9. DOCUMENTATION OF STATISTICAL METHODS

Statistical Analysis Plan (25 June 2020)

Errata to the Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy**
PROTOCOL NUMBER:	**Protocol FGCL-3019-079**
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CONFIDENTIALITY STATEMENT

Approvals

I have reviewed and accept the information in this document to be a true and accurate representation of the Statistical Analysis Plan for Study FGCL-3019-079.

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Table of Contents

1 Introduction 8
2 Study Design 8
3 General Statistical Considerations 8
3.1 Analysis Populations 8
3.1.1 Intent to Treat (ITT) Population 8
3.1.2 Safety Population (SAFETY) 8
3.1.3 PK Analysis Population 8
3.2 Adjustment for Multiple Comparisons 8
3.3 Handling Dropouts and Missing Data 9
3.3.1 Handling Missing/Incomplete AE Onset Date 9
3.3.2 Handling Missing/Incomplete Prior or Concomittant Medication Start/Stop Dates .. 9
3.4 Definition of Baseline 10
3.5 Analysis Visit Windows 10
3.6 Considerations for Figures 12
4 Statistical Analyses 12
4.1 External CINRG and Published Data 12
4.2 Subject Enrollment and Disposition 13
4.3 Demographic and Baseline Characteristics 13
4.3.1 Demographics and Other Baseline Characteristics 13
4.3.2 Medical History 13
4.3.3 DMD Disease History and Characteristics 13
4.4 Summary of Prior and Concomitant Medications 14
4.5 Summary of Study Drug Exposure 14
4.6 Analysis of Efficacy Endpoints 15
4.6.1 Efficacy Endpoints 15
4.6.2 Analysis Methods for Efficacy Endpoints 16
4.6.3 Primary Efficacy Endpoint - Annaul Change from Baseline to Week 104 in Percent Predicted FVC (ppFVC) 17
4.6.4 Change from baseline to Week 104 in percent predicted FEV1 and percent predicted PEF 17
4.6.5 Change from Baseline to Week 104 in LVEF (%) by MRI 18

4.6.6 Change from Baseline to Week 104 in Performance of Upper Limb (PUL) Score . 18
4.6.7 Change from Baseline to Week 104 in Grip Strength and Pinch Strength. 18
4.6.8 Change from Baseline to Week 104 in Cardiac Fibrosis Score by MRI 19
4.6.9 Change from Baseline to Week 104 in Upper Arm (Biceps Brachii) Muscle Fibrosis and Fat Score by MRI 19
4.6.10 Change in Fat Fraction Assessed by MRI 19
4.7 Exploratory Analysis and Analysis for Other Endpoints 19
4.7.1 Exploratory Correlation Analysis for Efficacy Endpoints 19
4.7.2 Analyses of Pharmacokinetic (PK) Parameters 20
4.7.3 Extent of Ventilation Use 21
4.7.4 Exploratory Endpoints 21
4.8 Safety Analyses 21
4.8.1 Adverse Events 21
4.8.2 Laboratory Data 22
4.8.3 Vital Signs 22
4.8.4 ECG 22
5 References 23
Appendices 24
Appendix I. 2-sample t-test for comparison to historical data 24
Appendix II. External Data from the CINRG DMD Natural History study (DNHS) 25
Appendix III. Historical Published Data 26
Appendix IV. Performance of the Upper Limb (PUL) Module 29
Appendix V. Laboratory Test CTCAE Criteria 35
Appendix VI. Conversion Table from Ulna Length to Height 36

List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BMI	Boday Mass Index
BP	Blood pressure
BPM	Beats per minute
BSA	Body Surface Area
CBC	Complete blood count
C_{max}	Maximal concentration
C_{min}	Minimal concentration
CRF	Case report form
CS	Clinically significant
CSR	Clinically study report
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective tissue growth factor
DBL	Database lock
DMD	Duchenne Muscular Dystrophy
ECG	Electrocardiogram
EE	Efficacy evaluable
EoS	End of study
EoT	End of treatment
FEV_1	Forced expiratory volume in 1 second
FG-3019	FibroGen-3019 (recombinant human monoclonal antibody), pamrevlumab
FVC	Forced vital capacity
HAHA	Human anti-human antibody
ICF	Informed consent form
ITT	Intent-to-treat
IV	Intravenous
kg	Kilogram
LLN	Lower limit of normal
LOCF	Last observation carried forward
LTFU	Lost to follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximal expiratory pressure
MIF50	Maximal inspiratory flow at 50%
MIP	Maximal inspiratory pressure
mg	Milligram
MMRM	Mixed Model Repeated Measures
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCS	Not clinically significant
NYHA	New York Heart Association
OLE	Open label extension
Pcough	Peak expiratory flow with cough
PEF	Peak expiratory flow
PFT	Pulmonary function test
PINP	Procollagen type I N-peptide
PIIINP	Procollagen type III N-peptide
PK	Pharmacokinetic
PODCI	Pediatrics Outcomes Data Collection Instrument

ppFVC	Percent predicted FVC
PRO	Patient reported outcome
PT	Preferred Term
PTT	Partial prothrombin time
QoL	Quality of life
ROM	Range of motion
RPM	Respirations per minute
RCM	Random coefficient model
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
SOC	System organ class
SDTM	Study Data Tabulation Model
TEAE	Treatment emergent adverse event
TLFs	Tables, listings and figures
ULN	Upper limit of normal
WHODrug	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed statistical analyses. Data that were included in the database lock (DBL) for the main study will be reported based on the analysis method described herein.

2 STUDY DESIGN

This study is designed as two parts, the main study and open label extension (OLE). The main study is an open-label, single arm study which enrolled 21 non-ambulatory subjects (at least 12 years of age) with Duchenne muscular dystrophy (DMD) subjects.

Each subject received pamrevlumab (35 mg/kg, every 2 weeks) for a minimum study duration of 104 weeks and will transition onto the open label extension (OLE).

Details of the study assessment schedule can be found in the protocol appendix.

3 GENERAL STATISTICAL CONSIDERATIONS

Safety and efficacy data will be summarized and presented by treatment group (Pamrevlumab or source of external data, as applicable), agre, and analysis visit in summary tables as appropriate.

All collected data will be provided in listings.

3.1 Analysis Populations

3.1.1 Intent to Treat (ITT) Population

The intent-to-treat (ITT) population consists of all subjects who enrolled in the study. The ITT population will be used in the analyses of efficacy endpoints and baseline summaries.

