STATISTICAL ANALYSIS PLAN
A Two-Part Study to Assess the Safety and Tolerability, Pharmacokinetics, and Effects on Histology and Different Clinical Parameters of Givinostat in Ambulant Children with Duchenne Muscular Dystrophy

Protocol Ref: DSC/11/2357/43

Version: Final Version 3.0

Date effective: 10-January-18

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16.1.9 Documentation of Statistical Methods

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SUMMARY OF SECTIONS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

6MWT	6-Minute Walk Test
6MWD	6-Minute Walk Distance
Ab	Antibodies
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma–concentration time curve
BID	twice daily
BUN	blood urea nitrogen
CI	confidence interval
CL	clearance
CL/F	volume of distribution
cm	Centimeter
Cmax	maximum plasma concentration
CMV	Cytomegalovirus
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRP	C-reactive protein
CSA	cross-sectional area
CSOM	Clinical Study Operations Manual
DMD	Duchenne muscular dystrophy
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiograph
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
FACS	fluorescence-activated cell sorting
FAP	fibroadipongenic progenitors
FEV1	forced expiratory volume at 1 second
FU	follow up
FVC	forced vital capacity
GI	Gastrointestinal
h	hour
H&E	hematoxylin and eosin
HbeAg	hepatitis B e antigen
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDAC	histone deacetylase

HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL	interleukin
IMP	investigational medicinal product
ITT	intent to treat
JIA	juvenile idiopathic arthritis
KA	absorption rate constant
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LTBP4	latent transforming growth factor beta binding protein 4
m	Meter
MFA%	muscle fibers area %
mg	Milligram
miRNA	micro ribonucleic acid
mL	Milliliter
MRI	magnetic resonance imaging
msec	Millisecond
MTD	maximum-tolerated dose
MuSC	muscle satellite cells
ng	nanogram
nmol	nanomole
NOAEL	no observed adverse effect level
NSAA	North Star Ambulatory Assessment
PD	Pharmacodynamic
PDGFR	platelet-derived growth factor receptor
PEF	peak expiratory flow
PET	polyethylene terephthalate
PFT	pulmonary function tests
PK	Pharmacokinetic
PUL	performance of upper limb
QT	QT interval
QTc	QT interval – corrected
RBC	red blood cells
RD	recommended dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOJIA	systemic onset juvenile idiopathic arthritis
SWI/SNF	switch/sucrose non-fermentable
TNF-α	tumor necrosis factor-alpha
V/F	plasma volume

V2/F	peripheral volume
WBC	white blood cells
WCT	Worldwide Clinical Trials

1. INTRODUCTION

This document details the statistical analysis of the data that will be performed for the Italfarmaco S.p.A. study DSC/11/2357/43.

The proposed analysis is based on the contents of the Final Version of the protocol (dated 01 Aug 2012) and amendments 1, 2, 3, 4, 5, 6 and 7 (dated 05 Dec 2012, 25 Mar 2013, 23 Oct 2013, 17 Apr 2014, 16 Mar 2015, 06 Jan 2016 and 11 Apr 2017 respectively).

The Clinical Study Report (CSR) will be written by WCT following the guidelines in the ICH E3 document.

The efficacy and safety analyses will be performed by Worldwide Clinical Trials (WCT).

The pharmacokinetic (PK) analyses will be performed by Accelera.

The primary objectives of this study are as follows:

- To establish the histologic effects of Givinostat administered chronically at the selected daily dose

The secondary objectives of this study are as follows:

- To establish the effects of Givinostat administered chronically at the selected daily dose on functional parameters, such as the 6-Minute Walk Test (6MWT), North Star Ambulatory Assessment (NSAA), and performance of upper limb (PUL)
- To establish the safety and tolerability of Givinostat administered chronically at the selected daily dose in children with Duchenne muscular dystrophy (DMD)
- To explore the effects of Givinostat administered chronically at the selected daily dose on parameters such as magnetic resonance imaging (MRI) and biomarkers
- To explore the acceptability/palatability of the oral suspension
- To explore whether the effects of Givinostat on disease progression may be related to the type of DMD mutation

Extension phase:

- The primary objective is to evaluate the safety and tolerability of long-term administration of Givinostat administered chronically at the selected daily dose in children with DMD.

The secondary objectives are:

- To establish the effects of Givinostat administered chronically at the selected daily dose on other functional parameters, such as the 6MWT, NSAA, and PUL
- To explore the effects of Givinostat administered chronically at the selected daily dose on parameters such as MRI
- To collect information related to 2 biomarkers, LTBP4 and osteopontin genotype (at the beginning of Extension 2 only).

The analysis populations of this study are as follows (see section 6.3 for definition):

- Intent-to-treat (ITT) Population
- Evaluable Population
- Completers Population
- Safety Population
- PK Population

This is a 2-part, phase 2 study to assess the effects of Givinostat on muscle histologic parameters and on clinical parameters in ambulant children with DMD. The safety, tolerability, and pharmacokinetics of Givinostat will also be assessed.

Approximately 20 children will be enrolled in the study as follows:

The first 4 children will be treated at a low dose level of Givinostat.

If none of the stopping criteria are met after 2 weeks of treatment at the low dose, the review team will determine the escalated dose level (i.e., intermediate dose level) to be used for the treatment of an additional 8 children who will be treated at the intermediate dose. The 4 children previously treated at the low dose level will also be switched to the intermediate dose level.
If none of the stopping criteria are met after 2 weeks of treatment at the intermediate dose, the review team will determine the subsequent escalated dose level to be used for the treatment of an additional 8 children who will be treated at the high dose. All children treated at the intermediate dose level will be switched to the high dose level.

Once all 20 children enrolled during the Part 1 of the study have been treated for at least 2 weeks, the review team will determine the RD to be used in Part 2 based on the safety and tolerability profile observed and on the PK analyses. All the children enrolled will switch to the RD level, which will be administered for the subsequent 12 months of the study (Part 2).

The additional children (if any) will be enrolled during Part 2 of the study and will receive the RD of Givinostat for 12 months.

At 12 months, efficacy and safety analysis will be conducted. If the results show a positive effect on patients, and no safety concern is raised, then patients will continue study

treatment for another 12 months (Extension phase 1) to evaluate the safety and tolerability of long-term administration of Givinostat and to evaluate the effect of treatment on muscle function. If, on the other hand, the final analysis of the results of the first 12 months of treatment does not support a beneficial effect of Givinostat in DMD, the study will be considered complete and the patient will be asked to discontinue the treatment and return to the site for early termination assessments (within 2 weeks after the last study drug intake) and follow up assessments (within 4 weeks after the last study drug intake). This extension phase will be up to 24 months.

Since the histology results of the first 12 months of treatment are positive, a second extension phase is foreseen in order to allow the patients to continue a study treatment that supports a beneficial effect of Givinostat in DMD. The children on treatment in the Extension 1 will be asked to continue in the Extension 2 and will receive Givinostat at the same ongoing dose for a maximum of an additional 12 months. During Extension 2, the dose will be adjusted based on the weight of the children. This extension phase will be up to 36 months.

A third extension phase is foreseen in order to allow the patients to continue a study treatment that supports a beneficial effect of Givinostat in DMD. The children on treatment in the Extension 2 will be asked to continue in the Extension 3 and will receive Givinostat at the same ongoing dose for a maximum of an additional 16 months. During Extension 3, the dose will be adjusted based on the weight of the children. This extension phase will be up to 52 months.

2. SAMPLE SIZE

The sample size estimation was based on the following assumptions:

A minimum of 20 evaluable children will be enrolled in this study.

In part 1 approximately 20 children will be enrolled in Part 1 (dose-finding) of this study.

A sample size of 20 children from part 1 completing the treatment period of part 2 should provide 90% power (at a 2-sided alpha level of 5%) to detect at least a 12.5% increase in muscle fiber area% (MFA%) between pre- and post-treatment (which corresponds approximately to a 26% relative increase given the observed mean in the Desguerre[1] publication of 48%), the “worst case” standard deviation of 16%, which assumes that there is no correlation within a subject in the muscle area fiber percentage between pre- and post-treatment. This sample size is based on a paired t-test and the assumption of normal distribution of MFA%.

3. RANDOMIZATION

This is a non-randomized trial, all subjects will receive study drug.

4. INTERIM ANALYSIS

After the first 20 baseline biopsies were collected, an interim analysis aimed at checking the real variability observed in the study was conducted: the within-subject standard deviation

of MFA% was calculated, the actual distribution of MFA% was checked and the final sample size was adjusted based on the observed standard deviation and actual distribution of MFA%. Results by Al-Sunduqchi[2] and Guenther indicate that power calculations for the Wilcoxon test may be made using the standard t-test formulations with a simple adjustment to the sample size. The size of the adjustment depended upon the actual distribution of the data. They gave sample size adjustment factors for four distributions. These were 1 for the uniform distribution, 2/3 for the double exponential distribution, $9/\pi^2$ for the logistic distribution, and $\pi/3$ for the normal distribution. So depending on the actual distribution of MFA%, sample size re-calculation was based on a Wilcoxon Signed Rank test with the corresponding adjustment if the observed distribution of MFA% was not normal.

The resulted sample size was smaller than the original and included 19 enrolled subjects.

5. STATISTICAL METHODS

5.1 Continuous

For continuous variables, the number of non-missing observations, mean, median, SD, minimum and maximum will be presented. For all tabulations of change from baseline data, the 95% confidence interval (CI) for the mean will also be provided.

Individual raw data will be presented to the precision in which it is recorded. The number of decimal places to display for individual derived data will be determined by the scale of measurement using the following rules unless otherwise stated in Section 6.2:

- No decimal places will be displayed if the smallest calculated value is ≥ 100;
- One decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive;
- Two decimal places are displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scale of measurement.

For both raw and derived data, means and medians will be displayed to one more decimal places, the individual data and dispersion statistics (e.g SD) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the individual data. Change from baseline will be reported to the same precision as the observed values.

5.2 Categorical

Categorical data will be presented in contingency tables with cell frequencies and percentages for the subject population. Percentages will be presented to one decimal place and will be calculated using the number of subjects with non-missing data as the denominator unless otherwise stated. The number of missing data points will also be presented where applicable.

6. ANALYSIS PLAN

6.1 General

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. The null hypothesis at all times will be that the pre-treatment and post-treatment values are equivalent. All comparisons between pre-treatment and post-treatment measurements will be reported with 95% CIs for the difference. For each statistical test, an observed significance level will be quoted. Where this value is less than 0.05, 0.01 or 0.001, attention will be drawn to the fact using the conventional "*", "**" or "***" annotation, respectively. P-values will be rounded to four decimal places.

Normality assumptions will be evaluated by an examination of the residual plots and the Shapiro-Wilk test of normality. Depending on the degree of departure from these assumptions, an alternate nonparametric approach may be used for supportive purposes.

With the exception of some hematology parameters (see section 6.15.3), post-baseline repeat/unscheduled assessments will be disregarded, although they will be listed in the relevant appendices to the report, in particular all clinically significant values will be noted.

All calculations and figures for the efficacy and safety analyses will be produced using SAS® Version 9.3.

PK analyses will be performed using Phoenix WinNonlin Version 6.3.

All summaries and analyses documented below will be presented in the final integrated statistical/clinical report and tables that will be based on the E3 guidelines published by ICH. However, it is noted here that no analysis plan prepared in advance of the data can be absolutely definitive and so the final report may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final report.

6.2 Derived Data

- **Baseline**
  Baseline is defined as the last value collected (from either a scheduled or unscheduled visit) before the first Givinostat treatment

- **Early Termination**
  Subjects who discontinue participation prior to completing the study should perform the Early Termination Visit within 2 weeks after the last drug intake.

- **End of Study**
  The end-of-study visit is defined as Visit 10 of part 2 (Month 12)/early termination..

- **End of Extension**
  End of Extension 1 is defined as Visit 16 (Month 24) of the Extension part of the study.

End of Extension 2 is defined as Visit 22 (Month 36) of the second Extension part of the study.

End of Extension 3 is defined as Visit 26 (Month 52) of the third Extension part of the study.

For subjects that had an early termination during one of the extensions, the end of the respective extension is defined as the date of the early termination.

- **MFA% change**
  Change in the value of MFA% at End of Study is calculated as the difference between MFA% at End of Study and its baseline value.

