time from the first dose of open-label study drug to the last study visit if the subject is enrolled into open-label extension period of the study.

4 GENERAL CONSIDERATIONS

4.1 General Methodology

Summary statistic tables will be provided for disposition, demography and baseline characteristics by each treatment and overall/total treatment group.

Continuous variables will be summarized by the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), and maximum (max) will be used to summarize continuous data by treatment group.

Categorical variables will be summarized by treatment group and overall using the frequency count (n) and percentage. The missing category will be display when missing values are present. The denominator for all percentage calculations, unless otherwise provided, will be the number of participants in the treatment group's analysis set. Unless otherwise stated, missing data will not be imputed.

The summary tables will only include data from protocol-scheduled visits. Unscheduled visits' data will be included only in the by-subject listings. For the safety and efficacy endpoints, descriptive summaries will be provided by visit, treatment group, and in total (where applicable). Statistical inferential statistics, in general, will only be performed at the 2-sided level of significance of 0.05.

Decimal Place**:** Unless otherwise specified, percentage values are output with one digit to the right of the decimal point (e.g., 12.3,4.5). Percentages that are >0.0 and <0.1(not 0.0) are reported as "<0.1". All numeric values between -1 and 1 are output with zero to the left of the decimal point (e.g. 0.12,0.3).

Maximum and minimum values will be provided with the same number of decimal places as the number of decimal places collected. Means and medians will be presented to one decimal place more. The collected data will be presented to two decimal places higher than the standard deviations and standard errors. Percentages will be given to the nearest decimal place.

P-values will be rounded to three decimal places (e.g., "0.xxx"). If p-value <0.001, then the p-value will be reported as "<0.001".

The Study day on and after the first dose of treatment is defined as: Day 1 assessment date-first dose date+1. The study day before the first dose of treatment is calculated as: the assessment date-first dose date.

4.2 Missing Data

For the primary endpoint and key secondary efficacy endpoints, missing data will not be imputed in the primary analyses. A supportive sensitivity analysis for the Month 12 LVEF endpoint will be conducted where missing LVEF values at Month 12 will be imputed using Month 6 values, if available. Subjects missing LVEF at both Month 6 and Month 12 will be excluded from this supportive analysis. For long-term analyses in the open-label extension, subjects missing data at key timepoints (Month 24, Month 36) will be excluded from the respective analyses. No other imputation will be provided for any endpoint.

Since LVEF is a key efficacy endpoint, the pattern of missing data will be carefully evaluated to assess potential bias. The frequency and reasons for missing LVEF measurements will be

summarized by treatment group to determine whether missingness might be related to treatment or disease progression. If systematic differences in missing data patterns are identified between treatment groups, additional sensitivity analyses may be conducted using multiple imputation methods that account for the potential relationship between the likelihood of missing data and the unobserved outcomes. This would involve creating multiple complete datasets based on observed covariates and outcomes, analyzing each dataset, and combining results according to Rubin's rules. These additional analyses would be considered exploratory and would be used to evaluate the robustness of the primary analysis approach.

4.3 Interim Analysis

An early analysis was performed when half the target enrollment has completed the six months visit and assessments. Key findings from the interim analysis were 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 were external and restricted from participating in data review or decisions following the early analysis but may participate in the analysis following final database lock.

4.4 Data Definitions and Analysis Issues

4.4.1 Baseline Definition

The baseline measurement for the DB period and the OL period is defined as the last non-missing measurement prior to or on initiation of ifetroban; unless otherwise specified, the baseline value for all endpoints will be the non-missing value. If the time of the assessment or measurement was not recorded and it occurred on the same day that the first dose of drug started, it will be assumed to be taken before the study drug.

Change from baseline will be calculated as follows for the purposes of calculating summary statistics for the outcome measures:

Change from baseline = post-baseline value – baseline value

4.4.2 Treatments

The following treatments will be given in the DB period:

- High Dose Ifetroban
- Low Dose Ifetroban
- Placebo

- Placebo group created from the Natural History dataset (see Section 4.5)
- Overall

The following treatments will be given in the OL period:

- High Dose Ifetroban

4.4.3 Multicenter Studies

The centers will be pooled for analysis.

4.4.4 Multiple Comparisons/Multiplicity

Multiplicity and multiple comparisons do not apply to these secondary and exploratory objectives. No adjustments will be made for multiple comparisons or multiplicity. Changes to Protocol Specified Analysis

There are no changes to the protocol specified analyses.

4.5 Natural History Study Comparisons

Natural history study (NHS) data will be incorporated into analyses to supplement the placebo group and serve as a comparator for open-label extension periods.

4.5.1 Propensity Score Matching Methodology

Propensity scores will be calculated separately for the DB and open-label periods using logistic regression models with treatment assignment as the dependent variable. The independent variables will include: age, baseline LVEF, background DMD medications (steroids, ASO/exon-skipping therapy), and cardiac medications (ACEi, ARB, ARNI, beta-blocker, calcium channel blocker, aldosterone receptor antagonist, diuretic) as defined in Section 14.3.4.

4.5.2 Matching Algorithm

For the DB period, NHS subjects will be matched to high-dose ifetroban subjects at a 2:1 ratio using a global optimal algorithm based on the nearest neighbor approach without replacement and without caliper. For the open-label period, NHS subjects will be matched to all open-label subjects at a 2:1 ratio using the same methodology.

4.5.3 Statistical Comparisons with NHS Data

Comparisons between treatment groups (high-dose ifetroban vs. NHS-supplemented placebo for DB period; all open-label ifetroban vs. NHS for open-label period) will be performed using the

Wilcoxon rank sum test for primary and key secondary efficacy endpoints. Results will be presented alongside the pre-specified DB randomized comparisons but will be clearly identified as supplementary analyses.

4.6 Technical and Formatting Issues

4.6.1 Cross-References and Figure Numbering

All cross-references within this document refer to sections, tables, and figures within this SAP unless explicitly stated otherwise. Figure and table numbers follow a consistent numbering system: Figure X-Y where X is the main section number and Y is the sequential figure number within that section.