3.1.2 Safety Population (SAFETY)

The Safety population (SAFETY) are subjects who received at least one dose of study drug. The SAFETY population will be used in the analyses of all safety parameters.

3.1.3 PK Analysis Population

The PK analysis population consists of all subjects who have received at least one dose of study medication and have at least one PK concentration data. There were 12 subjects participated in the PK study.

3.2 Adjustment for Multiple Comparisons

No adjustments of multiple tests will be considered. A 2-sided alpha level of 0.05 will be used for testing and confidence interval construction.

3.3 Handling Dropouts and Missing Data

All analyses will be based on observed data; missing data will not be imputed.

3.3.1 Handling Missing/Incomplete AE Onset Date

If the AE onset date is incomplete or missing, the following rules will be applied to impute AE onset date.

- If year and month are present, only day is missing,
  a) If AE onset Year/month = Day 0 Year/month, assign onset day = day part of Day 0 (Day 0 is the first infusion day);
  b) If AE onset Year/month ≠ Day 0 Year/month, assign onset day = 1st of the month;
- If year is present, month and day are missing, or when only month is missing (treating day as missing),
  a) If AE onset year = year of Day 0, assign onset date = month and day part of of Day 0 date;
  b) If AE onset year ≠ year of Day 0, assign onset date= January 1st.
- If onset date is completely missing, assign onset date = date of Day 0.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

3.3.2 Handling Missing/Incomplete Prior or Concomittant Medication Start/Stop Dates

For prior or concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date date is imputed the same way as for the AE described above. When the start date and the stop date are both incomplete for a patient, impute the start date first.

Incomplete Stop Date

The following rules are applied to impute the missing stop date, if needed.

- If year is present, month and day are missing, or when only month is missing (treating day as missing)
  a) If CM stop year = year of last dose, assign stop date = month and day part of of last dose date;
  b) If CM stop year ≠ year of last dose, assign stop date= December 31st.
- If year and month are present, only day is missing,
  a) If CM stop Year/month = Year/month of last dose date, assign stop day = day part of last dose date
  b) If CM stop Year/month ≠ year of last dose, assign onset day = last day of the month;

- Impute CM end date even if 'ONGOING' is checked so as to report the CM treatment duration in the study if needed.

3.4 Definition of Baseline

The following steps will be followed to define the baseline values:

- The acceptable value on Day 0 will be used;
- Otherwise, the acceptable value from the last visit on or before the first dose will be used
- When none of the above values were available, the first acceptable value (upto 8 weeks after Day 0) on study will be used as baseline.

3.5 Analysis Visit Windows

Efficacy parameters will be summarized by analysis visit defined by the following assessment windows. The date of the first dose will be considered as the date of Day 0 for all analysis.

Table 1. Assessment Windows for PFT and Muscle Function Tests

Analysis Visit	**Window**
Baseline	value at the visit on or prior to the first dose of study drug
Week X	X = 12, 24, 36, 48, 60, 72 Target day = 7 * X + 1 Window = [Target day – 42, Target day + 41]
Week 84	Window = [Target day – 42, Target day + 69]
Week 104	[Target day– 70, Target day +41]
Week 116, 128	[Target day– 42, Target day + 41]
Week 140	[Target day– 42, Target day + 55]
Week 156	[Target day– 56, Target day + 41]
Week 168, 180	[Target day – 42, Target day + 41]
Week 192	[Target day – 42, Target day + 55]
Week 208	[>=Target day – 56]*

*** There will be no upper bound; all assessments will be included.**

Table 2. Assessment Windows for Cardiac MRI and Muscle MRI

Analysis Visit	Window
Baseline	value at the visit on or prior to the first dose of study drug
Week 52	[Target day (365) – 84, Target day (365) + 83]
Week 104	[Target day (729) – 84, Target day (729) + 83]
Week 156	[Target day (1093) – 84, Target day (1093) + 83]
Week 208	[>=Target day (1456) - 279]*

*** There will be no upper bound; all assessments will be included.**

Table 3. Assessment Windows for Vital Signs

Analysis Visit	Window
Baseline	• Baseline are defined as the average of last Screening and Week 0 pre-infusion measurements.
Week X	X = 2 , 4, 6, 8, 10, 12 ……210 Target day = 7 * X + 1 Window = [Target day – 7, Target day + 6]*

***The last visit window will not have an upper bound; all assessment will be included.**

Table 4. Assessment Windows for Labs Tests

Analysis Visit	Window
Baseline	• Value at the visit on or prior to the first dose of study drug. When no value on or prior to the first dose date was available, the first acceptable value (upto 8 weeks after Day 0) on study will be used as baseline.
Week X	X = 4, 8 Target day = 7 * X + 1 Window = [Target day – 14, Target day + 13]
Week 12, 24, 36, 48, 60, 72, 84	Window = [Target day – 42, Target day + 41]
Week 96	[Target day (673) – 42, Target day + 69]
Week 116	[Target day (813) – 70, Target day + 41]
Week 128, 140	[Target day – 42, Target day + 41]

Week 152	[Target day – 42, Target day + 55]
Week 168	[Target day – 56, Target day + 41]
Week 180, 192	[Target day – 42, Target day + 41]
Week 204	[Target day – 42, Target day + 20]
Week 210	>=[Target day – 21]*

*** There will be no upper bound; all assessments will be included.**

All scheduled and unscheduled assessments are included in the by-visit summary. If more than two assessments are available in the same window, the last assessment will be used in the by-visit summary.

Safety data (lab tests, vital signs) are summarized according to the PFT visit windows and ECG are summarized by the MRI visit windows.

3.6 Considerations for Figures

The figures will be plotted as follows.

1. Different colors and shapes for subjects age <=16 versus >16 will be used in by-subject line plots and waterfall plots.
2. All relevant external data comparisons for the same endpoint will be presented in the same bar graph as appropriate.
3. Mean (SE) and mean (SE) change from baseline values over time will be plotted.

4 STATISTICAL ANALYSES

4.1 External CINRG and Published Data

A subset of subjects from the CINRG DMD Natural History study (DNHS) will be included in the analysis as an external group. The document listing the selection criteria used to create the subset of data is in Appendix II. The analyses tables, figures and listing will present the external group as a separate group on the same page as applicable. The variables in DNHS that will be used for analyses are as follows.

Demogrphics: Age, Race, Ethnicity, Weight, Height, BMI, BSA

Efficacy endpoints: % predicted FCV (ppFVC), LVEF, and grip strength in dominant hand.

In addition to this external CINRG data, historical published data will also be compared for selected endpoints as described in the following sections. The historial published data are listed in Appendix III.