- **Other histological endpoints**
  The same definition is used for the other histological endpoints: Perimysial Fibrosis %, Endomysial Fibrosis %, Total fibrosis %, Necrosis %, Inflammation: Total N° of Myofiber, Total of M2, Total of M1, Total of M2M1, single stained cells M2, single stained cells M1, Total Macrophages, Total of single stained M2 / total n. of fields, Total of single stained M1 / total n. of fields, Total of M2M1 / total n. of fields, Total of single stained M2 / total macrophages, Total of single stained M1 / total macrophages, Total of M2M1 / total macrophages, Muscle Regeneration: 1) Total n° of Develop Myosin positive cells – all fields / Total fibers biopsy – all fields, 2) Total n° of SC (sublaminal and extralaminal) – all fields /Total fibers biopsy – all fields, 3) Total n° of SC (sublaminal) – all field / Total fibers biopsy – all fields, 4) Total n° of SC (sublaminal) – all field / Total n° of SC (sublaminal and extralaminal) – all fields, 5) Total n° of sublaminal SC positive Ki67 – all fields / Total n° of SC (sublaminal) – all fields, 6) Total n° of SC (extralaminal) – all fields /Total n° of fibers – all fields, 7) Total n° of SC (extralaminal) – all fields / Total n°of SC (sublaminal and extralaminal) – all fields, 8) Total n° of extralaminal SC positive Ki67 – all fields /Total n° of SC (extralaminal) – all fields.

- **MRI**
  The MRI results are centrally scored as ‘Stage 0’, ‘Stage 1’, ‘Stage 2a’, ‘Stage 2b’, ‘Stage 3’, ‘Stage 4’ (please see ‘DSC_11_2357_43_MRI Manual_Final_5Feb2013_final.pdf’ for further information). The frequency of the MRI scores at Baseline, End of Study and End of Extension 1 calculated and presented per body location. Change in the MRI at End of Study/End of Extension 1 is determined by comparing the MRI score given at baseline to the MRI score given at End of Study/End of Extension 1.

- **miRNA**
  Changes from baseline to End of Study will be calculated for the following parameters – miR-1, miR-133, miR-206.

- **Changes in muscular function**
  - Change in muscular function based on the 6MWT at End of Study/End of Extension phases is calculated as the difference between the distance after 6 minutes (meters) at End of Study/End of Extension phases and its baseline value. If more than one value is recorded for the baseline, the mean value rounded to the integer will be taken. Calculation method is specified in section 6.12.

- Change in muscular function based on the NSAA at End of Study/End of Extension phases is calculated as the difference between Total NSAA Score at End of Study/End of Extension phases and its baseline value. Total NSAA score is achieved by summing the scores for all 17 individual items. Calculation method is specified in section 6.13.

- Change in muscular function based on the PUL at End of Study/End of Extension phases is calculated as the difference between the PUL at End of Study/End of Extension phases and its baseline value. Calculation method is specified in section 6.14.

- **Missing observations**
  - Unless specified, missing observations will be treated as missing at random, and no data imputation will be performed. All data from the CRFs, as well as any derived variables, will be presented in data listings

  - For 6MWT (but not for Number of falls), Time to stand up from floor (seconds), and Time to walk 10m (seconds, the rule for missing data handling is shown in Table 1 and specified as follows:

Table 1 Rule for missing data handling

Subject	Ambulatory at baseline	4SC baseline	Ambulatory at visit1	4SC visit1		Ambulatory at baseline	4SC baseline	Ambulatory at visit1	4SC visit1		change from baseline	low	up
001	y	15	y	10		y	15	y	10		-5	-5	-5
002	y	miss	y	8		y	14.8	y	8		-6.8	-6.8	-6.8
003	y	25	y	miss		y	25	y	12.9		-12.1	-12.1	-12.1
004	y	miss	y	miss		y	14.8	y	12.9		-1.9	-1.9	-1.9
005	**n**	**miss**	y	22		**n**	**>25**	y	22		<-3	.	-3
006	**n**	**miss**	y	miss		**n**	**>25**	y	12.9		<-12.1	.	-12.1
007	y	13	**n**	**miss**		y	13	**n**	**>22**		>9	9	.
008	y	miss	**n**	**miss**		y	14.8	**n**	**>22**		>7.2	7.2	.
009	**n**	**miss**	**n**	**miss**		**n**	**>25**	**n**	**>22**		.	.	.
010	y	7	y	13		y	7	y	13		6	6	6
011	y	4	y	12		y	4	y	12		8	8	8
012	y	15	y	8		y	15	y	8		-7	-7	-7
013	y	17	y	12		y	17	y	12		-5	-5	-5
014	y	15	y	10		y	15	y	10		-5	-5	-5
015	y	22	y	21		y	22	y	21		-1	-1	-1
max		**25**		**22**									
mean		14.8		12.9									

1) missing values will be imputed to:

(a) ≥ worst result observed in parts 1, 2 and the extension 1 for the extension 1 analysis, and
(b)≥ worst result observed in parts 1, 2, extension 1 and extension 2 for extension 2 analysis.
(c)≥ worst result observed in parts 1, 2, extension 1, extension 2 and extension 3 for extension 3 analysis.

For Time to Walk and Time to Stand up worst result is the maximal value, while for all other scores (excluding Total Score) worst result in the minimal value.

2) if missing not due to ambulation at visit x, then we impute using the mean of patients with values at visit x (and not the mean across all visits)

In addition, for missing values without reason of missing at Baseline, the mean of all baseline values will be imputed except subject 512 – "Time to stand up from floor". For Subject 512, missing values for test "Time to stand up from floor" at baseline and post-baseline (e.g., 12 months) the worst value collected during the trial for this subject will be used for imputation.

Missing values of 'time to walk 10 m' and 'time to stand up from floor' were imputed according to whether the subject was ambulatory or not. If a subject was ambulatory then the result was imputed to the mean result of the specific visit, and if the subject was not ambulatory, the result was imputed to the maximal result collected.
Missing score results were imputed to the minimal result collected. Missing 'Total score' was imputed as the sum of all non-missing score results per visit.

3) when both baseline and post baseline visit(s) values are both left or right censored, then the visit change from baseline will be set to missing

Such imputation necessarily leads to censored observations and therefore means and standard deviations will be estimated using PROC LIFEREG which provides a mechanism for handling right (and/or left) censored data when the underlying probability density function is Normal. In the absence of covariates, the mean is given by the intercept term and the SD by the scale parameter. See below for details.

- Identify the worst/maximum observed value (i.e., Time to stand up from floor (seconds)) from subjects with available data; apply this value to those patients will missing data due to an inability to perform the task; identify these patients as right censored in the dataset in accordance with SAS PROC LIFEREG instruction.. The SAS® code for this model is given below:

```
PROC lifereg DATA= Datasetname covout outEST=lifeout;
MODEL y*cens(0) = / dist=normal;
run;
```

The estimated mean and its standard deviation are the estimates of the intercept and the scale from following SAS output (i.e. 10.0021 and 4.4734 in this example, respectively).

Analysis of Maximum Likelihood Parameter Estimates							
Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	10.0021	1.5032	7.0559	12.9482	44.28	<.0001
Scale	1	4.4734	1.2962	2.5352	7.8935		

- Identify the worst/minimum observed value (i.e., 6MWT) from subjects with available data; apply this value to those patients will missing data due to an inability to perform the task; identify these patients as left censored in the dataset in accordance with SAS PROC LIFEREG instruction. The SAS® code for left censoring is given below:

```
DATA leftcensored; set data;
  if y=. then do; lower=.;y=minobs;end; else lower=y;
run;

PROC lifereg DATA=leftcensored  covout outEST=lifeoutleft;
  MODEL (lower,y) = / dist=normal;
run;
```

- Identify an interval data for change from baseline (i.e., 6MWT, time to walk 10m and time to stand up from floor) in accordance with SAS PROC LIFEREG with interval censoring to estimate mean and standard error. The SAS® code for left censoring is given below:

```
PROC lifereg DATA=CHG;
  MODEL (low, up) =   / dist=normal;
run;
```

For the NSAA scores the missing score is imputed with worst score, missing NSAA 'Total Score' observations were imputed as the sum of all test results per visit, regardless of whether the subject was ambulatory or not.

- **Incomplete dates**
  All incomplete dates will be entered on the database as they were recorded in the CRF. Thereafter for calculation purposes only, the incomplete dates will be completed using pre-defined rules. If a day or month is recorded as NK or NA it will be replaced by the first day of the month or January respectively, provided this does not contradict any other dates recorded. For missing adverse events (AEs) and medications dates/times during the trial, the worst-case date will be used (e.g. the end of the month for a stop date and 23:59 for the stop time, the date/time of initial dose for start of AE i.e. all events with missing start dates will be assumed to be treatment emergent).

- **Ambiguous values**

In the case where a variable is recorded as ">x", "≥x", "<x" or "≤x", then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken. In the case where a subject records more than one score at a timepoint for any particular efficacy measure, the worst of the recorded scores will be taken for analysis purposes.

- **ECG data**
  For ECG data recorded on continuous scales, if more than one value is recorded, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, then take most severe of the respective readings will be taken.

  - **QT Intervals**
    The analysis will use QT intervals that have been corrected for heart rate by the Bazett's[1] and Fridericia's[2] formula ($QTcB = QT/ [RR]^{1/2}$ and $QTcF = QT/[RR]^{1/3}$ respectively), as recorded on the CRF.

- **Pulmonary function tests (PFTs)**
  For PFT data recorded on continuous scales, if more than one value is recorded, the mean value rounded to the integer will be presented

- **Secondary Efficacy Assessment**
  Efficacy will be assessed through paired t-tests to test the changes from baseline in biopsy at End of Study and through descriptive statistics of changes from baseline in the MRI, 6MWT, PUL, and NSAA at End of Study and Extension Phases.

- **BMI**
  BMI will be calculated using the following equation –

  $$BMI\ (Kg/m^2) = weight(kg)/Height(meters)^2$$

6.3 Analysis populations

The intent-to treat (ITT) population will include all children who are enrolled in the Part 1 portion or entered the Part 2 portion of the study. Subjects will be analyzed according to the dose level to which they are allocated.

The Completers population will include all children who successfully completed Part 2 portion of the study. Subjects will be analysed according to the dose level to which they are allocated.

The evaluable population will include all subjects who are in Part 2 of the study, receive Givinostat of at least 80% dose in Part 2, have at least one baseline and one post-baseline assessment of biopsies, and have no major protocol violations. All protocol deviations will be assessed and documented on a case-by-case basis prior to the database lock, and deviations considered having a serious impact on the efficacy results will lead to the relevant subject being excluded from the population. Major protocol deviations include (but are not limited to):

- Not meeting inclusion criteria/meeting an exclusion criteria

- Taking an inadmissible concomitant medication likely to effect the primary efficacy endpoints
- Any other deviations likely to have an impact on the primary efficacy endpoint:
    - Unstable dose of systemic corticosteroids during the trial (e.g. change in type of drug, dose modification not related to body weight change, schedule modification, interruption, discontinuation, or re initiation)
- Visit 1 not performed
- Biopsy not Evaluable

Prior to the database lock, subject evaluability will be reviewed by the sponsor and detailed in the study evaluability document. A listing of all subjects excluded from the evaluable population and the reason for their exclusion should be included. The dose level under which a subject is analysed will be the dose of investigational product that is actually received.

The safety population will include all children who receive any investigational product. The dose level under which the subject is analysed will be the dose of investigational product that is actually received.

The PK population will include all children with at least one quantifiable post-dose concentration datum.

6.4 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2. Summaries of key protocol deviations will be provided. Major protocol violations will lead to exclusion from the evaluable population.

6.5 Data Summaries

Categorical data will be summarized by the number and percentage of children in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. CIs will be 2-sided.

All data will be summarized separately for part 1, part 2 and Extension phases. Data will be summarized by the initial dose level of part1 of the study (there will be 3 groups: 25.0 mg, 37.5 mg and 50.0 mg). For part 2 there will be only one group: 37.5 – 25.0 mg BID). For Extension phases (1, 2 and 3), data will be summarized by the initial dose at start of each Extension phase except for AE data which will be summarized by the dose level assigned to the adverse event in question (see Section 6.2 for details). Data will also be summarized for the appropriate population overall.