4.6.2 Decimal Places and Rounding Rules

The following conventions will be applied consistently throughout all analyses:

- Percentages will be presented to one decimal place
- Mean and median values will be presented to one decimal place more than the observed data
- Standard deviations will be presented to two decimal places more than the observed data
- P-values will be rounded to three decimal places; p-values <0.001 will be reported as "<0.001"
- Minimum and maximum values will be presented using the same number of decimal places as the collected data

5 SUMMARY OF STUDY POPULATION DATA

5.1 Subject Disposition

The following subject disposition variables, based on data reported on the screening disposition electronic case report form(eCRF), will be summarized (number and percent of subjects) by each treatment group and overall, for the safety population:

- Subjects screened
- Subjects completing the study and terminating early, with the reason for termination
- Subjects randomized, subjects in each study population and reasons for exclusion from the PP Population.

The disposition data will be listed by subject. along with protocol deviations.

5.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall.

Continuous demographic variables include age [years] at the time of informed consent, weight (kg), BMI (kg/m^2), and BMI z-scores.

Categorical demographic variables include BMI group (Underweight (<18.5), Normal weight (18.5-24.9), Overweight (25.0-29.9), and Obese ≥30), gender, race, ethnicity.

Categorical baseline characteristics variables are ambulatory (Yes/No), ventilatory support (Yes/No), stage of DMD (Late (35%-45%); Early (>45%)), Background DMD therapy (steroid alone, steroid + ASO (Exon-skipping therapy) ASO alone, none), and other cardiac medications (ACEi; ARB; ARNI; beta-blocker; diuretic; Aldosterone receptor antagonist; calcium channel blocker—outlined in the concomitant medication CRF; see Table 1 below for complete listing of drugs in each class). Mutational analysis results will be included with age of DMD diagnosis.

Summary statistics for continuous variables will be presented as mean, standard deviation, minimum, median, and maximum, and for categorical variables, frequency counts and percentages.

A subject-data listing of demographics will be provided.

5.3 Dosing and Extent of Exposure

Exposure and compliance will be summarized for the Safety Population by treatment group and overall. Comments recorded on the Study Drug Accountability eCRF 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).

Summary statistics for exposure and compliance will be presented in a table with the corresponding listing for the Safety Population. The number of subjects fasted at time of IMP administration for Month 6, Month 12 and both Month 6 and Month 12 will be summarized as categorical data (yes/no, %).

A subject-data listing of compliance will be provided.

5.4 Medical and Surgical History

The Medical History verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be coded to the MedDRA (Version 20.0 or higher) lower- level Term (LLT) to the closest verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

The number (percent) of subjects will be presented by treatment and overall, and by SOC and PT for safety population.

A subject data listing of medical and Surgical history will be provided.

5.5 Concomitant Medications

Concomitant medications are defined as all prescription medications, over-the-counter drugs, and significant non-drug therapies administered after treatment through 30-days post study treatment must be recorded on the eCRF.

Concomitant medications will be coded in WHODrug GLOBAL C3 and listed by medication name and preferred term. Concomitant medications will be summarized by Preferred Term using the count and percentage of subjects by treatment group and overall for the Safety Population will be displayed. Subjects who have taken the same medication (in terms of PT) more than once will be counted only once for that medication.

Separate subgroup summaries will be provided for early stage DMD (LVEF > 45%) and advance (late) stage DMD (LVEF 35% - 45%) and combined (Early Stage + Late Stage).

All Concomitant medications will be presented in a listing for the Safety Population.

6 EFFICACY ANALYSIS

The efficacy analyses in this study incorporate natural history data as a supplemental comparator, a strategy supported by recent research and regulatory perspectives in rare disease settings. This approach has demonstrated validity in DMD specifically (Goemans 2020), where matched external controls have shown utility in drug evaluation, especially when disease progression is relatively well-characterized. The FDA has acknowledged the importance of natural history data in rare disease clinical development and real-world evidence frameworks. Research by Soslow et al. (2023) supports the application of natural history data while acknowledging its limitations and necessary methodological considerations. The propensity score matching methodology employed in this study aims to address potential selection bias and confounding factors when incorporating this external data.

All hypothesis tests will be performed at the 0.05 level. Analyses of secondary efficacy variables will be performed using the ITT and PP population only. Summary statistics will be presented for all analyses of efficacy variables.

6.1 Primary Analyses

Not Applicable

6.2 Secondary Analyses

Change from baseline endpoints and pharmacokinetics endpoints over 12 months included in the secondary analyses.

6.2.1 Change from baseline in LVEF and Myocardial Strain using CMR

The secondary analysis will focus on the change from baseline in LVEF and myocardial strain over 12 months of dosing.

The change from baseline in LVEF and myocardial strain will be compared between the treatment groups (High-Dose Ifetroban vs Placebo; Low-Dose Ifetroban vs Placebo) using Wilcoxon rank sum test for ITT population.

The number and change from baseline in LVEF and myocardial strain for each treatment group and overall, in the ITT population will be summarized descriptively. The following myocardial strain endpoints will be summarized:

- Indexed left ventricular end diastolic volume (LVEDVi)
    - LVEDVi = LVEDV/body surface area (BSA)
    - BSA calculation from CMR dataset using the Haycock method for pediatrics = $0.024265 \times (ht\_cmr)^{0.3964} \times (wt\_cmr)^{0.5378}$
    - From CMR dataset: LVEDVi = “lvedv_cmr”/ “bsa_calc_cmr”
- Indexed left ventricular end systolic volume (LVESVi)
    - LVESVi = LVESV/body surface area
    - BSA calculation from CMR dataset using the Haycock method for pediatrics = $0.024265 \times (ht\_cmr)^{0.3964} \times (wt\_cmr)^{0.5378}$
    - From CMR dataset: LVESVi = “lvesv_cmr”/ “bsa_calc_cmr”
- Mid Ecc (circumferential strain)

- Global Ecc
- Late gadolinium enhancement, full-width half-maximum (LGE FWHM)
- Number of segments with LGE (number of LGE segments with values >0)
- Base T1
- Mid T1

A subject data listing of all LVEF and myocardial strain will be provided.