4.2 Subject Enrollment and Disposition

The number of subjects enrolled into the study and the number of subjects in each study population for the analysis (ITT, Safety and PK) will be summarized. The number of subjects who completed or discontinued the treatment/study prematurely as well as the reasons for early discontinuation will be summarized.

4.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics of the study and of the CINRG will be summarized using descriptive statistics based on the ITT population.

4.3.1 Demographics and Other Baseline Characteristics

Demographic variables will include age in years, sex (optional as all DMD subjects are male), race, and ethnicity. Age at baseline is defined as the age when signing inform consent:

age = YRDIF(Birth Date, Date of Informed Consent, 'Actual')

where YRDIF is a SAS function.

Other baseline characteristics include height (see conversion table in Appendix VI), weight, side of dominant hand, BSA, and body mass index (BMI).

Computation formulas:

$$BSA = [Weight^{0.425} (kg) * Height^{0.725} (cm)] \times 0.007184$$

$$BMI = Weight (kg) / (Height (m))^2$$

4.3.2 Medical History

Medical conditions, including allergies and surgeries, are coded in system organ class (SOC) and preferred term (PT) using MedDRA (version 18.1).

The medical conditions will be tabulated by SOC and PT. A subject with multiple medical conditions within an SOC is only counted once in this SOC. Similarly, a subject with multiple medical conditions within a PT is only counted once in this PT. The tabulation will be sorted alphabetically by SOC and by decreasing order of frequency of PT within each SOC.

4.3.3 DMD Disease History and Characteristics

DMD disease history and characteristics include

- Age in years when DMD was diagnosed = YRDIF(DOB, Date of diagnosis, 'actual')
- Years since subject became non-ambulant = Current age – Age when subject became non-ambulant.
- Ventilation support: yes or no. If yes, years since subject began ventilation support = Current age– Age when subject began ventilation support.

- Corticosteroids use: yes or no. If yes, years since subject began corticosteroids = Current age – Age when subject began corticosteroids.
- Spine surgery: yes or no. If yes, years since the most recent spine surgery = YRDIF(Date of spine surgery, Day 0 Visit Date, 'Actual')
- Genetic characteristics
    - Exonic deletion
    - Duplication
    - Point mutation
    - None of above
    - Unknown
- FVC and estimated annual decline of FVC prior to study entry

4.4 Summary of Prior and Concomitant Medications

The historical use of the medications listed on the Screening CRF is summarized using descriptive statistics for the Safety population.

Medications recorded on the Concomitant Medication CRF are classified in the analysis dataset in the following categories:

1. Prior medications - medications that were stopped prior to the first infusion
2. Concomittant medications - medications that are used concomitantly with the study drug, which are defined as medications that were not stoped before the first infusion.
3. Use of corticoseteroids

Prior and concomitant medications are summarized by ATC class and preferred term for the ITT population. Subjects reporting more than one use of the same medication will be counted only once in the summary tables.

All medications captured in screening Medication CRF and Concomitant Medication CRF, as well as Non-Drug Therapies CRF are presented in data listings.

4.5 Summary of Study Drug Exposure

Duration in weeks from first infusion to last infusion, calculated as (last dose date – first dose date +1)/7, will be summarized by the categories as follows:

<= 26 weeks

>26 weeks to <=52 weeks

>52 weeks to <=78 weeks

>78 weeks to <=104 weeks

>104 weeks to <=156 weeks

>156 weeks

The number of infusions and average infusion dose amount in mg and mg/kg, any interruption during infusion (Y/N), and reason for missed dose or interruption will be summarized for the Safety population.

The compliance will be presented as % of actual doses of infusion administered out of the expected total dose of infusions during study. Compliance = (actual doses received / expected doses during study) * 100%. Treatment compliance will be summarized as a continuous variable and as a categorical variable (<70%, 70% -<80%, 80% - 90%, and >90%).

4.6 Analysis of Efficacy Endpoints

The endpoint values calculated by the the Central Reader will be used for analyses. Only "acceptable" efficacy outcomes will be included in the analyses; "unacceptable" data will not be included in analyses.

4.6.1 Efficacy Endpoints

4.6.1.1 Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted forced vital capacity (ppFVC) during treatment with FG-3019 (pamrevlumab).

4.6.1.2 Secondary Endpoints

The following are the secondary endpoints:

1. Change from baseline to Week 104 in percent predicted forced expiratory volume (ppFEV1) and percent predicted peak expiratory flow (ppPEF)
2. Change from baseline to Week 104 in Left Ventricular Ejection Fraction percentage (LVEF %) by MRI
3. Change from baseline to Week 104 in Performance of Upper Limb (PUL) score (version 2.0)
4. Change from baseline to Week 104 in grip strength by Hand Held Myometry (HHM) and pinch strength by HHM
5. Change from baseline to Week 104 in cardiac fibrosis score by MRI
6. Change from baseline to Week 104 in upper arm (biceps brachii) muscle fat and fibrosis score by MRI
7. Change from baseline to Week 104 in fat fraction (%F) by MRI

4.6.1.3 Exploratory and Pharmacokinetic Parameters

Exploratory endpoints include plasma CTGF, human anti-human antibody (HAHA), and creatine kinase (CK)

PK parameters include C_{min}, C_{max}, AUC_{τ}, $T_{1/2}$, V_z, and CL.

4.6.2 Analysis Methods for Efficacy Endpoints

Unless otherwise noted, descriptive summary for change from baseline values by analysis visit according to visit windows, annual rate of change from baseline (using RCM) analysis, and the estimated change from baseline values at year 1 or year 2 (ie, week 52 or week 104) for the comparison to historical results and external data described in the following sub-sections will be implemented for the primary and secondary efficacy endpoints. The comparisons to the external data are specified in sections of the endpoint analyses.

4.6.2.1 Descriptive Summary

Continuous variables will be presented by descriptive statistics: n, mean, standard deviation (SD), standard error (SE), median, 25th and 75th percentile, minimum, and maximum. The 2-sided 95% confidence interval for the mean and median will be presented as appropriate. Categorical variables will be tabulated by frequency count and percentage. The confidence interval for the proportions for each will be calculated using the Clopper-Pearson method as appropriate.

The 95% CIs for medians will be from SAS UNIVARIATE procedure with option CIQUANTDF. The Clopper-Pearson exact 95% CIs for the dichotomous parameters will be from SAS FREQ procedures with option BINOMIAL (EXACT). The 95% CIs for means of normally distributed parameters will be from appropriate SAS procedures such as PROC MEANS.