Appendix 16.2 listings will be sorted by initial dose level and subject number with subject level data presented in chronological order within each parameter or measurement as appropriate.

Subject disposition will be summarized using the ITT Population. The primary efficacy endpoint will be analysed using the Evaluable Population, with the Completers and the ITT populations used for sensitivity analysis. The secondary efficacy endpoints will be analysed using the ITT Population only. The safety endpoints will be summarized using the Safety Population. The PK endpoints will be summarized using the PK Population.

6.6 Disposition of Subjects

- The number of subjects in the ITT population who completed Part 1, Part 2 and the extension phases of the study based on the protocol will be summarized.
- The number of subjects in each population will be summarized
- A subject will be considered to have completed Part 1 when the subject has completed Week 11 of part 1.
- A subject is considered to have completed Part 2 when the subject has completed 12 month visit of Part 2.
- The subject is considered to have completed the extension 1 study when the subject has completed after 12-month the end-of-extension study visit (Visit 16).
- The subject is considered to have completed the extension 2 study when the subject has completed after 12-month the end-of-extension 2 study visit (Visit 22).
- The subject is considered to have completed the extension 3 study when the subject has completed after 16-month the end-of-extension 3 study visit (Visit 26).

  Reasons for early termination should be summarized.

  - Death
  - Lost to follow up
  - Patient withdrew consent
  - Protocol violation
  - Adverse event
  - Other
- The number of subjects that entered the study, the numbers of subjects that completed each phase of the study should be summarized.
- Reason and timing (days since first dose) for withdrawal should be tabulated.
- Reasons for Screening Failures will be tabulated.

6.7 Baseline Comparability

The baseline data will be summarized in appropriate tables using the ITT population. The comparability of initial dose levels with respect to the subject demographics and baseline characteristics will be assessed in a descriptive manner, no formal statistical testing will be performed.

6.7.1 Variables Considered

Standard continuous or categorical variable summaries will be presented for the following variables based on the ITT population.

6.7.1.1 Demography

- Age at screening visit (years)
- Sex (Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Height (cm)
- Body Weight (kg)
- BMI (kg/m^2)
- Mutation Type

6.7.1.2 Medical and Surgical History

Separate tabulations will be produced for previous and ongoing conditions with all conditions coded using MedDRA Version 20.1 (primary system organ class and preferred term).

6.7.1.3 Physical Examination at Screening

- Cardiovascular (Normal, Abnormal [Not Clinically Significant {NCS}], Abnormal [Clinically Significant {CS}], Not done)
- Abdomen (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Ear/Eye/Nose/Throat (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Neck and Thyroid (Normal, Abnormal [NCS], Abnormal [CS], Not done)

- Spine (Normal, Abnormal Abnormal [NCS], Abnormal [CS], Not done)
- Lymph Nodes (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Skin and Mucosa (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Chest and Lungs (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Musculoskeletal system (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Neurological system (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Extremities (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Genitourinary (Normal, Abnormal [NCS], Abnormal [CS], Not done)
- Other (Normal, Abnormal [NCS], Abnormal [CS], Not done)

When calculating the percentage reporting each category, the "Not Done" category will not be included in the denominator.

6.7.1.4 Muscle biopsy at Screening

- MFAF%
- Perimysial Fibrosis %
- Endomysial Fibrosis %
- Total fibrosis %
- Necrosis %
- Fiber dimension distribution (CSA)
- No. of hypercontracted fibers [Number of fibers per microscopic field (20x)]
- Fatty replacement %
- N° of fiber [Number of fibers per microscopic field (20x)]
- Inflammation: (Total N° of Myofiber
- Inflammation: (Total of M2)

- Inflammation: (Total of M1
- Inflammation: (Total of M2M1)
- Inflammation: (single stained cells M2)
- Inflammation: (single stained cells M1)
- Inflammation: (Total Macrophages)
- Inflammation: (Total of single stained M2 / total n. of fields)
- Inflammation: (Total of single stained M1 / total n. of fields)
- Inflammation: (Total of M2M1 / total n. of fields)
- Inflammation: (Total of single stained M2 / total macrophages)
- Inflammation: (Total of single stained M1 / total macrophages)
- Inflammation: (Total of M2M1 / total macrophages)
- Muscle Regeneration: (Total n° of Develop Myosin positive cells – all fields / Total fibers biopsy – all fields)
- Muscle Regeneration: (Total n° of SC (sublaminal and extralaminal) – all fields /Total fibers biopsy – all fields)
- Muscle Regeneration: (Total n° of SC (sublaminal) – all field / Total fibers biopsy – all fields)
- Muscle Regeneration: (Total n° of SC (sublaminal) – all field / Total n° of SC (sublaminal and extralaminal) – all fields)
- Muscle Regeneration: (Total n° of sublaminal SC positive Ki67 – all fields / Total n° of SC (sublaminal) – all fields)
- Muscle Regeneration: (Total n° of SC (extralaminal) – all fields /Total n° of fibers – all fields)
- Muscle Regeneration: (Total n° of SC (extralaminal) – all fields / Total n° of SC (sublaminal and extralaminal) – all fields)

- Muscle Regeneration: (Total n° of extralaminal SC positive Ki67 – all fields /Total n° of SC (extralaminal) – all fields)

6.7.1.5 miRNA at Screening

- miR-1 (copies/mL)
- miR-133 (copies/mL)
- miR-206 (copies/mL)

6.7.1.6 MRI at Screening

- MRI central score

6.7.1.7 Quality Tests – PedsQL at Screening

- Multidimensional Fatigue Scale (CHILD and PARENT Reports):
    - General Fatigue
        - Feel tired (Never, Almost Never, Sometimes, Often, Almost Always)
        - Feel physically weak (Never, Almost Never, Sometimes, Often, Almost Always)
        - Too tired to do things I like to do (Never, Almost Never, Sometimes, Often, Almost Always)
        - Too tired to spend time with friends (Never, Almost Never, Sometimes, Often, Almost Always)
        - Trouble finishing things (Never, Almost Never, Sometimes, Often, Almost Always)
        - Trouble starting things (Never, Almost Never, Sometimes, Often, Almost Always)
    - Sleep/Rest Fatigue:
        - Sleep a lot (Never, Almost Never, Sometimes, Often, Almost Always)

- Hard to sleep through the night (Never, Almost Never, Sometimes, Often, Almost Always)
- Tired when waking up in the morning (Never, Almost Never, Sometimes, Often, Almost Always)
- Rest a lot (Never, Almost Never, Sometimes, Often, Almost Always)
- Take a lot of naps(Never, Almost Never, Sometimes, Often, Almost Always)
- Spend a lot of time in bed (Never, Almost Never, Sometimes, Often, Almost Always)

o Cognitive Fatigue:

- Hard to stay attentive(Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to remember what people tell me (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to remember what I just heard (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to think quickly (Never, Almost Never, Sometimes, Often, Almost Always)
- Have trouble remembering what I was just thinking (Never, Almost Never, Sometimes, Often, Almost Always)
- Have trouble remembering more than one thing at a time (Never, Almost Never, Sometimes, Often, Almost Always)

• Neuromuscular Module (CHILD and PARENT Reports):

o About my neuromuscular disease:

- Hard to breathe (Never, Almost Never, Sometimes, Often, Almost Always)

- Get sick easily (Never, Almost Never, Sometimes, Often, Almost Always)
- Get sores and/or rashes (Never, Almost Never, Sometimes, Often, Almost Always)
- Legs hurt (Never, Almost Never, Sometimes, Often, Almost Always)
- Feel tired (Never, Almost Never, Sometimes, Often, Almost Always)
- Back feels stiff (Never, Almost Never, Sometimes, Often, Almost Always)
- Wake up tired (Never, Almost Never, Sometimes, Often, Almost Always)
- Hands are weak (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to use the bathroom (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to gain or lose weight (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to use hands (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to swallow food (Never, Almost Never, Sometimes, Often, Almost Always)
- Takes a long time to bathe or shower (Never, Almost Never, Sometimes, Often, Almost Always)
- Get hurt accidentally (Never, Almost Never, Sometimes, Often, Almost Always)
- Take a long time to eat (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to turn during the night (Never, Almost Never, Sometimes, Often, Almost Always)

        - Hard to go places with my equipment (Never, Almost Never, Sometimes, Often, Almost Always)

    - Communication:

        - Hard to tell doctors and nurses how I feel (Never, Almost Never, Sometimes, Often, Almost Always)
        - Hard to ask the doctors and nurses questions (Never, Almost Never, Sometimes, Often, Almost Always)
        - Hard to explain the illness to other people (Never, Almost Never, Sometimes, Often, Almost Always)

    - Family Resources:

        - Hard for the family to plan activities (Never, Almost Never, Sometimes, Often, Almost Always)
        - Hard for the family to get enough rest (Never, Almost Never, Sometimes, Often, Almost Always)
        - Money is a problem (Never, Almost Never, Sometimes, Often, Almost Always)
        - The family has a lot of problems (Never, Almost Never, Sometimes, Often, Almost Always)
        - Don’t have the needed equipment (Never, Almost Never, Sometimes, Often, Almost Always)

- Pediatric Quality of Life Inventory (generic core scales) (CHILD and PARENT Reports):

    - Physical functioning:

        - Hard to walk (Never, Almost Never, Sometimes, Often, Almost Always)
        - Hard to run (Never, Almost Never, Sometimes, Often, Almost Always)

- Hard to play sports or exercise (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to lift something heavy (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to take a bath or shower by myself (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to do chores around the house (Never, Almost Never, Sometimes, Often, Almost Always)
- Hurt or ache (Never, Almost Never, Sometimes, Often, Almost Always)
- Have low energy (Never, Almost Never, Sometimes, Often, Almost Always)

- About my feelings:
  - Feel afraid or scared (Never, Almost Never, Sometimes, Often, Almost Always)
  - Feel sad or blue (Never, Almost Never, Sometimes, Often, Almost Always)
  - Feel angry (Never, Almost Never, Sometimes, Often, Almost Always)
  - Have trouble sleeping (Never, Almost Never, Sometimes, Often, Almost Always)
  - Worry what will happen to me (Never, Almost Never, Sometimes, Often, Almost Always)
- Getting along with others:
  - Have trouble getting along with other kids (Never, Almost Never, Sometimes, Often, Almost Always)
  - Other kids don’t want to be my friend (Never, Almost Never, Sometimes, Often, Almost Always)

- Other kids tease me (Never, Almost Never, Sometimes, Often, Almost Always)
- Cannot do things other kids my age can do (Never, Almost Never, Sometimes, Often, Almost Always)
- Hard to keep up when playing with other kids (Never, Almost Never, Sometimes, Often, Almost Always)

- About school:
  - Hard to pay attention in class (Never, Almost Never, Sometimes, Often, Almost Always)
  - Forget things (Never, Almost Never, Sometimes, Often, Almost Always)
  - Have trouble keeping up with school work (Never, Almost Never, Sometimes, Often, Almost Always)
  - Miss school because of not feeling well (Never, Almost Never, Sometimes, Often, Almost Always)
  - Miss school to go to the doctor or hospital (Never, Almost Never, Sometimes, Often, Almost Always)

6.7.1.8 Vital Signs at Screening

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Systolic/Diastolic blood pressure significance (normal/abnormal)
- Pulse rate (bpm)
- Pulse rate significance (normal/abnormal)
- Body temperature (degrees Celsius)
- Body temperature significance (normal/abnormal)

6.7.1.9 ECG (12-lead) at Screening

As stated in section 6.2, for data recorded on continuous scales, if more than one value is recorded, the mean value rounded to the integer will be presented. For the Overall Interpretation (Normal, Abnormal (NCS), Abnormal (CS)) if more than one value is recorded for a given visit, then the most severe interpretation of the respective readings will be taken.

- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTcF interval (ms) [Fridericia's formula - QTcF]
- Overall interpretation of the ECG (Normal, Abnormal (NCS), Abnormal (CS))

6.7.1.10 Pulmonary function tests (PFTs) at Screening

As stated in section 6.2, for data recorded on continuous scales, if more than one value is recorded, the mean value rounded to the integer will be presented.