6.2.2 Interobserver Variability

CMR images are reviewed by a primary internal reviewer and a secondary external reviewer to assess interobserver variability. The intraclass correlation coefficient (ICC) will be calculated to evaluate consistency between reviewers using a two-way mixed effects model where reviewers are treated as fixed effects and subjects as random effects.

ICC will be calculated as follows:

ICC = (MSR - MSE) / [MSR + (k-1) * MSE]

where MSR is the mean square for rows, MSE is the mean square error, and k is the number of reviewers.

The 95% confidence intervals for ICC values will be estimated using bootstrapping with 1000 resamples. P-values for agreement between observers will be tested using likelihood ratio tests comparing models with and without the reviewer effect.

ICC values will be interpreted as follows:

- < 0.5: Poor reliability

- 0.5 to 0.75: Moderate reliability

- 0.75 to 0.9: Good reliability

- > 0.9: Excellent reliability

ICC values along with 95% confidence intervals and p-values will be calculated for each CMR parameter at each visit and overall by treatment group.

6.2.3 Change from baseline in Pulmonary Function Test

The secondary analysis will focus on the change from baseline (see Section 4.4.1 for definition) in Pulmonary function test over 12 months of dosing.

The change from baseline in PFT will be assessed by the following efficacy variables:

- Forced Expiratory Volume 1 (FEV1)
    - FEV1 Value = Collected on the CRF. Measured as the "best effort" of the 3 collected measurements at each time point where "best effort" = Max (FEV1_1, FEV1_2, FEV1_3)
    - FEV1 percent predicted (FEV1%p) = Collected on CRF. Calculated from subject metrics and measured FEV1 values.
    - CFB FEV1 = post-treatment measurement – baseline
    - CFB FEV1%p = post-treatment measurement – baseline
- Forced Vital Capacity in liters (FVC)
    - FVC Value = Collected on the CRF. Measured as the "best effort" of the 3 collected measurements at each time point where "best effort" = Max (Fvc_1, Fvc _2, Fvc _3)
    - FVC percent predicted (FVC%p) = Collected on CRF. Calculated from subject metrics and measured FVC values.
    - CFB FVC= post-treatment measurement – baseline
    - CFB FVC%p= post-treatment measurement – baseline
- Maximal Expiratory Pressure in cm of water (MEP)
    - MEP Value = Collected on the CRF. Measured as the "best effort" of the 3 collected measurements at each time point where "best effort" = Max (MEP_1, MEP _2, MEP _3)
    - CFB MEP = post-treatment measurement – baseline
- Maximal Inspiratory Pressure in cm of water (MIP)
    - MIP Value = Collected on the CRF. Measured as the absolute value of the "best effort" of the 3 collected measurements at each time point where "best effort" = Max (MIP_1, MIP _2, MIP _3).
    - CFB MIP = post-treatment measurement – baseline
- Peak Expiratory Flow rate in liters/second (PEF)

- PEF Value = Collected on the CRF. Measured as the "best effort" of the 3 collected measurements at each time point where "best effort" = Max (PEF_1, PEF_2, PEF_3)
- PEF percent predicted (PEF%p) = Collected on CRF. Calculated from subject metrics and measured PEF values.
- CFB PEF= post-treatment measurement – baseline
- CFB PEF%p= post-treatment measurement – baseline

The number and change from baseline in PFT for each treatment group and overall, in the ITT population will be summarized descriptively.

A subject data listing of all PFT will be provided.

6.2.4 Change from baseline in Pediatric quality of life inventory (PEDsQL)

For the ITT population, the number and change from baseline in Pediatric Quality of Life Inventory (PedsQL) scores, including the generic core scales, gastrointestinal (GI) module, and neuromuscular module (NMM)

- CFB PedsQL =Post Treatment Measurement-Baseline
- CFB gastrointestinal (GI)= Post Treatment Measurement-Baseline
- CFB gastrointestinal (NMM)= Post Treatment Measurement-Baseline

For the derivation of PedsQL data, please refer to Section 9.1.3.

In addition, the change from baseline in PedsQL total scores will also be summarized descriptively for the age cohort specified on the survey (5-7 years, 8-12 years. 13-17 years, 18-25 years, 26+ years (for Neuromuscular and GI modules, 18+ years is the highest age group)) by responder (parent and child), visit, treatment group and overall, for the ITT population:

PedsQL data and scores for each module and dimension, as well as the overall score, will be displayed.

6.3 Exploratory Endpoints

6.3.1 Change from baseline in QMT

Change from baseline in quantitative muscle testing (QMT) to assess the muscle strength. Separate summaries will be provided for early stage DMD (LVEF > 45%) and advance (late) stage DMD (LVEF 35% - 45%) and combined (Early Stage + Late Stage).

Additionally, the number and percentage of subjects will be summarized by treatment group and overall.

- QMT
    - QMT Value = Collected on the CRF. Measured as the "best effort" of the 3 collected measurements at each time point where "best effort" = Max (QMT_1, QMT_2, QMT_3)
    - Arm QMT Value = Sum of left elbow extension, left elbow flexion, right elbow extension, and right elbow flexion
    - Leg QMT value = Sum of left knee extension, left knee flexion, right knee extension, and right knee flexion
    - Total QMT Score = Sum of Arm QMT Value and Leg QMT Value
    - Indexed QMT Score = Arm, Leg, or Total QMT Score divided by subject age up to 20 years (lbs/years). For subjects >20 years of age, scores will be divided by 20.

A subject data listing of all QMT will be provided.

6.3.2 Change from baseline in daily life activity

Accelerometry was presented as an alternative approach for measuring physical activity and as a potential outcome measurement for DMD during this study.

Accelerometry:

Subjects wore an Actigraph accelerometer (Actigraph) on their dominant wrist and ankle for 7 days. Actigraph accelerometers were used to measure acceleration in three orthogonal axes (x, y, and z) at 30 Hz (i.e., 30 records per second per axis). ActiLife software (Actigraph, version 6.11.5 or higher) was used to upload accelerometer recordings, which were then integrated into 15s epochs and converted into an omni-directional acceleration estimate (VM), calculated as the square root of the sum of the triaxial signals squared, or ($x^2 + y^2 + z^2$). Choi's method was utilized to distinguish between accelerometer wear and non-wear phases.