The obseverd values by subject and the group mean (SE) and mean change from baseline (SE) in endpoint values will be plotted in line plots over analysis visits.

Waterfall Plot of Change from Baseline to week 52 and week 104 values will also be provided.

4.6.2.2 Analysis of Change from Baseline in Efficacy Variables

The change from baseline values will be analyzed using random coefficient model (RCM) based on all observed data for each variable.

The model will include avisityr (calculated as the elaspsed days of assessment date from baseline date in the unit of year) as a continuous variable and baseline endpoint value, where baseline endpoint value is included as a fixed effect, while the intercept and avisityr are included as random effect.

The unstructured covariance will be applied first. If the algorithm for unstructured covariance pattern does not converge then heterogeneous Toeplitz structure will be used. If this second model does not converge then the (homogeneous) Toeplitz structure will be tried, and if all of these covariance failed to converge then the compound symmetry will be used.

When the random effects model does not converge or do not have a positivie definite Hessian, the fixed effects instead of random effects for the intercept and slope will be performed instead.

The LSMean(SE) and 95% CI for annual change (slope) as well as estimated changes from baseline at year-1 and year-2 (in regards to weeks 52 and 104) will be presented.

SAS code for this model, using the primary endpoint ppFVC as example, is provided below.

```
/*Random Coefficient Model (RCM) to estimate the change at year 1 and at year
2*/
/*avisityr is the actual number of years from Day 1, avisityr=2 will be the
change from baseline at year 2 */
/* fvc0= baseline ppFVC, should be be used for change in FVC */
/* &meanfvc0= the mean of the baseline ppFvc  */

proc mixed data = fvc_obs;
  class subjid;
  model chgfvc = avisityr fvc0/solution cl covb outp=pred_fvc cl;
  random intercept avisityr /subject=subjid type=CS;
  ESTIMATE 'Change from Baseline at Year 1' intercept 1 avisityr 1 fvc0
&meanfvc0 / CL;
  ESTIMATE 'Change from Baseline at Year 2' intercept 1 avisityr 2 fvc0
&meanfvc0 / CL;
  ods output SolutionF=mxparms CovB=mxcovb Estimates=chgfrbl;
run;
```

4.6.2.3 Comparison to External and Historical Published Data

The LSmean (SE) of changes from baseline at year-1 and year-2 (in regards to weeks 52 and 104), and the corresponding 95% CI from this study and similar estimates from each of the relevant external sources will be presented in bar graphs. The difference in the estimates, the corresponding 95% CI for the difference, and p-value between this study result and external data using the 2-sample t-test (Appendix I) will be presented in the same bar graph as appropriate.

4.6.3 Primary Efficacy Endpoint - Annaul Change from Baseline to Week 104 in Percent Predicted FVC (ppFVC)

4.6.3.1 Analysis method

The observed and change from baseline % predicted FVC (ppFVC) will be summarized by analysis visit, and the annual rate of change from baseline pp FVC and change from baseline at week 52 and 104 will be estimated using the RCM model described above.

In addition, the percent of subjects with ≥10% decline (change ≤-10%) and its 95% CI will also be summarized.

4.6.3.2 Comparison to External and Historical Published Data

The results will be plotted and compared with the results from Meier 2017 (placebo and GC use), Ricotti 2019, and CINRG data.

4.6.4 Change from baseline to Week 104 in percent predicted FEV1 and percent predicted PEF

4.6.4.1 Analysis Method

The observed and change from baseline in percent predicted forced expiratory volume (ppFEV1) and percent predicted peak expirator flow (ppPEF) will be summarized by analysis visit and analyzed using the RCM model as described above.

4.6.4.2 Comparison to Historical Published Data

The results will be plotted and compared with the results from Meier 2017 (placebo and GC use) and Ricotti 2019 (ppPEF only), respectively.

4.6.5 Change from Baseline to Week 104 in LVEF (%) by MRI

4.6.5.1 Analysis Method

The observed and change from baseline LVEF (%) assessed by MRI will be summarized by analysis visit and analyzed using RCM model as described above.

4.6.5.2 Comparison to Historical Published Data

The results will be plotted and compared with the results from McDonald 2018, and CINRG data.

In addition, the global myocardial circumferential strain assessed by MRI will be compared with the result from Hagenbuch, 2010.

4.6.6 Change from Baseline to Week 104 in Performance of Upper Limb (PUL) Score

The PUL scores include middle and distal score, and total score.

4.6.6.1 Analysis Method

The observed and change from baseline in PUL middle and distal score, and PUL total score, will be summarized by analysis visit and analyzed using RCM model as described above.

4.6.6.2 Comparison to Historical Published Data

The results for the PUL total score will be compared with the results from Ricotti, 2019.

The results for the upper limb (PUL) middle and distal arm score will be compared with the results from Pane, 2018.

4.6.7 Change from Baseline to Week 104 in Grip Strength and Pinch Strength.

4.6.7.1 Analysis Method

The observed and change from baseline grip strength, and pinch strength will be summarized and analyzed using the RCM model as described before. The grip and pinch strength should be reported by dominant and non-dominant hand separately.

4.6.7.2 Comparison to Historical Published Data

The results will be plotted and compared with the results from Seferian 2015 (dominant and non-dominant hands) and Ricotti 2019 (dominant hand only available), and CINRG (grip strength in dominant hand).

4.6.8 Change from Baseline to Week 104 in Cardiac Fibrosis Score by MRI

4.6.8.1 Analysis Method

Cardiac fibrosis assessed by MRI, the mass of late gadolinium enhancement (Scar Mass), will be summarized and analyzed as described above.

4.6.9 Change from Baseline to Week 104 in Upper Arm (Biceps Brachii) Muscle Fibrosis and Fat Score by MRI

4.6.9.1 Analysis Method

The observed and change from baseline Upper arm (biceps) muscle fibrosis and fat assessed by MRI as CAD assessment of muscle fibrosis and fat (mean T2-mapping within the bicep ROI: MEANT2) will be summarized and analyzed with the RCM model described above.

4.6.9.2 Comparison to Historical Published Data

The results will be compared with results from Horgrel, 2016.

4.6.10 Change in Fat Fraction Assessed by MRI

4.6.10.1 Analysis Method

The observed and change from baseline upper arm (bicep) muscle fat fraction (%F) assessed by MRI will be summarized and analyzed using the RCM model as decribed before.

4.6.10.2 Comparison to Historical Published Data

The results of the fact fraction by MRI will be plotted and compared with the result from Hogrel, et al 2016.