- Forced expiratory volume at 1 second [FEV_1] (L)
- Forced vital capacity [FVC] (L)
- FEV_1/FVC (ratio)
- Peak Expiratory Flow [PEF] (L/min)

6.7.1.11 Echocardiographs at Screening

- M Mode
    - Left atrial (LA) dimension (cm)
    - Left ventricular end-diastolic internal dimension (LVEDD) (cm)
    - Left ventricular end-systolic internal dimension (LVESD) (cm)
    - Left ventricular septal (LVS) wall thickness:(mm)
    - Left ventricular posterior wall (PW) thickness:(mm)
- 2D
    - Left ventricular end-diastolic (LVED) volume (ml)

- Left ventricular end-systolic (LVES) volume (4-ch) (ml)
- Left ventricular end-systolic (LVES) volume (2-ch) (ml)
- Left ventricular end-systolic (LVES) volume (Biplane) (ml)
- Left atrial (LA) volume (ml)
- Left ventricular outflow tract (LVOT) diameter (cm)
- Maximal LV wall thickness (cm)
- Left Ventricular Ejection Fraction (LVEF) (%)

- Colour Doppler:
  - Semi qualitative grade of mitral regurgitation reg (1,2,3,4)
  - Semi qualitative grade of tricuspid regurgitation reg (1,2,3,4)
- Pulse wave Doppler:
  - Mitral E max (m/s)
  - A max (m/s)
  - A duration (ms)
  - Pulmonary S max (m/s)
  - D max (m/s)
  - A pulm duration (ms)
- Continuous wave Doppler:
  - Tricuspid regurgitation v max (m/s)
  - Isovolumic relaxation time (ms)
  - Stroke volume (ml)

6.7.1.12 Haematology at Screening

- Hemoglobin (g/L)
- Hematocrit (%)
- Red blood cell count (10^12/L)
- White blood cell count (10^9/L)
- Platelets (10^9/L)

- Absolute Neutrophil Count (10^9/L)
- Neutrophil (%)
- Lymphocytes (10^9/L) / (%)
- Monocytes (10^9/L) / (%)
- Basophils (10^9/L) / (%)
- Eosinophils (10^9/L) / (%)
- Abnormal cells (10^9/L) / (%)

6.7.1.13 Chemistry at Screening

- Alanine transaminase (ukat/L)
- Albumin (g/L)
- Alkaline phosphatase (ukat/L)
- Amylase (ukat/L)
- Aspartate transaminase (ukat/L)
- Total bilirubin (umol/L)
- Blood urea nitrogen (mmol/L)
- C-reactive Protein (mmol/L)
- Calcium (mmol/L)
- Chloride (mmol/L)
- Creatine Phosphokinase
- Creatine kinase (ukat/L)
- Creatinine (umol/L)
- Creatinine Clearance (mL/Sec)

- Glucose (mmol/L)
- Lactate dehydrogenease (ukat/L)
- Potassium (mmol/L)
- Total protein (g/L)
- Sodium (mmol/L)
- Uric acid (umol/L)

6.7.1.14 Urinalysis at Screening

- Specific gravity
- pH
- Protein (Positive, Negative, Trace)
- Glucose (Positive, Negative, Trace)
- Ketones Cytology – results will only be listed.
- Myoglobin (mmol/L)

6.7.1.15 Serology at Screening

- HIV Antibody (HIV-Ab)
- Hepatitis C (antibody HCV-Ab)
- Hepatitis B: surface antigen (HbsAg)
- Hepatitis B: surface e antigen (HbeAg)
- Anti Epstein Barr Virus (anti-EBV)
- Anti Cytomegalovirus antibody (anti-CMV IgM)

6.7.1.16 Six Minutes Walk Test at Screening (6MWT) at Screening

- Falls (Distance, Time of fall (minutes and seconds), restart time (minutes and seconds))
- Distance reached in 6 minutes (meters)

- Percentage of predicted value at screening. The predictive value is calculated using the following equation by Geiger[7]:

$$6MWT_{pred} = 196.72 + 39.81 * age - 1.36 * age^2 + 132.28 * height_m$$

6.7.1.17 North Star Ambulatory Assessment (NSAA) at Screening

Scores (0, 1, or 2) for each of the following:

- Stand
- Walk (10m)
    - Score
    - Time (seconds)
- Stand-up after seating
- Stand on 1 leg – R
- Stand on 1 Leg – L
- Climb one step – R
- Climb one step – L
- Step down from a step – R
- Step down from a step – L
- Seating and supine
- Stand up from floor
    - Score
    - Time (seconds)
    - Comments (A,B,C,D,E)
- Rise head

- Stand on heels
- Jumps
- Hops on one leg – R
- Hops on one leg – L
- Run
    - Score
    - Comments (A,B,C,D,E)
- Total score

6.7.1.18 Performance of Upper Limb (PUL) at Screening

- Item A. Entry item
    - This item defines the gross ability of an individual and is based on the Brooke Scale. It directs the evaluator to the appropriate items to assess next (0,1,2,3,4,5,6)
- High level shoulder dimension (for left arm, right arm or both arms):
    - Item B. Shoulder abduction to shoulder height (0,1,2,3,4)
    - Item C. Shoulder abduction above shoulder height (0,1,2,3,4)
    - Item D. Shoulder flexion to shoulder height (0,1,2,3,4)
    - Item E. Shoulder flexion above shoulder height (0,1,2,3,4)
- Mid level elbow dimension (for left arm, right arm or both arms)::
    - Item F. Hand(s) to mouth (0,1,2,3)
    - Item G. Hand(s) from lap to table (0,1,2,3)
    - Item H. Move weight on table (0,1,2,3,4,5)
    - Item I. Lifting light cans (0,1,2,3,4,5)

- Item J. Lifting heavy cans (0,1,2,3,4,5)
- Item K. Stacking light cans (0,1,2,3,4)
- Item L. Stacking heavy cans (0,1,2,3,4)
- Item M. Remove lid from container (0,1)
- Item N. Tearing paper (0,1,2,3,4)

- Distal size of wrist and hand
  - Item O. Tracking a path (0,1,2,3,4)
  - Item P. Push on light (0,1,2,3)
  - Item Q. Supination (0,1,2,3,4)
  - Item R. Picking up coins (0,1,2,3)
  - Item S. Placing finger on number diagram (0,1,2,3)
  - Item T. 2 points pliers or tongs?
    - Score (0,1,2)
    - Weight (5 gr, 10 gr)
  - Item U. 3 points pliers
    - Score (0,1,2)
    - Weight (5 gr, 10 gr)
  - Item V. Key grip / thumb
    - Starting position (Hand close, Hand open)
    - Score (0,1,2,3)
    - Weight (5 gr, 10 gr)

6.8 Concomitant medications

Concomitant medication verbatim terms (as recorded on the CRFs) ongoing at the time of the initial dose of study medication will be mapped to and summarized by Anatomical Therapeutic Chemical (ATC) Level 2 and Drug Reference Names using the World Health Organization (WHO) dictionary (Version September 2017 Enhanced).

6.9 Measurement of Treatment Compliance

Medication containers (the bottles of oral suspension and/or capsules used) are returned at each visit, for compliance/non-compliance assessment. Non-compliance is defined as taking less than 80% of the study medication during any outpatient evaluation period (visit to visit).

Treatment compliance will be assessed as part of the protocol deviations.

The subject compliance with treatment will be summarized by initial dose, Initial dose of study drug administered BID based on body weight, exposure to study drug, number and percentage of subjects who received the treatment.
The date/time of IMP dispensed will be also listed for all subjects.

6.10 Primary Endpoint

The primary endpoint of this study is change of MFA%, comparing the histology biopsies at baseline with the results at the End of Study.

Null Hypotheses:

MFA% at Month 12 is equal MFA% at Baseline.

Alternative Hypotheses:

MFA% at End of Study is not equal to MFA% at Baseline.

6.11 Principal Analysis

Measurements and changes in MFA% will be presented using appropriate summary tables by visit.
The Paired T-test or non-parametric Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the change from baseline to End of Study. MFA% $P<0.05$ will be set as significant. The SAS® code for this model is given below:

```
proc ttest data=data sides=2 alpha=0.05 h0=0;

paired MFAEOS * MFABL;

run;
```

Where MFAEOS is the MFA at the end of Study and MFABL is he MFA at baseline

Imputation techniques

No data imputation will be performed; missing observations will be treated as missing at random.

6.11.1 **Sensitivity Analysis**

The primary endpoint analysis will be repeated using Completers and ITT population.

6.11.2 **Exploratory Analysis**

- The correlation between change in MFA% and DMD mutation will be assessed using the ANOVA method:

Proc glm order=internal;

Ods select OverallANOVA=anova;

Class DMD;

Model c_MFA=DMD;

Means DMD/scheffe;

Run;

Quit;

- If possible, change in MFA% will be summarized according to the arm sequence of the measurements (Left-Right or Right-Left).
- MFA% will be summarized by LTBP4 (IAMM vs VTTT+ other)

MFA% will be summarized by Osteopontin (TT vs GT+GG)

6.12 Secondary Endpoints

Analysis of secondary endpoints is done at both End of Study and End of Extension phases for the following endpoints:

- 6MWT
- NSAA
- PUL

6.12.1 **Additional histological endpoints**

Additional histological endpoints will be analyzed in a similar manner as for the primary analysis.

- Perimysial Fibrosis %
- Endomysial Fibrosis %
- Total fibrosis %
- Necrosis %
- Inflammation: (Total of single stained M2 / total n. of fields)
- Inflammation: (Total of single stained M1 / total n. of fields)
- Inflammation: (Total of M2M1 / total n. of fields)
- Inflammation: (Total of single stained M2 / total macrophages)
- Inflammation: (Total of single stained M1 / total macrophages)
- Inflammation: (Total of M2M1 / total macrophages)
- Muscle Regeneration: (Total n° of Develop Myosin positive cells – all fields / Total fibers biopsy – all fields)
- Muscle Regeneration: (Total n° of SC (sublaminal and extralaminal) – all fields /Total fibers biopsy – all fields)
- Muscle Regeneration: (Total n° of SC (sublaminal) – all field / Total fibers biopsy – all fields)
- Muscle Regeneration: (Total n° of SC (sublaminal) – all field / Total n° of SC (sublaminal and extralaminal) – all fields)
- Muscle Regeneration: (Total n° of sublaminal SC positive Ki67 – all fields / Total n° of SC (sublaminal) – all fields)
- Muscle Regeneration: (Total n° of SC (extralaminal) – all fields /Total n° of fibers – all fields)
- Muscle Regeneration: (Total n° of SC (extralaminal) – all fields / Total n° of SC (sublaminal and extralaminal) – all fields)
- Muscle Regeneration: (Total n° of extralaminal SC positive Ki67 – all fields /Total n° of SC (extralaminal) – all fields)
- Fiber dimension distribution (CSA)
- No of Hypercontracted fibers
- Fatty replacement %

The analysis methodology for changes in the above endpoints except for CSA will compare End of Study to baseline using Paired-T test subject to normality assumption or non-parametric Signed rank test for two means (paired observations) as is appropriate. Additionally descriptive statistics per visit will be provided.

The 2.5th, 10th, 25th, 50th, 75th, and 97.5th percentiles will be tabulated for baseline CSA score and the end of treatment CSA score. The hypothesis that the median scores are the same between the baseline and the end of treatment will be tested using SAS procedure npar1way with option ‘median’.

This will be shown descriptively by plotting the cumulative distribution of all measurements at End of Study alongside a cumulative distribution plot for all measurements at Baseline.

6.12.2 **Change in muscular function based on the 6MWT at End of Study/End of Extension phases**

Descriptive statistics (including CI) for the actual values and change from baseline (mean of two baseline measurements) will be provided per visit for the total score. The descriptive statistics will also be presented by the following categories:

- By age group
- By corticosteroids treatment (i.e. continuous vs intermittent regimen)
- By LTBP4 (IAMM vs VTTT+ other)
- By Osteopontin (TT vs GT+GG)
- By predicted value at baseline (≥80% predicted value vs <80% predicted value)

Additionally a graph of the achieved distance over time for each subject will be presented.

In addition, descriptive statistics of the change from baseline in the percentage of predicted distance (as described in 6.2) per visit will be presented.

6.12.3 **Change in muscular function based on the NSAA at End of Study/End of Extension phases**

Descriptive statistics (including CI) for the actual values and change from baseline will be provided per visit for each item and total score. The descriptive statistics will also be presented by the following categories:

- By LTBP4 (IAMM vs VTTT+ other)

6.12.4 **By Osteopontin (TT vs GT+GG) Change in muscular function based on the PUL at End of Extension phase**

Descriptive statistics (including CI) for the actual values and change from baseline will be provided per visit for each item and total score.