The accelerometer recordings of a participant were considered valid if they covered ≥2 days.

Wrist accelerometer recordings were divided into X min epochs while awake and used to calculate the time spent in activity intensity categories such as sedentary, low intensity, and moderate to vigorous physical activity (MVPA).

The adherence and physical activity parameters calculated for the wrist and ankle accelerometers of subjects with DMD included VMs generated while wearing (VM total), VMs generated per minute while wearing (VM/min wear), and VMs generated per minute while wearing and awake (VM/min awake).

It is necessary to undertake standard methods for the cleaning and management of accelerometer dataset.

Change from baseline in total VM Counts/min; VM Counts awake/min and physical activity intensities to assess the lifestyle behavior patten will be provided.

Additionally, the number and percentage of subjects will be summarized by treatment group and overall.

6.4 Open Label Extension Analyses

The open-label extension (OL) provides an opportunity to assess long-term safety and efficacy of high-dose ifetroban. Analyses will be performed for subjects completing 12, 24, and 36 months of treatment.

6.4.1 Efficacy Analyses in Open-Label Extension

The following analyses will be performed for OL participants:

- One-year OL data (Month 12 to Month 24): Change from Month 12 in CMR parameters, PFT, QMT, and accelerometry will be summarized for all OL subjects, and by DB treatment assignment subgroups (High to High, Low to High, Placebo to High)

- Two-year total study data (Baseline to Month 24): Change from baseline in CMR parameters, PFT, QMT, and accelerometry will be summarized for continuous high-dose subjects compared to NHS matched subjects.

- Three-year total study data (for subjects completing 36 months): Change from baseline and from Month 36 in CMR parameters and PFT will be summarized

6.4.2 Treatment Effect Durability

To assess durability of treatment effects, subjects will be analyzed based on their double-blind treatment assignment and subsequent open-label treatment. Slope analyses using mixed models for repeated measures will be performed to evaluate trajectory of change in key efficacy parameters over the entire study period.

6.5 Subgroup Analyses

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 for the variables below.

The following subgroups will be assessed using the primary endpoint and primary endpoint related to clinical assessments, secondary endpoints, and exploratory endpoints.

- DMD disease stage (Early LVEF>45%, Late LVEF 35%-45%)
- Ambulation status (ambulatory vs non-ambulatory)
- Background therapy (none, steroids, ASO, steroids + ASO)

For each subgroup analysis, results will be presented as stratified analyses with descriptive statistics and treatment effect estimates within each subgroup level. Forest plots will be used to display treatment effects across subgroup levels for key endpoints. No formal statistical testing for interaction between subgroup and treatment will be performed due to limited sample sizes within subgroups, but the consistency of treatment effects across subgroup levels will be evaluated qualitatively. These analyses are considered exploratory and intended to identify potential patterns that may inform future research rather than to draw definitive conclusions about differential treatment effects.

Missing data in each factor, which will be limited if any, will not be included (as a separate group) in subgroup analyses. This does not apply to the PSM analysis.

7 SAFETY ANALYSIS

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, laboratory safety test variables, abnormal ECG findings, Vital signs (including weight), Physical examination along with change from baseline will be summarized by visit, treatment group, subgroup and overall.

Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

7.1 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 27.0 or higher) LLT closest to the verbatim term. The linked MedDRA PT and primary SOC will also be captured in the database.

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after dosing or starts prior to dosing and increases in severity after dosing.

A treatment related AE will be defined as an AE with a relationship of possible, probable, unlikely, or unrelated to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for TEAEs only.

The frequency of subjects with TEAEs/serious adverse events (SAEs) and the number of TEAEs/SAEs will be summarized for the following categories:

- TEAEs/SAEs (overall, serious, leading to discontinuation, and leading to death)
- TEAEs by severity
- Treatment-related AEs/SAEs (overall, serious, leading to discontinuation, and leading to death)
- Treatment-related AEs by severity
- TEAEs leading to discontinuation of study drug.
- TEAEs by SOC and PT.
- TEAEs by PT

A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (related and not related).

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started after dosing.
- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the calculation of TEAE summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as one TEAE for that treatment under the maximum severity recorded. Adverse events (AEs) will be

coded using the most updated MedDRA version. Uncoded events will be grouped together as 'Uncoded' for system organ class (SOC) and PT.

All AEs, SAE, TEAE leading to treatment discontinuation and TEAE with Grade 1/2/3 will also be provided in by-subject listings.

In addition to AE summaries, safety monitoring will include thorough evaluation of ECG parameters. Changes from baseline in ECG parameters and incidence of abnormal ECG findings will be summarized by visit and treatment group. ECG parameters will include heart rate, PR interval, QRS duration, QT interval, and QTc (Fridericia's formula). Abnormal ECG findings will be categorized as clinically significant or not clinically significant based on investigator assessment.

All adverse events will be coded using MedDRA version 27.1. Consistent coding will be maintained across all study periods, including the open-label extension. Laboratory abnormalities meeting predefined criteria for clinical significance will be flagged and summarized separately as potential adverse events of special interest.

7.2 Clinical Laboratory Parameters

Laboratory results will be summarized using Système International (SI) units, as appropriate.

Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each post-baseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit, treatment group and overall using descriptive statistics and changes from baseline to each post-baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post-baseline results.

Blood and urine samples for clinical chemistry and hematology will be collected at the timepoints described in APPENDIX 1. PROTOCOL SCHEDULE OF ASSESSMENTS AND PROCEDURES. Laboratory parameters that will be assessed will include, but not be limited to:

Clinical laboratories to be assessed will be as below:

- Complete Blood Count with differential: must include hemoglobin, hematocrit, platelet count, total white blood cell counts 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 Panel: partial thromboplastin time (PTT) and prothrombin time international normalized ratio (INR).