4.7 Exploratory Analysis and Analysis for Other Endpoints

4.7.1 Exploratory Correlation Analysis for Efficacy Endpoints

Scatter plot and spearman correlation of change from baseline to week 52 and week 104 (separately), for the following pairs of endpoints will be provided:

1. Change from baseline in LVEF (%) *vs.* change in cardiac fibrosis score (scar mass).
2. Change from bassline in CAD assessment of muscle fibrosis and fat score (mean T2-mapping within the bicep ROI) and fat fraction (%F) assessed by MRI versus the following:
   a. Change from baseline in FVC (% Predicted)
   b. Change in PEF (%Predicted),
   c. Change in pinch strength (dominant and non-dominant hand),
   d. Change in grip srength (dominant and non-dominant hand)
   e. Change in PUL Score

4.7.2 Analyses of Pharmacokinetic (PK) Parameters

Pharmacokinetic (PK) profile of pamrevlumab includes Cmin, Cmax, $AUC_{0\text{-}tau}$, and $t_{1/2}$. The PK parameters will be estimated with available data from concentration-time curve of each individual by non-compartmental analysis using ((Phoenix) WinNonlin 6.2 (Pharsight, A Certara™ Company). (Pharsight , A Certara™ Company). The PK parameters will be estimated based on actual time of sample collection relative to the actual dose time in subjects of the PK population.

- Cmin: minimum concentration
- Cmax: maximum concentration
- Tmax: time when Cmax occurs
- $t_{1/2}$: terminal elimination half-life
- $AUC_{0\text{-}tau}$: area under the plasma concentration-time curve to tau, where tau is the dosing interval
- Cmin at Week 26 and 52: minimum concentration
- Cmax at Week 52: maximum concentration
- Ctrough on Day 14

AUC estimates will be conducted by using the option of linear trapezoidal/linear interpolation within WinNonlin.

Line plots of individual concentration for all subjects overlay on 1 graph in semi-log scale will be provided.These PK parametres will be summarized for the overall and by age group (12 to 16 years of age, inclusive and older than 16 years, if applicable, plotted in different colors and shapes). The descriptive summary statistics includes number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation.

The natural-log transformed Cmin at Week 26 and Week 52 will be compared using the mixed model repeated measures (MMRM) using PROC MIXED with week in the model and compound

symmetery as the within-subject variance-covariance structure. The difference in Cmin between weeks 26 and 52 and the correspoinding two-sided 90% CI on the difference will be constructed. The anti-natural log (expoenent) transformation of the difference and the confidence interval for the difference will be presented.

4.7.3 Extent of Ventilation Use

The frequency and percent of subjects with extent of ventilation use as recorded below will be summarized over time. The confidence intervals for the proportion of subjects will be calculated using the Clopper-Pearson method as appropriate.

1. None
2. Nighttime use only or <8 hours per day on average
3. Use for >= 8 but < 16 hours per day on average
4. Requires >= 16 hours continuous ventilation

4.7.4 Exploratory Endpoints

Exploratory endpoints: plasma CTGF, human anti-human antibody (HAHA), and creatine kinase (CK), if available, will be summarized by analysis visit as described previously.

Exploratory endpoint of use of corticosterioids will also be summarized.

4.8 Safety Analyses

Safety analyses will include descriptive summaries of adverse events, lab test results, vital signs, and ECGs in the Safety population.

4.8.1 Adverse Events

All reported AEs will be presented in listings. For the main study, the treatment emergent period of safety reporting for the Clinical Study Report (CSR) is defined as from the first infusion date to the last infusion date + min (28 days, EOS date -last infusion date+1) for those subjects did not enter the open label extension (OLE) or to the time before the first infusion in the OLE for those entered the OLE.

Number (%) of subjects with a treatment emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT). The summary tables will be sorted alphabetically by SOC and by decreasing order of frequency of PT within each SOC. A subject with multiple adverse events within a SOC is only counted once in this SOC. Similarly, a subject with multiple adverse events within a PT is only counted once in this PT.

The exposure adjusted incidence rate, number of subjects with the event/total patient exposure years (PEY)*100, will be summarized, system organ class (SOC) and preferred term (PT). The patient exposure years (PEY), (last infusion date – first infusion date + 1)/365.25, for each subject will be

summed to calculate the total patient exposure years. The summary tables will be sorted alphabetically by SOC and by decreasing order of frequency of PT within each SOC. A subject with multiple adverse events within a SOC is only counted once in this SOC. Similarly, a subject with multiple adverse events within a PT is only counted once in this PT.

In addition to listing of all reported AEs and summary of all TEAEs, the following TEAE summaries will be provided:

- TEAEs
- TEAEs (grade 3 and higher per CTCAE)
- TEAE leading to study or treatment discontinuation
- TEAE and relationship to FG-3019 (pamrevlumab)
- TEAE and severity
- TESAE and relationship to FG-3019 (pamrevlumab)
- Listing of Deaths
- Listing of Serious Adverse Events
- Listing of TEAE leading to discontinuation

4.8.2 Laboratory Data

Blood samples are drawn for the following analyses: complete blood count, gamma glutamyl transferase (GGT), total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), and albumin, creatine kinase (CK), and cystatin C.

Laboratory test results and change from baseline are summarized by analysis visit.

CTCAE grade 3 or higher lab test results will be considered potentially clinically significant. These results are summarized and presented in a data listing.

Shift tables to summarize changes from baseline to each visit in CTCAE categories are tabulated. Shift from baseline to most severe CTCAE category during the study is also summarized.

An eDISH (evaluation of drug induce severe hepatotoxicity) analytical graph, which is a scatter plot of maximum observed total bilirubin versus maximum observed ALT or AST, will be generated to identify cases in Hy's law range.

4.8.3 Vital Signs

Pulse (beat/min), diastolic and systolic blood pressure (mmHg), respiration (breaths/min), and temperature (C) will be summarized for selected analysis visit.

4.8.4 ECG

Number (%) of subjects with ECG results (normal/abnormal/Clinical Significant) will be summarized by analysis visit.