6.12.5 **Change in muscular function based on the Histology parameters at End of Study**

Descriptive statistics will also be presented by the following categories:

- By LTBP4 (IAMM vs VTTT+ other)
- By Osteopontin (TT vs GT+GG)

6.12.6 **Proportion of patients who loss the ambulation at End of Study/End of Extension phases**

The proportion of subjects who lose ambulation (i.e. who are not able to perform the 6MWT and the 10 meter walk test) will be summarized yearly until the end of the study (i.e. at 12 month, 24 month, 36 month and end of study (52 months).

For patients who lost the ambulation, the time to wheelchair and how much time the children spend in wheelchair were assessed and reported in a listing.

Additionally, the time from first use of study drug to loss of ambulation will be illustrated with a Kaplan-Meier plot. Patients who did not lose ambulation will be censored at the time of last assessment.

6.13 Exploratory Analysis

The exploratory endpoints will include the following:

- Shift changes of the MRI scores, per muscle and body location, after treatment with Givinostat (also evaluated during the extension 1 phase).
- Change in muscle biomarkers (e.g., miRNA) following treatment with Givinostat (Part 1 and Part 2 of the study)

  The analysis methodology for changes in the above endpoints will compare month 12 to baseline using Paired-T test subject to normality assumption or non-parametric Signed rank test for two means (paired observations) as is appropriate. Additionally descriptive statistics per visit will be provided.

- Evaluation of acceptability/palatability of the oral suspension
  An incidence table will be presented including the following
  - Taste of medicine
    - For child (dislike very much, dislike a little, not sure, like a little, like very much)
    - For parent (pleasant, not sure, unpleasant)
  - Difficulties in giving medication to child (yes, no)
- The exploratory analysis for testing the relations between PK and PD parameters will be discussed in a separate SAP. Evaluation of any correlation between the effects of Givinostat on disease progression and the type of DMD mutation subjects may have in relation to their disease.
  Disease progression will be measured by change from baseline to End of Study/End of Extension phases for 6MWT summarized by DMD mutation type.
- PedsQL. Descriptive statistics for the total score and the score of the subscales and change from baseline will be presented per visit. A listing of PedsQL will be presented.

Evaluation of LTBP4 and osteopontin genotype (at the beginning of Extension 2 only) . An incidence table of all sequences of LTBP4 and Osteopontin will be presented.

6.14 Multiplicity

As this is a Phase 2 exploratory study, no adjustments for multiplicity will be made.

6.15 Safety analysis

All subjects who receive at least one dose of study medication will be included in the analysis of safety.

For all analysis by visit, results at 'any time post baseline' will be presented.

The following visits will be included in the safety analysis –

- Visits 1-6 in Part 1
- Visits 1-10 in Part 2
- Visits 11-16 and follow-up in the extension 1 phase
- Visits 17-22 and follow-up in the extension 2 phase
- Visits 23-26 and follow-up in the extension 3 phase

6.15.1 **Extent of exposure**

Overall exposure will be calculated, per study part, as the number of days the subject took study medication: (last date of dosing - first day of dosing + 1). No allowance will be made for breaks in therapy. If the date of last dosing is completely missing then the date of last dosing will be taken for analysis purposes as the date the relevant medication was last dispensed. If only the month of the last dose is recorded, the first day of the month will be assumed as the last dosing date.

6.15.2 **Adverse Events**

A treatment emergent adverse event (TEAE) is defined as any AE that has an onset on or after the dose of study treatment, or any pre-existing condition that has worsened during or after the first dose of study treatment. Whether TEAEs will be attributed to a treatment or not is a clinical decision based on all available information at the time of the completion of the eCRF.

A treatment-related adverse event is defined as an adverse event as being unlikely, possibly, probably or definitely related to the study treatment. If adverse event has missing relationship it is assumed to be related to the study treatment for analysis purposes.

The number and incidence of TEAEs, Serious adverse events (SAEs), AEs related to study treatment, SAEs related to treatment and AEs leading to study discontinuation will be summarized by study part (part 1, part 2, extension phases) and treatment.

The treatment associated with the TEAE will be determined by finding which treatment dates the adverse event onset date falls in.

For the summarization by severity or relationship to the study drug, if more than one event occurred with the same Preferred Term for the same patient, the patient will be counted only once for that Preferred Term using the most severe or related occurrence respectively. The summary will include the number of TEAEs, the total number and percentage of subjects reporting at least one event. An individual patient will be counted only once for any specific Preferred Term regardless to the number of times that Preferred Term occurred for that patient (First Ever Incidence approach). Adverse events will be coded using MedDRA version 17.0.

Narratives of deaths, serious and other significant adverse events will be provided in the relevant section of the study report.

A complete subject listing of all adverse events will be provided in Appendix 16.2 to the study report. This listing will include treatment, AE verbatim, MedDRA primary system organ class and preferred term, the time of onset and cessation of event relative to first dosing of study medication, duration of AE (for ongoing AEs use the date of investigator signature as the cessation date for calculation purposes), whether serious, severity, relationship to study medication, action taken and outcome.

6.15.3 **Clinical Laboratory Evaluations**

Descriptive statistics will be calculated for each follow-up assessment (Visits 1-6 in Part 1, Visits 1-10 in Part 2 and Visits 11-26 and follow-up in the extension phases) as well as changes from baseline for hematology and serum chemistry. Each measurement will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from screening to each follow-up visit will be presented.

In addition, for parts 1 and 2, descriptive statistics of the minimal values, time to nadir and time to recovery, will be calculated for Platelets, Red Blood Cells (RBC) and Neutrophils. A graph of the results (including normal range reference lines) over time (including unscheduled results) for each subject per test will be provided.

Descriptive statistics for urinalysis will be calculated for each follow-up assessment as well as changes from baseline.

Details of microscopic urinalysis will be provided in Appendix 16.2 of the report.

A listing of any clinically significant laboratory measurements recorded throughout the study will be provided.

In addition, a listing of laboratory results will be provided.

6.15.4 **Pulmonary function tests (PFTs)**

Descriptive statistics for forced expiratory volume at 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC and PEF will be calculated for each follow-up assessment as well as changes from baseline at Month 12 (Part II), Month 24 (Ext 1), Month 36 (Ext 2) and Month 52 (Ext 3). If more than one value is recorded, the mean value rounded to the integer will be presented. In addition, the percentage of predictive value of FVC, FEV_1 and FEV_1/FVC will be calculated according to the Quanjer Global Lungs Initiative (GLI) 2012 regression equation[8](http://www.lungfunction.org/tools.html).

The percentage of predictive value of PEF will be calculated according to the Buyse et al, 2015 Lancet formula: PEF*100 / (-422.8 + 5.288 * height)

A listing of PFTs will be provided.

6.15.5 **Echocardiographs**

Descriptive statistics for all the parameters will be presented by the following categories - Mode, 2D, Colour Doppler, Pulsed Wave Doppler and Continuous Wave Doppler.

A listing of echocardiographs will be provided.

6.15.6 **Vital Signs**

Summary statistics for observed and changes from pre-dose in the following vital signs will be tabulated at each follow-up:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart Rate (bpm)
- Body temperature (degrees Celsius)
- Weight (Kg)
- Height (cm)

An outlier value following dosing for systolic and diastolic blood pressure is defined as an increase or decrease from the baseline value of more than 20 mmHg. The number and percentage of subjects with outlier values following dosing for systolic and diastolic blood pressure at each assessment will be presented.

Mean profiles by treatment will be presented for each vital sign.

6.15.7 **ECG**

Summary statistics for observed and changes from pre-dose in the following ECG variables will be tabulated at each follow-up:

- RR interval (ms)
- PR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTc interval (ms) [Fridericia's formula - QTcF]

Mean profiles by treatment will be presented for each ECG variable.

The incidence of outliers in absolute QT, QTcF and QTcB intervals (>450, >480, and >500 msec), and the change from baseline in QT, QTcF and QTcB intervals (>30 and >60 msec) will be summarized by treatment as defined in ICH E14 guideline[4].

The incidence of outliers of absolute QRS (<75, >110 msec) and absolute PR (<100, >220 msec) will be summarized by treatment.

Both the number and percentage of subjects who meet the ECG outlier criteria at each assessment will be presented by treatment sequence.

Moreover, the analysis of outliers will be done dividing the group by age.

The individual subject ECG data that meets the ECG outlier criteria will be listed in Appendix 16.2.

In addition, the change from baseline at each follow-up in the overall interpretation of the ECG (Normal, Abnormal NCS, and Abnormal CS) will also be tabulated.

A listing of ECG will be provided.

6.15.8 **Physical Examination**

The body systems within the physical examination data at the end of the study will be summarized by treatment (Normal; Abnormal NCS, Abnormal CS). Changes from baseline will also be tabulated.

A listing of physical examination will be provided.

6.15.9 **Concomitant medications**

Concomitant medication verbatim terms (as recorded on the CRFs) after the initial dose of study drug will be mapped to Anatomical Therapeutic Chemical (ATC) Level 2 and Drug Reference Names using the World Health Organization (WHO) dictionary (Version March 2014 Enhanced).

Concomitant medication verbatim terms (as recorded on the CRFs) after the initial dose of study drug will be summarized by Anatomical Therapeutic Chemical (ATC) Level 2 and Drug Reference Names using the World Health Organization (WHO) dictionary (Version March 2014 Enhanced) and Study Part.

A listing of concomitant medications will be provided.

6.16 Pharmacokinetic Analysis

The PK analysis will be performed on the PK population.

Listing of PK concentration data and of PK derived parameters will be provided.

The following plots will also be provided:

Individual plasma concentration vs. time profiles of Givinostat following different dose levels of the compound.

Mean (±SD) vs. time profile following different dose levels of the compound.

Descriptive statistics of PK parameters of Givinostat will include mean, SD, coefficient of variation (CV), min, median, and max.

The PK analysis will be conducted as follows:

Plasma actual sampling times will be used:

Plasma concentrations below the lower limit of quantification (BLQ) before the first detectable concentration will be set equal to zero.

All BLQ values after the last detectable plasma concentration will be excluded from the PK calculation. A BLQ value between two detectable plasma concentrations will be excluded from the PK calculations.

BLQ values will be set equal to zero for the descriptive statistic evaluations. BLQ values between two detectable plasma concentrations will be excluded for the descriptive statistics evaluations.

Individual values considered to be anomalous will be excluded from the PK analysis and descriptive statistics.Justification for exclusion will be provided in the PK report.

Plasma Givinostat, Cmax, tmax Clast, tlast will be taken directly from the raw data.

Areas under the plasma concentration vs. time curve (AUClast) will be calculated using the trapezoidal rule. If the concentration vs. time profile allows, the half-life of the terminal phase of LF-BP, t½,z, will be determined by linear regression analysis of the natural-log concentration vs. time curve according to the formula:

$t_{½,z} = \ln(2)/z$ where z is the slope of the regression line.

6.17 Key Data Items

A second statistician within WCT will check all the analyses relating to the primary efficacy endpoint and key secondary endpoints.

The checking procedure will involve writing independent SAS® programs and comparing the output produced with the results in the relevant tables. Any disagreements will be reconciled appropriately.

6.18 Change to Planned Protocol Analysis

Not applicable, no changes from the planned analysis described in the protocol.

6.19 Post-Hoc Analysis

After database lock for Part 1 and Part 2 data, a post-hoc analysis will be performed to calculate the correlations and associated p-values, using the Pearson correlation analysis, between the histological parameters (MFAF, Fibrosis %, Necrosis %, Fatty replacement %, Mean CSA, Total n° Develop Myosin positive cells / Total fibers) and the demographic and functional parameters (age, corticosteroids duration, 6MWT, NSAA total score, time to walk 10m (seconds), time to stand up from floor (seconds), PUL: total score, PUL: high level shoulder dimension) at baseline value, the value at Visit 10 and the change from baseline.

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(4) Fridericia LS. Die systolendauer in elektrokardio-gram bei normalen menschen und bei herzkranken. Acta Med Scand 1920; 53: 469.