Clinical laboratory assessments taken from blood sampling, such as hematology, chemistry, and coagulation, will be summarized and listed for the Safety Population.

7.3 Other Analyses

Not Applicable

8 CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

Not Applicable

9 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

9.1 Algorithms for Efficacy Parameters

The following procedures will be used to determine the PFT and total scores for the efficacy parameters PedsQL Generic core scales, GI, and NMM.

9.1.1 Pulmonary Function Test

Three sets of observations are measured for each variable in PFT. The “best” of the 3 values to be flagged according to the following procedure:

STEP 1: Order the 3 values to low, middle, high

STEP2: Calculate the % difference between the middle and the high value.

%difference= (high-middle)/high

STEP3:

if the %difference is <=10% then flag the high value as the best value

If the %difference is >10% then flag the middle value as the best value

The **low** value will never be used.

9.1.2 Quantitative Muscle Testing (QMT)

QMT is measured by strength measured in pounds for flexion and extension of both elbows and knees. QMT is reported as an Arm QMT Value, Leg QMT Value, and Total QMT Value.

STEP 1: Calculate Arm QMT Value: left elbow flexion + left elbow extension + right elbow flexion + right elbow extension

STEP 2: Calculate Leg QMT Value: left knee flexion + left knee extension + right knee flexion + right knee extension

STEP 3: Calculate Total QMT Score: Arm QMT Value + Leg QMT Value

STEP 4: Calculate indexed Arm QMT Value, Leg QMT Value, and Total QMT Value as follows:

For subjects ≤20 years of age:

Indexed Arm QMT = Arm QMT Value/age (lbs/years)

Indexed Leg QMT = Leg QMT Value/age (lbs/years)

Indexed Total QMT = Total QMT/age (lbs/years)

For subjects greater than 20 years, QMT values will be divided by 20.

9.1.3 Pediatric Quality of Life Inventory (PEDsQL) 4.0 Generic Core Scales

The Child, Young Adult, Adult, and Parent Reports of the **PedsQL™ 4.0 Generic Core Scales** for:

- Young Children (ages 5-7)
- Children (ages 8-12)
- Teens (ages 13-17)
- Young adults (ages 18-25)
- Adults (ages over 26)

are composed of 23 items comprising 4 dimensions.

Total Score were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning.

DESCRIPTION OF THE QUESTIONNAIRE:

Dimensions	Number of Items	Cluster of Items	Reversed scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	Higher scores = Better HRQOL
Emotional Functioning	5	1-5	1-5	
Social Functioning	5	1-5	1-5	
School Functioning	5	1-5	1-5	

SCORING OF DIMENSIONS

Item Scaling	CHILD and PARENT Reports for Young Children (ages 5-7), Children (ages 8-12), and Teens (ages 13-18)	Young adult, adult and Parent Reports for young Adults (ages 18-25) and Adults (ages over 26)
	5-point Likert scale from: 0 (Never) to 4 (Almost always) 3-point Likert scale from: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child (ages 5-7) child report	5-point Likert scale from: 0 (Never) to 4 (Almost always)
Weighting of Items	No	
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100	
Scoring Procedure	**Step 1: Transform Score** Items are reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0 **Step 2: Calculate Scores by Dimensions:**	

	• If more than 50% of the items in the scale are missing, the scale scores should not be computed • Mean score = Sum of the items over the number of items answered **Psychosocial Health Summary Score** = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales **Physical Health Summary Score** = Physical Functioning Scale Score **Total Score:** Sum of all the items over the number of items answered on all the Scales
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

9.1.4 PEDsQL™ 3.0 Gastrointestinal Symptom Module Total Score

The Child, Young Adult, Adult, and Parent Reports of the PedsQL™ 3.0 Gastrointestinal Symptoms Module for:

- Young Children (ages 5-7)
- Children (ages 8-12)
- Teens (ages 13-18)
- Young adults (ages 18-25)
- Adults (ages over 26)

are composed of 74 items comprising 14 dimensions and sum of all 74 non-missing transformed variables divided by the questions answered(non-missing).

DESCRIPTION OF THE GASTROINTESTINAL SYMPTOMS MODULE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Stomach Pain and Hurt	6	1-6	1-6	Higher scores = Better HRQOL and fewer problems or symptoms
Stomach Discomfort When Eating	5	1-5	1-5	
Food and Drink Limits	6	1-6	1-6	
Trouble Swallowing	3	1-3	1-3	
Heart Burn and Reflux	4	1-4	1-4	
Nausea and Vomiting	4	1-4	1-4	
Gas and Bloating	7	1-7	1-7	
Constipation	14	1-14	1-14	
Blood in Poop (Bowel Movement)	2	1-2	1-2	
Diarrhea	7	1-7	1-7	
Worry About Going Poop (Bowel Movements)	5	1-5	1-5	
Worry About Stomach Aches	2	1-2	1-2	
Medicines	4	1-4	1-4	
Communication	5	1-5	1-5	

SCORING OF DIMENSIONS

Item Scaling	CHILD and PARENT Reports for Young Children (ages 5-7)	CHILD, YOUNG ADULT, ADULT, and PARENT Reports for Children (ages 8-12), Teens (ages 13-18) Young Adults (ages 18-25), and Adults (ages over 26)
	5-point Likert scale from: 0 (Never) to 4 (Almost always) 3-point Likert scale from: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child (ages 5-7) child report	5-point Likert scale from: 0 (Never) to 4 (Almost always)
Weighting of Items	No	

Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100
Scoring Procedure	**Step 1: Transform Score** Items are reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0 **Step 2: Calculate Scores by Dimensions:** • If more than 50% of the items in the scale are missing, the scale scores should not be computed • Mean score = Sum of the items over the number of items answered **Symptoms Total Scales Score:** Sum of the items over the number of items answered in the 10 Symptoms Scales **Total Score:** Sum of all the items over the number of items answered on all the Scales
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

9.1.5 PEDsQL™ 3.0 Neuromuscular Module Total Score

The Child, Young Adult, Adult, and Parent Reports of the PedsQL™ 3.0 Neuromuscular Module for:

- Young Children (ages 5-7)
- Children (ages 8-12)
- Teens (ages 13-18)
- Young adults (ages 18-25)
- Adults (ages over 26)

are composed of 25 items comprising 3 dimensions, whereas the Child Report for young children (ages 5-7) consists of only 17 items and comprising 1 dimension. sum of all 25 non-missing transformed variables (parent and child reports) and 17 non-missing transformed variables (child report) divided by the non-missing questions.