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APPENDICES

Appendix I. 2-sample t-test for comparison to historical data

In the barplot, a simple comparison based on the two sample t-test will be implemented using the following formula, where n_1, m_1, $se_1$and sd_1 is the number of subjects, LS mean, standard errors and standard deviations, respectively, with the subscript 1 represents this study (079) and subscript 2 represents reference external data):

In generation the $SD = SE * sqrt(n)$

This study (079), $sd_1 = \mathrm{se}_1 * \mathrm{sqrt}(\mathrm{n}_1)$

The reference external study, $sd_2 = \frac{\text{the 95\% upper bound – the lower bound}}{3.92} * \mathrm{sqrt}(\mathrm{n}_2)$

Degree of freedom for two sample t-test (Welch-Satterthwaite formula): $df = \frac{\left(\frac{s_1^2}{n_1}+\frac{s_2^2}{n_2}\right)^2}{\frac{\left(\frac{s_1^2}{n_1}\right)^2}{n_1-1}+\frac{\left(\frac{s_2^2}{n_2}\right)^2}{n_2-1}}$

Standard Errors for two sample t-test $se = \sqrt{\frac{s_1^2}{n_1}+\frac{s_2^2}{n_2}}$

Two Sample Test statistics $\delta = \frac{(m_1-m_2)}{se}$

T-test:

95% CI: $\delta \pm t(\delta, df) * se$

$p = t(\delta, df)$ (SAS function: $probt(\delta, df)$.

Please note that if $\delta \leq 0$, p-value=p; if δ>0, p-value=1-p.

Appendix II. External Data from the CINRG DMD Natural History study (DNHS)

External CINRG data were obtained from the DNHS study. Subset dataset selection criteria used to create the subset of the DNHS are as follows.

1. Criteria Information

Requested criteria	Summary statistics to verify criteria has been met.
Diagnosis of DMD by medical history or confirmed Duchenne mutation in available genetic testing using a validated genetic test	All DNHS participants fulfill this criterion.
Must be non-ambulatory	All participants non-ambulatory at baseline visit (amb=2 for all)
At least 12 years of age	Age range at baseline visit: minimum=12.0 years
The patient's BMI is < 40 kg/m^2, weight ≤ 117 kg at the baseline visit	Weight range at baseline visit: minimum=29 kg, maximum=90 kg
Brooke Score for Arms and Shoulders ≤5	Brooke score range at baseline visit: minimum=1, maximum=5
Percent predicted FVC (while non-ambulatory) ranged between 40% and 90%, inclusive	FVC%p range at baseline visit: minimum=42%, maximum=88%
LVEF% ≥45% (while non-ambulatory)	LVEF% range at baseline visit: minimum=46%, maximum=75.7%
On a stable dose of corticosteroids for a minimum of 6 months with no substantial change in dosage for a minimum of 3 months prior to baseline (except for adjustments for changes in body weight) and no change in corticosteroid use during the study period.	Total lifetime steroid use at baseline visit (all participants current steroid users): minimum=360 days, maximum=4622 days
Each participant must have at a minimum two FVC % predicted assessments and two LVEF% assessments. One assessment must be at the observation interval start, the second at a later study visit. The second FVC% predicted and LVEF% assessment do not have to occur at the same visit.	Number of FVC%p assessments per participant: minimum=2; maximum=12 Number of LVEF% assessments per participant: minimum=2; maximum=7
Exclusion: On invasive mechanical ventilation	No participants on mechanical ventilation
Exclusion: Severe heart disease defined as a prior hospitalization for congestive heart failure or other cardiac issue	No participants with prior hospitalization for heart failure or other cardiac issue

Exclusion: Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to the baseline visit with the exception of deflazacort.	No participants with reported exposure to DMD approved drug.

Appendix III. Historical Published Data

A. T. Meier et al. / Neuromuscular Disorders 27 (2017) 307–314

Table 4 Yearly rate of change in pulmonary function outcomes .

Pulmonary function parameter	All placebo (N = 33)	GC use status (prior GC-use) Yes (N = 19)
PEF%p	−8.9 (2.0)	−7.8 (2.7)
	(−13.0, −4.7)	(−13.5, −2.2)
	$p = 0.0001$	$p = 0.0090$
FVC%p	−8.7 (1.1)	−8.7 (1.3)
	(−11.0, −6.5)	(−11.4, −5.9)
	$p < 0.0001$	$p < 0.0001$
FEV1%p	−10.2 (2.0)	−8.7 (1.9)
	(−14.2, −6.2)	(−12.7, −4.7)

Data are estimated means from MMRM (SEM) and 95% confidence intervals; *p*-values indicate whether the yearly change was significant.

B. V. Ricotti, V. Selby and D. Ridout et al. ; Neuromuscular Disorders; March 7, 2019;3:50

Table 2
Estimated annual changes from baseline for respiratory and upper limb measurements.

	NON-AMBULANT ($n = 29$) Mean change (95% CI)	*p*-value
FVC% predicted	−5.47 (−6.48, −4.45)	<0.001
PEF% predicted	−4.81 (−6.79, −2.82)	<0.001
PUL total score	−4.13 (−4.79, −3.47)	<0.001
Myogrip absolute value (Kg)	−0.39 (−0.50, −0.29)	<0.001
Myogrip absolute value (Newton)	−3.82 (−4.91, −2.84)	<0.001
Myopinch absolute value (Kg)	−0.08 (−0.13, −0.03)	<0.01

Myopinch absolute value (Newton)	−0.78 (−1.28, −0.29)	<0.01

FVC= force vital capacity; PEF= peak expiratory force; PUL= Performance of the Upper Limb. 1 Kg=9.81 Newtons

C. Supplement (Vol 391 February 3, 2018) to: McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet 2017; published online Nov 22

Table S7. Mixed effects linear regression model of cardiac ejection fraction (dependent variable) and age and GC use (independent variables).

		Age	
N (observations)	**N (participants)**	**Coefficient (95% CI)**	**P-value**
894	305	-0.82 (-0.94 to -0.70)	<0.0001

D. A.Seferian, et al. ULENAP Study: One-Year Follow-Up in Non-Ambulant Patients with DMD, February 2, 2015

Table 5. Differences in MyoSet scores between baseline and one year.

	Non-dominant side		Dominant side	
	N	mean diff (SD)	N	mean diff (SD)
MyoGrip (kg)	34	-0.31 (0.46) **	34	-0.28 (0.65) *
MyoPinch (kg)	35	-0.22 (0.31) **	35	-0.17 (0.28) **

*p-value<0.05, **p-value<0.01

E. Hogrel American Academy of Neurology, 2016

Table 2 Changes in functional and nuclear magnetic

	Nonambulatory	p
T2, ms	-0.67 [-2.22; 0.85] (26)	0.096
%F	3.20 [-1.33; 5.51] (26)	0.014[a]

Abbreviations: %F = fat percentage
[a] Significant

F. M. Pane, PLOS ONE, June 20, 2018, Upper limb function in DMD: 24 month longitudinal data

Table 1. Details of PUL2.0 scores in ambulant and non ambulant patients at baseline, 12 and 24 months.