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(6) ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

(7) Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, Elfring G, Reha A, Barth J, McDonald CM. Percent-predicted 6-minute walk distance in duchenne muscular dystrophy to account for maturational influences. Version 2. PLoS Curr. 2012 Jan 25 [revised 2012 Feb 2];4:RRN1297. PubMed PMID: 22306689

(8) Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, Stocks J, and the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40 1324-1343

7. TABLES TO BE INCLUDED IN THE CLINICAL STUDY REPORT

14.1.1	Patient Disposition – ITT population
14.1.1.1	Patient Disposition – ITT population– Part 1+2, Extension 1, 2 and 3
14.1.2	Datasets Analyzed – ITT population
14.1.3	Screening Failures
14.1.4	Demography – ITT Population
14.1.5	Previous Medical History – ITT Population
14.1.6	Ongoing Medical History – ITT Population
14.1.7a	Muscle Biopsy at Screening – ITT Population
14.1.7b	Muscle Biopsy at Screening Inflammation– ITT Population
14.1.7c	Muscle Biopsy at Screening Regeneration– ITT Population
14.1.8	miRNA at Screening – ITT Population
14.1.9	MRI at Screening – ITT Population
14.1.10a	PedsQL-Child at Screening – ITT Population
14.1.10b	PedsQL- Parent at Screening – ITT Population
14.1.11	Pulmonary Function Tests (PFTs) at Screening – ITT Population
14.1.12	Echocardiographs at Screening – ITT Population
14.1.13	Six Minutes Walk Test (6MWT) at Screening – ITT Population
14.1.14	North Star Ambulatory Assessment (NSAA) at Screening – ITT Population
14.1.15	Performance of Upper Limb (PUL) at Screening – ITT Population
14.1.16	Vital Signs at Screening – ITT Population
14.1.17	12-Lead ECG at Screening – ITT Population
14.1.18	Physical Examination at Screening – ITT Population
14.1.19	Hematology at Screening – ITT Population

14.1.20	Chemistry at Screening – ITT Population
14.1.21	Urinalysis at Screening – ITT Population
14.1.22	Serology Test at Screening – ITT Population
14.1.23	Concomitant Medication Ongoing at Time of the Dose of Study Medication – ITT Population
14.2.1.1.1	Primary Analysis of Primary Endpoint: Summary Statistics for Change in MFA% - Evaluable Population
14.2.1.1.2	Primary Analysis of Primary Endpoint: Measurement and changes in MFA% - Evaluable Population
14.2.1.2.1.1	Sensitivity Analysis of Primary Endpoint: Summary Statistics for Change in MFA% - Completers Population
14.2.1.2.1.2	Sensitivity Analysis of Primary Endpoint: Measurement and changes in MFA% - Completers Population
14.2.1.2.2.1	Sensitivity Analysis of Primary Endpoint: Summary Statistics for Change in MFA% - ITT Population
14.2.1.2.2.2	Sensitivity Analysis of Primary Endpoint: Measurement and changes in MFA% - ITT Population
14.2.1.3.1	Exploratory Analysis of Primary Endpoint: Summary Statistics for MFA% by DMD - Evaluable Population
14.2.1.3.2	Exploratory Analysis of Primary Endpoint: Correlation between changes in MFA% and DMD - Evaluable Population
14.2.1.3.3	Exploratory Analysis of Primary Endpoint: Summary Statistics for MFA% by Arm Sequence - Evaluable Population
14.2.1.4.1a 14.2.1.4.1b 14.2.1.4.1c	Analysis of Secondary Endpoint: Summary Statistics for Additional Histological Endpoint - ITT Population Analysis of Secondary Endpoint: Summary Statistics for Additional Histological Endpoint - ITT Population Analysis of Secondary Endpoint: Summary Statistics for Additional Histological Endpoint - ITT Population
14.2.1.4.2	Analysis of Secondary Endpoint: Additional Histological Endpoint - ITT Population

14.2.1.4.3.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in MFA% and histology at each Follow-up Assessment by Osteopontin - ITT Population
14.2.1.4.3.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in MFA% and histology at each Follow-up Assessment by LTBP4 - ITT Population
14.2.1.5.1	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment - Part 2 - ITT Population
14.2.1.5.2.1	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment – Extension 1 - ITT Population
14.2.1.5.2.2	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment – Extension 2 - ITT Population
14.2.1.5.2.3	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment – Extension 3 - ITT Population
14.2.1.5.3	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by DMD mutation - Part 2 - ITT Population
14.2.1.5.4.1	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by DMD mutation – Extension 1 - ITT Population
14.2.1.5.4.2	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by DMD mutation – Extension 2 - ITT Population
14.2.1.5.4.3	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by DMD mutation – Extension 3 - ITT Population
14.2.1.5.5.1	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Age - Part 2 - ITT Population
14.2.1.5.5.2.1	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Age – Extension 1 - ITT Population
14.2.1.5.5.2.2	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Age – Extension 2 - ITT Population
14.2.1.5.5.2.3	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Age – Extension 3 - ITT Population

14.2.1.5.6.1	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by corticosteroids regimen - Part 2 - ITT Population
14.2.1.5.6.2.1	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Corticosteroids Regimen - Extension 1- ITT Population
14.2.1.5.6.2.2	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by corticosteroids regimen – Extension 2 - ITT Population
14.2.1.5.6.2.3	Analysis of Secondary Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by corticosteroids regimen – Extension 3 - ITT Population
14.2.1.5.7.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Osteopontin - ITT Population
14.2.1.5.7.1.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Osteopontin – Extension 1 - ITT Population
14.2.1.5.7.1.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Osteopontin – Extension 2 - ITT
14.2.1.5.7.1.3	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by Osteopontin – Extension 3 - ITT
14.2.1.5.7.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by LTBP4 - ITT Population
14.2.1.5.7.2.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by LTBP4 –Extension 1 - ITT Population
14.2.1.5.7.2.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by LTBP4 –Extension 2 - ITT Population
14.2.1.5.7.2.3	Analysis of Exploratory Endpoint: Summary Statistics for Change in 6MWT at each Follow-up Assessment by LTBP4 –Extension 3 - ITT Population
14.2.1.6.1.1	Analysis of Secondary Endpoint: Change in Percentage of Predicted Distance 6MWT at each Follow-up Assessment - Part 2 - ITT Population
14.2.1.6.1.2.1	Analysis of Secondary Endpoint: Change in Percentage of Predicted Distance 6MWT at each Follow-up Assessment - Extension 1- ITT Population

14.2.1.6.1.2.2	Analysis of Secondary Endpoint: Change in Percentage of Predicted Distance 6MWT at each Follow-up Assessment - Extension 2- ITT Population
14.2.1.6.1.2.3	Analysis of Secondary Endpoint: Change in Percentage of Predicted Distance 6MWT at each Follow-up Assessment - Extension 3- ITT Population
14.2.1.6.2.1	Analysis of Secondary Endpoint: Change in 6MWT (Absolute Value) at each Follow up Assessment by < and >=80% of Predicted Distance 6MWT at Baseline - Part 2 - ITT Population
14.2.1.6.2.2.1	Analysis of Secondary Endpoint: 6MWT (Absolute Value) at each Follow up Assessment by < and >=80% of Predicted Distance 6MWT at Baseline - Extension 1- ITT Population
14.2.1.6.2.2.2	Analysis of Secondary Endpoint: Change in 6MWT (Absolute Value) at each Follow up Assessment by < and >=80% of Predicted Distance 6MWT at Baseline - Extension 2- ITT Population
14.2.1.6.2.2.3	Analysis of Secondary Endpoint: Change in 6MWT (Absolute Value) at each Follow up Assessment by < and >=80% of Predicted Distance 6MWT at Baseline - Extension 3- ITT Population
14.2.1.7.1	Analysis of Secondary Endpoint: Change in NSAA at each Follow-up Assessment - Part 2 - ITT Population
14.2.1.7.1b	Analysis of Secondary Endpoint: Change in NSAA at each Follow-up Assessment (excluding pt. 219 at End of Part 2)- Part 2 - ITT Population
14.2.1.7.2.1	Analysis of Secondary Endpoint: Change in NSAA at each Follow-up Assessment – Extension 1 - ITT Population
14.2.1.7.2.2	Analysis of Secondary Endpoint: Change in NSAA at each Follow-up Assessment – Extension 2 - ITT Population
14.2.1.7.2.3	Analysis of Secondary Endpoint: Change in NSAA at each Follow-up Assessment – Extension 3 - ITT Population
14.2.1.7.3.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by Osteopontin - ITT Population
14.2.1.7.3.1.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by Osteopontin- Extension 1 - ITT Population
14.2.1.7.3.1.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by Osteopontin- Extension 2 - ITT Population

14.2.1.7.3.1.3	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by Osteopontin- Extension 3 - ITT Population
14.2.1.7.3.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by LTBP4 - ITT Population
14.2.1.7.3.2.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by LTBP4 –Extension 1 - ITT Population
14.2.1.7.3.2.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by LTBP4 –Extension 2 - ITT Population
14.2.1.7.3.2.3	Analysis of Exploratory Endpoint: Summary Statistics for Change in NSAA at each Follow-up Assessment by LTBP4 –Extension 3 - ITT Population
14.2.1.8.1	Analysis of Secondary Endpoint: Change in PUL at each Follow-up Assessment - Part 2 - ITT Population
14.2.1.8.2.1	Analysis of Secondary Endpoint: Change in PUL at each Follow-up Assessment - Extension 1- ITT Population
14.2.1.8.2.2	Analysis of Secondary Endpoint: Change in PUL at each Follow-up Assessment - Extension 2- ITT Population
14.2.1.8.2.3	Analysis of Secondary Endpoint: Change in PUL at each Follow-up Assessment - Extension 3- ITT Population
14.2.1.8.3.1	Analysis of Exploratory Endpoint: Summary Statistics for Change in PUL from baseline to Extension 3 by LTBP4 - ITT Population
14.2.1.8.3.2	Analysis of Exploratory Endpoint: Summary Statistics for Change in PUL from baseline to Extension 3 by Osteopontin - ITT Population
14.2.1.9	Analysis of Secondary Endpoint: Additional Histological Endpoint, fiber dimension distribution (CSA) - Completers Population
14.2.1.10.1	Exploratory Analysis: Summary Statistics of Change in miRNA at End of Study (Part 2) - ITT Population
14.2.1.10.2	Exploratory Analysis: Change in miRNA at End of Study - ITT Population
14.2.1.11.1	Exploratory Analysis: Acceptability/Palatability of the Oral Suspension at each Follow-up Assessment - ITT Population
14.2.1.12.1a	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL-Child at each Follow-up Assessment – Part 2 – ITT Population

14.2.1.12.1b	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL- Parent at each Follow-up Assessment – Part 2 – ITT Population
14.2.1.12.2.1a	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL-Child at each Follow-up Assessment – Extension 1– ITT Population
14.2.1.12.2.1b	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL- Parent at each Follow-up Assessment – Extension 1– ITT Population
14.2.1.12.2.2a	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL-Child at each Follow-up Assessment – Extension 2– ITT Population
14.2.1.12.2.2b	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL- Parent at each Follow-up Assessment – Extension 2– ITT Population
14.2.1.12.2.3a	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL-Child at each Follow-up Assessment – Extension 3– ITT Population
14.2.1.12.2.3b	Exploratory Analysis: Summary Statistics for the Change from Baseline in PedsQL- Parent at each Follow-up Assessment – Extension 3– ITT Population
14.2.1.13.1	Exploratory Analysis: MRI Scores Shift from Baseline (Screening) to each Follow-up Assessment Part 2 –ITT Population
14.2.1.13.2	Exploratory Analysis: MRI Scores Shift from Baseline (Screening) to each Follow-up Assessment – Extension 1–ITT Population
14.2.1.14.1	Exploratory Analysis: Evaluation of LTBP4 and Osteopontin Genotype - Extension 1-ITT Population
14.2.1.14.2	Exploratory Analysis: Evaluation of LTBP4 and Osteopontin Genotype - Extension 2-ITT Population
14.2.1.14.3	Exploratory Analysis: Evaluation of LTBP4 and Osteopontin Genotype - Extension 3-ITT Population
14.2.15.1	Number and Percent of Subjects Who Lost Ambulation - ITT Population
14.3.1.1	Extent of Exposure to Study Medication - Part 1 - Safety Population
14.3.1.2	Extent of Exposure to Study Medication - Part 2 - Safety Population
14.3.1.3.1	Extent of Exposure to Study Medication - Extension 1- Safety Population
14.3.1.3.2	Extent of Exposure to Study Medication - Extension 2- Safety Population
14.3.1.3.3	Extent of Exposure to Study Medication - Extension 3- Safety Population