THE CHILD DESCRIPTION OF THE NEUROMUSCULAR MODULE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
About My Neuromuscular Disease	17	1-17	1-17	Higher scores = Better HRQOL and fewer problems or symptoms

THE CHILD AND PARENT DESCRIPTION OF THE NEUROMUSCULAR MODULE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
About Neuromuscular Disease	17	1-17	1-17	Higher scores = Better HRQOL and fewer problems or symptoms
Communication	3	1-3	1-3	
About Our Family Resources	5	1-5	1-5	

SCORING OF DIMENSIONS

Item Scaling	CHILD Reports for Young Children (ages 5-7)	CHILD, YOUNG ADULT, ADULT, and PARENT Reports for Young Children (ages 5-7), Children (ages 8-12), Teens (ages 13-18), Young Adults (ages 18-25), and Adults (ages over 26)
	3-point Likert scale: 0 (Not at all), 2 (Sometimes), 4 (A lot)	5-point Likert scale from: 0 (Never) to 4 (Almost always)
Weighting of Items	No	

Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100
Scoring Procedure	**Step 1: Transform Score** Items are reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0 **Step 2: Calculate Scores by Dimensions:** • If more than 50% of the items in the scale are missing, the scale scores should not be computed • Mean score = Sum of the items over the number of items answered **Total Score:** Sum of all the items over the number of items answered on all the Scales
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

9.2 Interobserver Variability

The level of agreement or consistency between different observers (or reviewers) when they evaluate, measure, or categorize the same test on the same subjects is referred to as interobserver variability, also known as interrater reliability or interrater variability.

10 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The rules for programming derivations and dataset specifications are provided in separate documents.

11 STATISTICAL SOFTWARE

All statistical analyses will be performed by using SAS Version 9.4 or later.

12 MOCK TABLE, LISTING AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

13 REFERENCES

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14 APPENDIX

14.1 APPENDIX 1. PROTOCOL SCHEDULE OF ASSESSMENTS AND PROCEDURES

	Screening Period		Treatment Period						Opt Ext	
	Visit(s)		Visit[e]	Phone Call/At-home	Phone Call	At-home	Visit[e]	Visit[e]	Phone Call/At-home	Visit[e]
	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)
Informed Consent/Assent	X									
Medical/Surgical History, Demography	X									
Screening CMR or ECHO	X[a]									
Cystatin C		X								
Research CMR			X[a]				X	X		X
Physical Exam with vital signs		X	X[b]				X	X		X
Pulmonary Function Test			X				X	X		X
ECG, QMT & Actigraphy			X				X	X		X
PROs: PedsQL, GI & NMM			X			X	X	X	X[d]	X
CBC, CMP & Coagulation		X	X[b]				X	X		X
PK Blood Sampling			X[c]	X[c]						
Urine & blood for biomarkers			X				X	X		X
Review subject diary			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 – 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.
e - The site may split on-site study visits on Day 0, Month 6, Month 12, and Month 24 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.

14.2 APPENDIX 2: Partial Date Recovery

Missing partial dates for prior/concomitant medications, and adverse events will be recovered with the following rules.

- If Start date is partial:
    - Missing day only
        - If the month and year are the same as the year and month of the first study treatment date, then the first dosing date will be assigned to the missing field.
        - If the partial date (year and month) is prior to the first study treatment date (year and month), then the last day of the month will be assigned to the missing field.
    - If the partial date (year and months) is after the first study treatment date (year and month), then the first day of the month will be assigned to the missing field.
    - Missing month only
        - The day will be treated as missing and both month and day will be imputed according to the imputation's rules for missing day and month.
    - Missing day and month
        - If the year is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing field.
        - If the year is prior to the year of the first dosing date, then December 31 will be assigned to the missing field.
        - If the year is after the year of the first dosing date, then January 1st will be assigned to the missing field.
    - Missing year
        - No Imputation will be done.
        - If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by stop date.
- If End Date is partial:
    - Missing day only

- If the month and year are the same as the year and month of the last study treatment date, then the last dosing date will be assigned to the missing field.
- If the partial date (year and month) is prior to the last study treatment date (year and month), then the last day of the month will be assigned to the missing field.
- If the partial date (year and months) is after the last study treatment date (year and month), then the first day of the month will be assigned to the missing field.

- Missing month only
  - The day will be treated as missing and both month and day will be imputed according to the imputation's rules for missing day and month.
- Missing day and month
  - If the year is the same as the year of the last dosing date, then the last dosing date will be assigned to the missing field.
  - If the year is prior to the year of the last dosing date, then December 31 will be assigned to the missing field.
  - If the year is after the year of the last dosing date, then January 1st will be assigned to the missing field.
- Missing year
  - No Imputation will be done.
  - If the start date is non-missing and the imputed stop date is before the start date, the stop date will be imputed by start date.

14.3 APPENDIX 3: Treatment Comparisons with Natural History (NH) Subjects

14.3.1 Propensity Score Modeling and Calculation

A propensity score (PS) is an estimated probability that a subject will be assigned to a specific treatment group based on observed characteristics or covariates, typically derived from a logistic regression model. In this study, PS will be used to match ifetroban-treated subjects with those from a DMD natural history study (NHS), ensuring that the control/placebo group has comparable disease characteristics with the ifetroban-treated group. This approach enhances the reliability of comparisons between ifetroban-treated and untreated subjects by reducing imbalances in observed prognostic factors, mitigating confounding, and improving the validity of the analysis.