PUL2.0	**Baseline**		**12 months**	**24 months**
MID- SCORES	**Range**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
NON AMBULANT	0–17	7.77 (5.81)	6.61 (5.59)	5.355 (4.83)
DISTAL SCORES	**Range**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
NON AMBULANT	3–13	9.86 (2.55)	9.50 (2.59)	9.08 (2.82)

G. Hagenbuch, American Journal of Cardiology 2010;105:1451–1455

Table 1 Age, ejection fraction (EF), and mean circumferential strain (s_{cc}) at initial and follow-up studies

Variable	Study Number 1 mean ***(n=51)***	Study Number 2 mean ***(n=51)***	p-value
Mean circumferential strain	-13.8 ± 1.9%	-12.0 ± 1.9%	<0.001

Appendix IV. Performance of the Upper Limb (PUL) Module

Performance of the Upper Limb Module for DMD 2.0 (PUL for DMD)

Dominant arm (used for all tests): ☐ **Right** ☐ **Left**

Elbow extension ROM full = 0**°: Right: Left:**

e.g. 10° contracture = -10°

Supination ROM: Right: ☐ Full ☐ ¾ ☐ ½ ☐¼ **Left:** ☐ Full ☐ ¾ ☐ ½ ☐¼

Entry item A. – start with A to identify starting point for subsequent tests. Circle score for each item. DO NOT INCLUDE IN TOTAL SCORE

Item	Score	Description
A	**0**	No useful function of hands
	1	Can use hands to hold pen or pick up a coin or drive a powered chair
	2	Can raise 1 or 2 hands to mouth but cannot raise a cup with a 200g weight in it to mouth
	3	Can raise plastic cup with 200g weight in it to mouth using 1 or 2 hands
	4	Can raise both arms (to shoulder height with or without compensation), i.e. elbow bent or in extension
	5	Can raise both arms simultaneously above head only by flexing the elbow (shortening circumference of the movement /using accessory muscles)
	6	Can abduct both arms simultaneously elbows in extension in a full circle until they touch above the head.

For item A: A score of 3, 4, 5, 6 on item A, start with item 1. A score of, 1, 2 start with item 7

High level shoulder Dimension : Administer only if subject scored 3, 4, 5, 6 on item A

Item	Description	0	1	2
1 **Score from Entry item above**	**Shoulder abduction both arms above head** "Raise your arms above your head out to the side – try and keep straight elbows"	Unable	Can raise both arms simultaneously **above head** only by flexing the elbow - **with** compensation	Can abduct both arms simultaneously elbows in extension in a full circle until they touch above the head
2	**Raise both arms to shoulder height (elbows at shoulder height)**	Unable	Can raise both arms to shoulder height either one at a time or with	Can raise both elbows to shoulder height **without** compensation

	"Raise your arms to shoulder level"		elbows flexed (**with compensation**)	e.g. simultaneously with elbows straight
3	**Shoulder flexion to shoulder height (no weights)** "Reach out and touch my hand" –elbow to eye level	Unable	Able **with** compensation	Able **without** compensation
4	**Shoulder flexion to shoulder height with 500g weight** "Reach out and touch my hand" –elbow to eye level	Unable	Able to lift 500g weight **with compensation**	Able to lift 500g weight **without compensation**
5	**Shoulder flexion above shoulder height with 500 g weight** Hand on lap – "give me the weight"	Unable	Able to lift 500g weight **with compensation**	Able to lift 500g weight **without compensation**
6	**Shoulder flexion above shoulder with 1 kg weight** Hand on lap – "give me the weight"	Unable	Able to lift 1 kg weight **with compensation**	Able to lift 1 kg weight **without compensation**

Mid level elbow Dimension

Do these tests on all individuals

Item	Description	0	1	2
7	**Hand(s) to mouth** "Bring the cup to your mouth with one hand"	Unable	Able to bring 200g in cup with any compensation to mouth (can use more than one hand and / or bring head to hands)	Able to bring 200g in cup to mouth with one hand no elbow support (without compensation)
8	**Hands to table from lap**	Unable	Able to bring two hands completely (to wrist crease) to table but	Two hands completely on table simultaneously

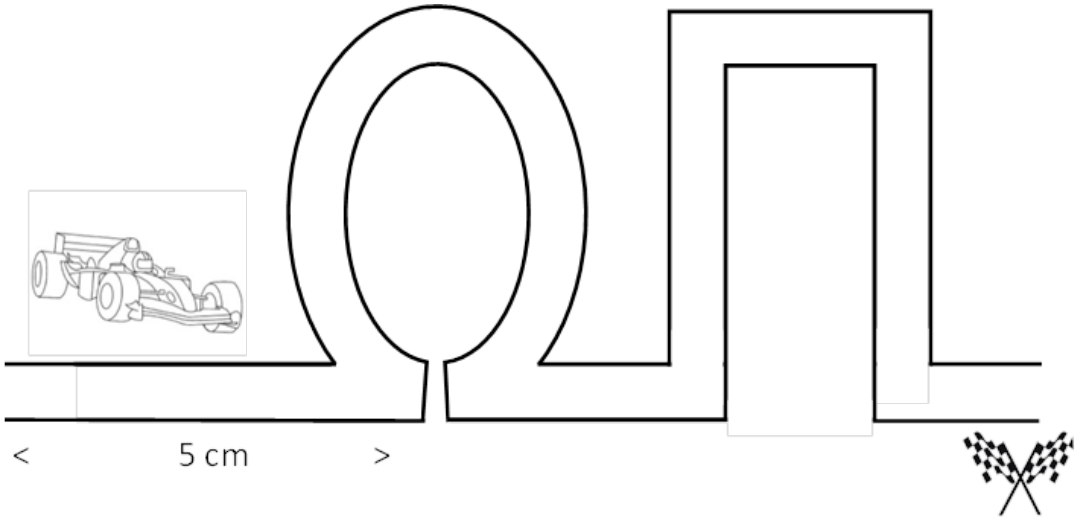
	"Bring both hands from lap to table"		**NOT simultaneously or in one action**	
9	**Move weight on table 100g** "Move the weight from outside circle to centre circle"	Unable	Can move **100g** weight from outer to centre circle using compensation (slide forearm or elbow make contact with table)	Can lift **100g** weight from outer to centre circle without compensation
10	**Move weight on table 500g** "Move the weight from outside circle to centre circle"	Unable	Can move **500g** weight from outer to centre circle using compensation (slide forearm or elbow make contact with table)	Can lift **500g** weight from outer to centre circle without compensation
11	**Move weight on table 1kg** "Move the weight from outside circle to centre circle"	Unable	Can move **1kg** weight from outer to centre circle using compensation (slide forearm or elbow make contact with table)	Can lift **1kg** weight from outer to centre circle without compensation
12	**Lift heavy can diagonally** "Lift can from this circle nearest your hand to this circle furthest away and across your body"	Unable	Can move heavy can from nearest circle across body with compensation (slide forearm or elbow make contact with table)	Can lift heavy can from nearest circle across body without compensation
13	**Stack of three cans** "Stack these two cans, one at a time on the middle can using one hand"	Unable to stack third can even with compensation	Able to stack third can with compensation	Able to stack third can without compensation
14	**Stack of five cans** "Stack these two additional cans, one at a time on top of this can using one hand"	Unable to stack fifth can even with compensation	Able to stack fifth can with compensation	Able to stack fifth can without compensation
15	**Remove lid from container** **"**Use your hands to open this container"	Unable	Opens completely	