14.3.2.1	Summary of Treatment-Emergent Adverse Event Reporting – Part 1 – Safety Population
14.3.2.2	Summary of Treatment-Emergent Adverse Event Reporting – Part 2 – Safety Population
14.3.2.3.1	Summary of Treatment-Emergent Adverse Event Reporting – Part 1+2 and Extension 1– Safety Population
14.3.2.3.2	Summary of Treatment-Emergent Adverse Event Reporting – Part 1+2 Extension 1 and Extension 2 – Safety Population
14.3.2.3.3	Summary of Treatment-Emergent Adverse Event Reporting – Part 1+2, Extension 1, Extension 2 and Extension 3 – Safety Population
14.3.3.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term – Part 1 – Safety Population
14.3.3.2	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term – Part 2 – Safety Population
14.3.3.3.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term – Part 1+2 and Extension 1 – Safety Population
14.3.3.3.2	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term – Part 1+2 Extension 1 and Extension 2– Safety Population
14.3.3.3.3	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term – Part 1+2, Extension 1, Extension 2 and Extension 3– Safety Population
14.3.4.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Severity – Part 1 – Safety Population
14.3.4.2	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Severity – Part 2 – Safety Population
14.3.4.3.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Severity – Part 1+2 and Extension 1– Safety Population

14.3.4.3.2	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Severity – Part 1+2 Extension and Extension 2– Safety Population
14.3.4.3.3	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Severity – Part 1+2, Extension 1, Extension 2 and Extension 3– Safety Population
14.3.5.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Relationship to Study Drug – Part 1 – Safety Population
14.3.5.1.2	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Relationship to Study Drug – Part 1 + 2 – Safety Population
14.3.5.2	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Relationship to Study Drug – Part 2 – Safety Population
14.3.5.3.1	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Relationship to Study Drug – Part 1+2 and Extension 1 – Safety Population
14.3.5.3.2	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Relationship to Study Drug – Part 1+2, Extension 1 and Extension 2– Safety Population
14.3.5.3.3	MedDRA Summary of Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Relationship to Study Drug – Part 1+2, Extension 1, Extension 2 and Extension 3– Safety Population
14.3.6.1	MedDRA Summary of Treatment-Emergent Adverse Events Resulting in Study Discontinuation by Primary System Organ Class and Preferred Term – Part 1 – Safety Population
14.3.6.2	MedDRA Summary of Treatment-Emergent Adverse Events Resulting in Study Discontinuation by Primary System Organ Class and Preferred Term – Part 2 – Safety Population
14.3.6.3.1	MedDRA Summary of Treatment-Emergent Adverse Events Resulting in Study Discontinuation by Primary System Organ Class and Preferred Term – Part 1+2 and Extension 1 – Safety Population
14.3.6.3.2	MedDRA Summary of Treatment-Emergent Adverse Events Resulting in Study Discontinuation by Primary System Organ Class and Preferred Term – Part 1+2, Extension 1 and Extension 2– Safety Population

14.3.6.3.3	MedDRA Summary of Treatment-Emergent Adverse Events Resulting in Study Discontinuation by Primary System Organ Class and Preferred Term – Part 1+2, Extension 1, Extension 2 and Extension 3– Safety Population
14.3.7.1	MedDRA Summary of Treatment-Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term – Part 1 – Safety Population
14.3.7.2	MedDRA Summary of Treatment-Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term – Part 2 – Safety Population
14.3.7.3.1	MedDRA Summary of Treatment-Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term – Part 1+2 and Extension 1 – Safety Population
14.3.7.3.2	MedDRA Summary of Treatment-Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term – Part 1+2, Extension 1, and Extension 2– Safety Population
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14.3.24.2.3.1	Summary Statistics for the Change from Baseline in ECG PR Interval (ms) at each Follow-up Assessment by Age – Extension 1– Safety Population
14.3.24.2.3.2	Summary Statistics for the Change from Baseline in ECG PR Interval (ms) at each Follow-up Assessment by Age – Extension 2– Safety Population
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14.3.25.1.2	Summary Statistics for the Change from Baseline in ECG RR Interval (ms) at each Follow-up Assessment – Part 2 – Safety Population
14.3.25.1.3.1	Summary Statistics for the Change from Baseline in ECG RR Interval (ms) at each Follow-up Assessment– Extension 1– Safety Population
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14.3.25.2.1	Summary Statistics for the Change from Baseline in ECG RR Interval (ms) at each Follow-up Assessment by Age – Part 1 – Safety Population
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14.3.25.2.3.1	Summary Statistics for the Change from Baseline in ECG RR Interval (ms) at each Follow-up Assessment by Age – Extension 1– Safety Population
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14.3.25.2.3.3	Summary Statistics for the Change from Baseline in ECG RR Interval (ms) at each Follow-up Assessment by Age – Extension 3– Safety Population
14.3.26.1.1	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment by Initial Dose – Part 1 – Safety Population
14.3.26.1.2	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment – Part 2 – Safety Population

14.3.26.1.3.1	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment – Extension 1– Safety Population
14.3.26.1.3.2	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment – Extension 2– Safety Population
14.3.26.1.3.3	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment – Extension 3– Safety Population
14.3.26.2.1	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment by Age– Part 1 – Safety Population
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14.3.26.2.3.1	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment by Age – Extension 1– Safety Population
14.3.26.2.3.2	Summary Statistics for the Change from Baseline in ECG QRS Interval (ms) at each Follow-up Assessment by Age – Extension 2– Safety Population
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14.3.27.1.1	Summary Statistics for the Change from Baseline in ECG QT Interval (ms) at each Follow-up Assessment by Initial Dose – Part 1 – Safety Population
14.3.27.1.2	Summary Statistics for the Change from Baseline in ECG QT Interval (ms) at each Follow-up Assessment – Part 2 – Safety Population
14.3.27.1.3.1	Summary Statistics for the Change from Baseline in ECG QT Interval (ms) at each Follow-up Assessment – Extension 1– Safety Population
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14.3.27.2.1	Summary Statistics for the Change from Baseline in ECG QT Interval (ms) at each Follow-up Assessment by Age – Part 1 – Safety Population
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14.3.27.2.3.1	Summary Statistics for the Change from Baseline in ECG QT Interval (ms) at each Follow-up Assessment by Age – Extension 1– Safety Population

14.3.27.2.3.2	Summary Statistics for the Change from Baseline in ECG QT Interval (ms) at each Follow-up Assessment by Age – Extension 2– Safety Population
14.3.27.2.3.3	Summary Statistics for the Change from Baseline in ECG QT Interval (ms) at each Follow-up Assessment by Age – Extension 3– Safety Population
14.3.28.1.1	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment by Initial Dose – Part 1 – Safety Population
14.3.28.1.2	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment – Part 2 – Safety Population
14.3.28.1.3.1	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment – Extension 1– Safety Population
14.3.28.1.3.2	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment – Extension 2– Safety Population
14.3.28.1.3.3	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment – Extension 3– Safety Population
14.3.28.2.1	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment by Age – Part 1 – Safety Population
14.3.28.2.2	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment by Age – Part 2 – Safety Population
14.3.28.2.3.1	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment by Age – Extension 1– Safety Population
14.3.28.2.3.2	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment by Age – Extension 2– Safety Population
14.3.28.2.3.3	Summary Statistics for the Change from Baseline in ECG QTcF Interval (ms) at each Follow-up Assessment by Age – Extension 3– Safety Population
14.3.29.1.1	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment by Initial Dose – Part 1 – Safety Population
14.3.29.1.2	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment – Part 2 – Safety Population
14.3.29.1.3.1	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment – Extension 1– Safety Population
14.3.29.1.3.2	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment– Extension 2 – Safety Population

14.3.29.1.3.3	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment– Extension 3 – Safety Population
14.3.29.2.1	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment by Age – Part 1 – Safety Population
14.3.29.2.2	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment by Age – Part 2 – Safety Population
14.3.29.2.3.1	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment by Age – Extension 1– Safety Population
14.3.29.2.3.2	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment by Age – Extension 2– Safety Population
14.3.29.2.3.3	Summary Statistics for the Change from Baseline in ECG QTcB Interval (ms) at each Follow-up Assessment by Age – Extension 3– Safety Population
14.3.30.1.1	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment by Initial Dose – Part 1 – Safety Population
14.3.30.1.2	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment – Part 2 – Safety Population
14.3.30.1.3.1	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment– Extension 1– Safety Population
14.3.30.1.3.2	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment– Extension 2– Safety Population
14.3.30.1.3.3	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment– Extension 3– Safety Population
14.3.30.2.1	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment by Age – Part 1 – Safety Population
14.3.30.2.2	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment by Age – Part 2 – Safety Population
14.3.30.2.3.1	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment by Age – Extension 1– Safety Population

14.3.30.2.3.2	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment by Age – Extension 2– Safety Population
14.3.30.2.3.3	Summary Statistics for the Change from Baseline in the Overall Interpretation of the ECG at each Follow-up Assessment by Age – Extension 3– Safety Population
14.3.31.1	Summary Statistics for the Change from Baseline in Physical Examination at each Follow-up Assessment – Part 1 – Safety Population
14.3.31.2	Summary Statistics for the Change from Baseline in Physical Examination at each Follow-up Assessment – Part 2 – Safety Population
14.3.31.3.1	Summary Statistics for the Change from Baseline in Physical Examination at each Follow-up Assessment – Extension 1– Safety Population
14.3.31.3.2	Summary Statistics for the Change from Baseline in Physical Examination at each Follow-up Assessment – Extension 2– Safety Population
14.3.31.3.3	Summary Statistics for the Change from Baseline in Physical Examination at each Follow-up Assessment – Extension 3– Safety Population
14.3.32.1	Concomitant Medication Commencing After the Dose of Study Medication – Parts 1 and 2 – Safety Population
14.3.32.2.1	Concomitant Medication Commencing After the Dose of Study Medication – Part 1+2 and Extension 1 – Safety Population
14.3.32.2.2	Concomitant Medication Commencing After the Dose of Study Medication – Part 1+2 , Extension 1 and Extension 2– Safety Population
14.3.32.2.3	Concomitant Medication Commencing After the Dose of Study Medication – Part 1+2 , Extension 1, Extension 2 and Extension 3– Safety Population

8. FIGURES TO BE INCLUDED IN THE CLINICAL STUDY REPORT

14.2.1.1	6MWT Achieved Distance per Subject Over Time - Parts 1 and 2 - Completers Population
14.2.1.2.1	6MWT Achieved Distance per Subject Over Time - Extension 1- ITT Population
14.2.1.2.2	6MWT Achieved Distance per Subject Over Time - Extension 2- ITT Population

14.2.1.2.3	6MWT Achieved Distance per Subject Over Time - Extension 3- ITT Population
14.2.1.1.1	6MWT Achieved Distance per Subject Over Time to end of Extension 3 – Completers Population
14.2.2	6MWT Mean Changes from Baseline to All Time Points - Parts 1 and 2 - Completers Population
14.2.3.1.1	Mean of the PEF percentage of predicted values at Baseline, End of part 2 (visit 10) and End of Extension 1- Completers Population
14.2.3.1.2	Mean of the PEF percentage of predicted values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) and Extension 2 - Completers Population
14.2.3.1.3	Mean of the PEF percentage of predicted values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) , Extension 2 (visit 22) and Extension 3 (visit 26) - Completers Population
14.2.3.2	FVC predicted values at Baseline, End of part 2 (visit 10) and Extension- Completers Population
14.2.3.2.1	FVC predicted values at Baseline, End of part 2 (visit 10) and End of Extension 1- Completers Population
14.2.3.2.2	Mean of the FVC percentage of predicted values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) and Extension 2- Completers Population
14.2.3.2.3	Mean of the FVC percentage of predicted values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) , Extension 2 (visit 22) and Extension 3 (visit 26) - Completers Population
14.2.3.3	FEV predicted values at Baseline, End of part 2 (visit 10) and Extension- Completers Population
14.2.3.3.1	FEV predicted values at Baseline, End of part 2 (visit 10) and End of Extension 1- Completers Population
14.2.3.3.2	Mean of the FEV percentage of predicted values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) and Extension 2- Completers Population
14.2.3.3.3	Mean of the FEV percentage of predicted values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) , Extension 2 (visit 22) and Extension 3 (visit 26) - Completers Population