The DMD NHS used for these analyses is a multicenter, FDA-funded registry study evaluating patients with DMD yearly. CPI-IFE-007 study design mirrors the NHS in terms of endpoints (except the PedsQL), making between group comparisons possible. NHS visits are approximately one year apart (dates provided) with demographic data, cardiac function data, concomitant medications, pulmonary function, accelerometry, muscle strength, and quality of life assessed at each visit. Propensity score matching (PSM) will be used to select NHS patients comparable to ifetroban-treated patients in terms of age, baseline LVEF, and background therapy as specified below.

The PSM will be calculated separately for the DB and OL periods. The purpose of the matching in the DB period is to supplement the already existing placebo subjects with NH subjects. In the OL period, the purpose of the matching is to create a new placebo/control group to compare to the treated patients. Each period's propensity score will be based on different model covariates model that reflects the respective study period. For the DB period the matching will be performed on the high-dose ifetroban only, for the OL, the propensity score will be calculated for all treated subjects.

For both the DB and the OL, Natural History subjects with non-missing cardiac efficacy data (LVEF and Myocardial strain) at baseline and month 12 will not be included in the matching process. Also, the global optimal algorithm, based on the nearest neighbor approach without replacement and without caliper subject level matching, will be performed for the placebo subjects to achieve 2:1 ratio (Placebo: High-Dose Ifetroban).

14.3.2 DB Inclusion/Exclusion for NH

Subjects from the NH were selected to reflect the baseline criterion of the CPI-IFE007 study before the propensity score is calculated. The following criteria will be applied for matching with the DB subjects given the High dose:

- Male subjects $\geq$ 7 years old.

- 2 years data of LVEF.
- Baseline value LVEF of >= 35% (baseline is pre-dose in study)
- No current treatment with givinostat (Duvyzyat®), empagliflozin (Jardiance®), dapagliflozin (Farxiga®), canagliflozin (Invokana®) (Variables: other_meds_listed ≠ "givinostat," "emplagliflozin," "dapagliflozin," "canaglifloxin," "duvyzyat," "Jardiance," "farxiga," "Invokana")
- Corticosteroids Stable Dose (Stable dose for >= 56 of corticosteroids days or no corticosteroids for < 30 days prior to the start of baseline).
- Subjects with no history of heart failure.
- Live subjects with non-missing cardiac efficacy data (CFB LVEF and CFB Myocardial strain) at baseline and month 12
- Patients given High dose in DB

14.3.3 OL Matching Inclusion/Exclusion for NH

Subjects from the NH were selected to reflect the baseline criterion of the CPI-IFE007 study before the propensity score is calculated. The following criteria were applied for matching with the OL subjects:

- Male subjects ≥ 7 years old.
- 2 years data of LVEF
- Baseline value LVEF of >= 35% (baseline is month 12 in study)
- Subjects with no history of heart failure.
- No current treatment with givinostat (Duvyzyat®) (Variables: other_meds_listed ≠ "givinostat," "duvyzyat")
- Live subjects with non-missing cardiac efficacy data (CFB LVEF and CFB Myocardial strain) at baseline and month 12 for OL. Live subjects with non-missing cardiac efficacy data (LVEF and Myocardial strain) at month 12 and month 24 for OL. Missing data will not be imputed.

14.3.4 List of Baseline Covariates for Modeling

The following baseline covariates will be included in the DB and OL Model to create the propensity score.

- Age
- Baseline left ventricular ejection fraction (LVEF). Baseline will represent pre-treatment values in DB and Month 12 visit values will be the baseline in the OL study.
- Background DMD medications (current steroids, Current ASO/exon skipping)
- Additional cardiac medications (Aldosterone antagonists, Beta-blocker, ACEi, ARB, Calcium channel blockers, ARNI)

The following chart will be used to define the baseline med covariates in the NH dataset.

Table 1 Background DMD Therapies and Cardiac Medications of Relevance by Class

Med Type (Natural Data Variable name)	Definition of Generic (Brand Name)
ASO/Exon skipping therapy (aso_yn)	Exondys 51 (eteplirsen) Amondys 45 (casimersen) Viltepso (viltolarsen) Vyondys 53 (golodirsen)
Aldosterone antagonists (aldosterone_yn)	Eplerenone (Inspra) Finerenone Spironolactone (Aldactone/CaroSpir)
Beta-blocker (bb_yn)	Acebutolol Atenolol (Tenormin) Bisoprolol Metoprolol (Lopressor, Toprol XL) Nadolol (Corgard) Nebivolol (Bystolic) Propranolol (Inderal LA, InnoPran XL) Carvedilol (Coreg)
ACEi /angiotensin converting enzyme inhibitor (taking_ace)	Benazepril (Lotensin) Captopril Enalapril (Vasotec) Fosinopril Lisinopril (Zestril) Moexipril

Med Type (Natural Data Variable name)	Definition of Generic (Brand Name)
	Perindopril Quinapril Ramipril (Altace) Trandolapril
ARB /angiotensin receptor blocker (ARB_YN)	Azilsartan (Edarbi) Candesartan (Atacand) Irbesartan (Avapro) Losartan (Cozaar) Olmesartan (Benicar) Telmisartan (Micardis) Valsartan (Diovan)
Calcium channel blockers (cach_yn)	Amlodipine (Norvasc) Diltiazem (Cardizem, Tiazac) Felodipine (Plendil) Nifedipine (Procardia) Nisoldipine (Sular) Verapamil (Calan, Isoptin, Tarka, Verelan)
Steroids (new_med_steroid_v1— new_med_steroid_V.., steroid_change_type, start_date_steroid)	Prednisone/prednisolone Hydrocortisone (note that hydrocortisone cannot be the cream) Deflazacort (Emflaza) Deflazcort Deflazocort Emflaza Emflaza-Delfazacort Solu-Cortf Agamree/vamorolone
ARNI/angiotensin receptor/neprilysin inhibitor (ARNI_yn)	Sacubitril/Valsartan (Entresto)

14.3.5 Missing data handling

Missing data in natural history collection will not be imputed for PSM analysis.

14.3.6 Analysis Population

For the DB period, only high dose active and placebo subjects with Month 12 evaluable cardiac efficacy data will be included in the analysis.

For OL, all ifetroban treated subjects in the ITT population will be matched with natural history data.

14.3.7 Analysis with Natural History Data

Multiple analyses will be completed using matched NH subjects as a historical comparator. See Figure 2 below for a detailed analysis diagram.

In the DB study (Baseline to Month 12), the tables will be presented by the following treatment groups:

- ifetroban High
- Placebo with supplemented NH

In the OL study, the tables will be presented by:

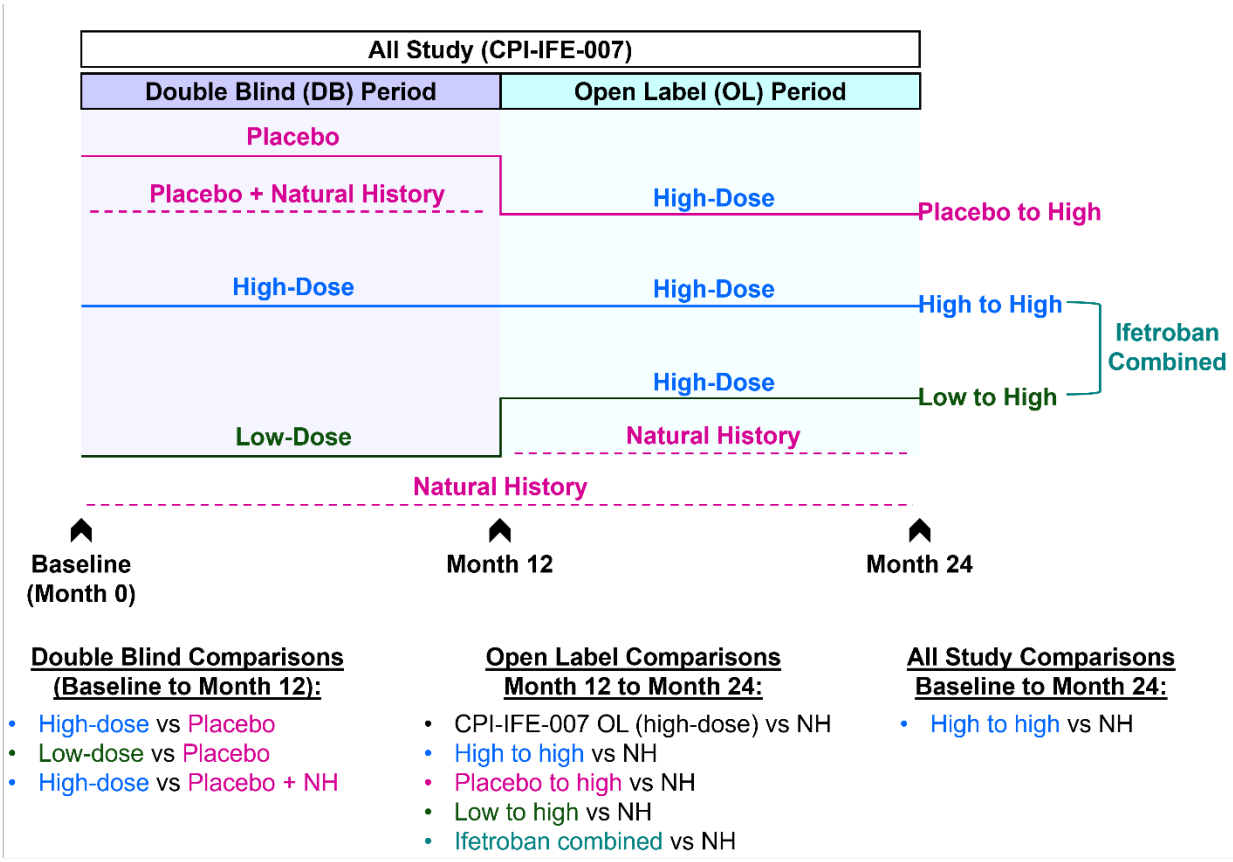
One year data (Month 12 to Month 24):

- All OL
- High to High ifetroban
- Low to High ifetroban
- Ifetroban (High and Low combined)
- Placebo to High ifetroban
- NH

All study two-year data (Baseline to Month 24):

- High to High ifetroban
- NH

Figure 2 All Study Analyses Diagram



For both the OL and the DB, demographic and baseline characteristics will be summarized for by treatment group including baseline LVEF, concomitant medication usage and propensity score by treatment group for the DB period and the OL period. Summary tables will be provided for the observed value and the change from baseline for each endpoint. In addition, 95% confidence intervals will be presented for each treatment group for the demographic variables and baseline characteristics. For categorical variables, proportion confidence intervals will be created using the binomial approximation.

A listing of natural history subjects' demographic and baseline characteristics will also be included.

For the DB period, the endpoints CFB in LVEF and myocardial strain at 12 Months. For the OL period, the endpoints to be evaluated at the 24 months after treatment are CFB LVEF, CFB myocardial strain, PET, QMT, and accelerometry. All endpoints will be evaluated using the change from baseline will be compared between the ifetroban vs. Placebo or natural history groups using a Wilcoxon rank sum test

14.3.8 Sensitivity Analysis

A sensitivity analysis will be performed for the DB period, by re-selecting natural history subjects (Placebo:High-Dose ifetroban) using the average Treatment Effect (ATE), by applying the inverse probability of treatment weighting (IPTW). These weights will create pseudo-population of the untreated, which has the same covariate distribution as the treated. While every treated subject received as weight of [1/PS], every untreated subject is weighted by [1/(1-PS)]. An additional exact matching analysis will be explored for feasible categorical variables.

Two separate sensitivity analyses will be performed using caliper 0.2 and using exact matching.

An additional sensitivity analysis will be performed comparing the ifetroban treatment groups to the entire eligible NH cohort (before matching) to evaluate the robustness of findings from the matched analysis. This will help assess whether the treatment effect observed in the matched comparison remains consistent when compared against the broader NH population. This analysis will use appropriate covariate adjustment in the statistical models to account for baseline differences between groups rather than relying solely on matched pairs.