14.2.3.4.3	Mean of the PEF absolute values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) , Extension 2 (visit 22) and Extension 3 (visit 26) - Completers Population
14.2.3.5.3	Mean of the FVC absolute values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) , Extension 2 (visit 22) and Extension 3 (visit 26) - Completers Population
14.2.3.6.3	Mean of the FEV absolute values at Baseline, End of part 2 (visit 10), End of Extension 1 (visit 16) , Extension 2 (visit 22) and Extension 3 (visit 26) - Completers Population
14.2.4	Kaplan- Meier Curve for Patient Who Lost Ambulation - Baseline to End of Extension 3 – ITT Population
14.3.1.1	Platelets Results per Subject Over Time - Part 1- Safety Population
14.3.1.2	Platelets Results per Subject Over Time - Part 2 - Safety Population
14.3.1.1.1	Mean Platelets Results Over Time - Baseline to end of Extension 3 – Safety Population
14.3.2.1	RBC Results per Subject Over Time - Part 1 - Safety Population
14.3.2.2	RBC Results per Subject Over Time - Part 2- Safety Population
14.3.3.1	Neutrophils Results per Subject Over Time - Part 1- Safety Population
14.3.3.2	Neutrophils Results per Subject Over Time - Part 2 - Safety Population
14.3.4.1.1	Mean Profile for Systolic Blood Pressure (mmHg) – Part 1 – Safety Population
14.3.4.1.2	Mean Profile for Systolic Blood Pressure (mmHg) – Part 2 – Safety Population
14.3.5.1.1	Mean Profile for Diastolic Blood Pressure (mmHg) – Part 1 – Safety Population
14.3.5.1.2	Mean Profile for Diastolic Blood Pressure (mmHg) – Part 2 – Safety Population
14.3.6.1.1	Mean Profile for Heart Rate (bpm) – Part 1 – Safety Population
14.3.6.1.2	Mean Profile for Heart Rate (bpm) – Part 2 – Safety Population
14.3.7.1.1	Mean Profile for Body Weight (kg) – Part 1 – Safety Population

14.3.7.1.2	Mean Profile for Body Weight (kg) – Part 2 – Safety Population
14.3.7.1.3.1	Mean Profile for Body Weight (kg) – Extension 1– Safety Population
14.3.7.1.3.2	Mean Profile for Body Weight (kg) – Extension 2– Safety Population
14.3.7.1.3.3	Mean Profile for Body Weight (kg) – Extension 3– Safety Population
14.3.7.1.3.1.1	Mean Profile for Body Weight (kg) – Baseline to end of Extension 3– Safety Population
14.3.8.1.1	Mean Profile for ECG PR Interval (ms) – Part 1 – Safety Population
14.3.8.1.2	Mean Profile for ECG PR Interval (ms) – Part 2 – Safety Population
14.3.9.1.1	Mean Profile for ECG QRS Interval (ms) – Part 1 – Safety Population
14.3.9.1.2	Mean Profile for ECG QRS Interval (ms) – Part 2 – Safety Population
14.3.10.1.1	Mean Profile for ECG QT Interval (ms) – Part 1 – Safety Population
14.3.10.1.2	Mean Profile for ECG QT Interval (ms) – Part 2 – Safety Population
14.3.10.1.3.1	Mean Profile for ECG QT Interval (ms) – Extension 1– Safety Population
14.3.10.1.3.2	Mean Profile for ECG QT Interval (ms) – Extension 2– Safety Population
14.3.10.1.3.3	Mean Profile for ECG QT Interval (ms) – Extension 3– Safety Population
14.3.10.1.1.1	Mean Profile for ECG QT Interval (ms) – Baseline to end of Extension 3 – Safety Population
14.3.11.1.1	Mean Profile for ECG QTcF Interval (ms) – Part 1 – Safety Population
14.3.11.1.2	Mean Profile for ECG QTcF Interval (ms) – Part 2 – Safety Population
14.3.11.1.3.1	Mean Profile for ECG QTcF Interval (ms) – Extension 1– Safety Population
14.3.11.1.3.2	Mean Profile for ECG QTcF Interval (ms) – Extension 2– Safety Population
14.3.11.1.3.3	Mean Profile for ECG QTcF Interval (ms) – Extension 3– Safety Population
14.3.11.1.1.1	Mean Profile for ECG QTcF Interval (ms) – Baseline to end of Extension 3 – Safety Population
14.3.12.1.1	Mean Profile for ECG QTcB Interval (ms) – Part 1 – Safety Population

14.3.12.1.2	Mean Profile for ECG QTcB Interval (ms) – Part 2 – Safety Population
14.3.12.1.3.1	Mean Profile for ECG QTcB Interval (ms) – Extension 1– Safety Population
14.3.12.1.3.2	Mean Profile for ECG QTcB Interval (ms) – Extension 2– Safety Population
14.3.12.1.3.3	Mean Profile for ECG QTcB Interval (ms) – Extension 3– Safety Population
14.3.12.1.1.1	Mean Profile for ECG QTcB Interval (ms) – Baseline to end of Extension 3 – Safety Population
14.3.13a	Comparison of CSA Cumulative Distribution at End of Study and Baseline - Completers Population
14.3.13b	Comparison of CSA Cumulative Distribution at End of Study and Baseline - Completers Population
14.3.13c	Comparison of CSA1 Cumulative Distribution at End of Study and Baseline - Completers Population

9. APPENDIX 16.2 LISTINGS

16.2.1.1	Patients Disposition – ITT Population
16.2.1.1.1	Patients Disposition – Extension 1 – ITT Population
16.2.1.1.2	Patients Disposition – Extension 2 – ITT Population
16.2.1.1.3	Patients Disposition – Extension 3 – ITT Population
16.2.1.2	Datasets Analyzed – ITT population
16.2.1.2.1	Datasets Analyzed –Part 1+2, Extension 1, 2 and 3 ITT population
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16.2.2.1.1	Protocol Deviations – Extension 1 – ITT Population
16.2.2.1.2	Protocol Deviations – Extension 2 – ITT Population
16.2.2.1.3	Protocol Deviations – Extension 3 – ITT Population
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16.2.4.2	Previous Medical History – ITT Population

16.2.4.3	Ongoing Medical History – ITT Population
16.2.5.1	Dosing Information – ITT Population
16.2.5.1.1	Dosing Information – Extension 1 – ITT Population
16.2.5.1.2	Dosing Information – Extension 2 – ITT Population
16.2.5.1.3	Dosing Information – Extension 3 – ITT Population
16.2.5.2	Study Drug Dose Modification – ITT Population
16.2.5.2.1	Study Drug Dose Modification – Extension 1 – ITT Population
16.2.5.2.2	Study Drug Dose Modification – Extension 2 – ITT Population
16.2.5.2.3	Study Drug Dose Modification – Extension 3– ITT Population
16.2.6.1	MFA% – ITT Population
16.2.6.2	6MWT – ITT Population
16.2.6.2.1	6MWT – Extension 1 – ITT Population
16.2.6.2.2	6MWT – Extension 2 – ITT Population
16.2.6.2.3	6MWT – Extension 3 – ITT Population
16.2.6.3	NSAA – ITT Population
16.2.6.3.1	NSAA – Extension 1 – ITT Population
16.2.6.3.2	NSAA – Extension 2 – ITT Population
16.2.6.3.3	NSAA – Extension 3 – ITT Population
16.2.6.4	PUL – ITT Population
16.2.6.4.1	PUL – Extension 1 – ITT Population
16.2.6.4.2	PUL – Extension 2– ITT Population
16.2.6.4.3	PUL – Extension 3– ITT Population
16.2.6.5	Biopsy Collection Information – ITT Population
16.2.6.6	miRNA Results - ITT Population

16.2.6.7	MRI Results – ITT Population
16.2.6.8	Acceptability/Palatability of the Oral Suspension – ITT Population
16.2.6.9	Histological Parameters – ITT Population
16.2.6.10	General Comments of Wheelchair - Subjects Who Lost Ambulation
16.2.7.1	All Adverse Events – Safety Population
16.2.7.1.1	All Adverse Events – Extension 1 – Safety Population
16.2.7.1.2	All Adverse Events – Extension 2 – Safety Population
16.2.7.1.3	All Adverse Events – Extension 3 – Safety Population
16.2.7.2	All Adverse Events Coding – Safety Population
16.2.7.2.1	All Adverse Events Coding – Extension 1 – Safety Population
16.2.7.2.2	All Adverse Events Coding – Extension 2 – Safety Population
16.2.7.2.3	All Adverse Events Coding – Extension 3 – Safety Population
16.2.7.3	Drug-Related Treatment Emergent Adverse Events – Safety Population
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16.2.7.3.2	Drug-Related Treatment Emergent Adverse Events – Extension 2 – Safety Population
16.2.7.3.3	Drug-Related Treatment Emergent Adverse Events – Extension 3 – Safety Population
16.2.7.4	Serious Adverse Events – Safety Population
16.2.7.4.1	Serious Adverse Events – Extension 1 – Safety Population
16.2.7.4.2	Serious Adverse Events – Extension 2 – Safety Population
16.2.7.4.3	Serious Adverse Events – Extension 3 – Safety Population
16.2.8.1	Hematology – Safety Population
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16.2.8.1.2	Hematology – Extension 2 – Safety Population

16.2.8.1.3	Hematology – Extension 3 – Safety Population
16.2.8.2	Serum Chemistry – Safety Population
16.2.8.2.1	Serum Chemistry– Extension 1 – Safety Population
16.2.8.2.2	Serum Chemistry – Extension 2 – Safety Population
16.2.8.2.3	Serum Chemistry – Extension 3 – Safety Population
16.2.8.3	Urinalysis – Safety Population
16.2.8.3.1	Urinalysis – Extension 1 – Safety Population
16.2.8.3.2	Urinalysis– Extension 2 – Safety Population
16.2.8.3.3	Urinalysis– Extension 3 – Safety Population
16.2.8.4	Serology – Safety Population
16.2.8.4.1	Serology – Extension 1 – Safety Population
16.2.8.4.2	Serology – Extension 2 – Safety Population
16.2.8.4.3	Serology – Extension 3 – Safety Population
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16.2.8.5.1	Clinically Significant Laboratory Results – Extension 1 – Safety Population
16.2.8.5.2	Clinically Significant Laboratory Results – Extension 2 – Safety Population
16.2.8.5.3	Clinically Significant Laboratory Results – Extension 3 – Safety Population
16.2.8.6	Pulmonary Function Tests – Safety Population
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16.2.8.7	Echocardiographs – Safety Population
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16.2.8.7.3	Echocardiographs – Extension 3 – Safety Population

16.2.8.8	PedsQL – ITT Population
16.2.8.8.1	PedsQL – Extension 1 – ITT Population
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16.2.8.8.3	PedsQL – Extension 3 – ITT Population
16.2.8.9	Vital Signs Data – Safety Population
16.2.8.9.1	Vital Signs Data – Extension 1 – Safety Population
16.2.8.9.2	Vital Signs Data – Extension 2 – Safety Population
16.2.8.9.3	Vital Signs Data – Extension 3 – Safety Population
16.2.8.10	ECG Data – Safety Population
16.2.8.10.1	ECG Data – Extension 1 – Safety Population
16.2.8.10.2	ECG Data – Extension 2 – Safety Population
16.2.8.10.3	ECG Data – Extension 3 – Safety Population
16.2.8.11	Physical Examination – Safety Population
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16.2.8.11.3	Physical Examination – Extension 3 – Safety Population
16.2.8.12	Concomitant Medication – Safety Population
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16.2.8.12.2	Concomitant Medication – Extension 2 – Safety Population
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16.2.8.13	Biomarkers: LTBP4 and Osteopontin –Safety Population
16.2.8.13.1	Biomarkers: LTBP4 and Osteopontin – Extension 1 –Safety Population
16.2.8.13.2	Biomarkers: LTBP4 and Osteopontin – Extension 2 –Safety Population