Distal wrist and hand Dimension: **Do these tests on all individuals**				
Item	**Description**	**0**	**1**	**2**
16	**Tearing paper** "Tear the sheet of paper beginning from here"	Unable	Tears the sheet of paper folded in half from the folded edge	Tears the sheet of paper folded in 4,beginning from the folded edge
17	**Tracing path** "Use your pencil to complete the path in one smooth movement"	Unable	Completes the path with compensation - needs to raise pencil from paper or pivot arm	Able to complete the path **without stops** or raising hand from paper
18	**Push on light** "Push on the light with the fingers of one hand"	Unable	Able to turn the light on momentarily with fingers of one hand	Able to turn the light on permanently with fingers of one hand
19	**Supination** "Pick up the light and turn your hand over"	Unable	Picks up the light but either turns hands over incompletely or uses compensation to turn it over	Picks up the light, and turns the hand over completely with no compensatory movements
20	**Picking up coins** **"**Using one hand, Pick up 6 coins, one at a time"	Cannot pick up one coin	Can pick up **one** coin/ token	Can pick up six coins in one hand
21	**Placing finger on number diagram** (precision not essential) **"**Using one finger to touch each number on the diagram"	Cannot raise the finger or slide it on the diagram	Able to place finger (slide or lift) between at least two squares	Able to place finger successively on the numbers of the diagram (with or without compensation)
22	**Pick up 10g weight finger pinch** "Pick up this small weight like this (by body of weight)"	Unable	Able to grip and lift weight off surface	

Total Score PUL	

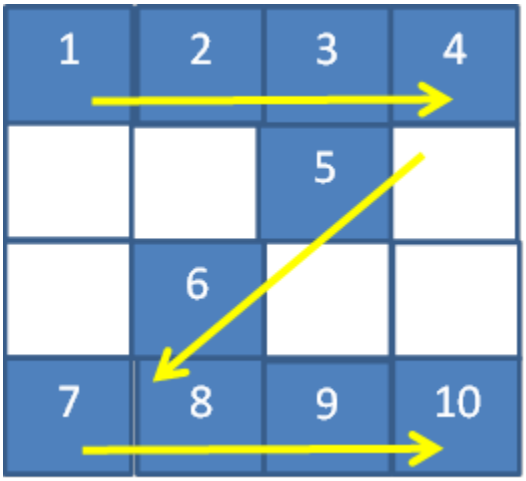
Additional Material

Item 17: Tracing a path



Item 21: Placing finger on number diagram

Instruction: Starting on the yellow number 1 point to the numbers 1 to 10 in turn following the arrow



Were all tests valid?

(i.e. representative of child's true function) Yes ☐ No ☐

If no, which tests were invalid?		And why?
Hand Held Myometry	☐	☐ Testing Environment (i.e. equip. malfunction, fire alarm, disruption) ☐ General health (i.e. stomach ache, cold, flu) ☐ Travel delays (i.e. lack of sleep; testing not performed at regular time) ☐ Inappropriate clothing ☐ Behavior ☐ Musculoskeletal issue (i.e. injury, muscle cramping, tendinitis) ☐ Other *(please explain in comment section of worksheet)*
PUL	☐	☐ Testing Environment (i.e. equip. malfunction, fire alarm, disruption) ☐ General health (i.e. stomach ache, cold, flu) ☐ Travel delays (i.e. lack of sleep; testing not performed at regular time) ☐ Inappropriate clothing o ☐ Behavior ☐ Musculoskeletal issue (i.e. injury, muscle cramping, tendinitis) ☐ Other *(please explain in comment section of worksheet)*

Appendix V. Laboratory Test CTCAE Criteria

The following table is extracted from NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010)

Chemistry

		Grade 1	Grade 2	Grade 3	Grade 4
Albumin	Decreased	3 g/dL – LLN	2 - <3 g/dL	<2 g/dL	
Alkaline phosphatase (ALP)		ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	> 20.0 x ULN
ALT		ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST		ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Total bilirubin		ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Calcium (Corrected)	Decreased	8.0 mg/dL – LLN	7.0 - <8.0 mg/dL	6.0 - <7.0 mg/dL	<6.0 mg/dL
		ULN – 11.5 mg/dL	>11.5 – 12.5 mg/dL	>12.5 – 13.5 mg/dL	>13.5 mg/dL
GGT		ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose (Random)	Decreased	55 mg/dL – LLN	40 - <55 mg/dL	30 - <40 mg/dL	<30 mg/dL
Glucose (Fasting)		ULN – 160 mg/dL	>160 – 250 mg/dL	>250 – 500 mg/dL	> 500 mg/dL
Phosphorous	Decreased	2.5 -<LLN mg/dL	2.0 -<2.5 mg/dL	1.0 - <2.0 mg/dL	<1.0 mg/dL
Potassium	Decreased	3.0 mmol/L – LLN	3.0 mmol/L – LLN[1]	2.5 - <3.0 mmol/L	<2.5 mmol/L
		ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L
Sodium	Decreased	130 mmol/L – LLN	None	120 - <130 mmol/L	<120 mmol/L
		ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L
Magnesium	Decreased	1.2 mg/dL – LLN	0.9 - <1.2 mg/dL	0.7 - <0.9 mg/dL	<0.7 mg/dL
		ULN – 3.0 mg/dL	None	>3.0 – 8.0 mg/dL	>8.0 mg/dL

Decreased: below LLN; Otherwise, above ULN;

Serum Hematology

		Grade 1	Grade 2	Grade 3	Grade 4
Uric acid		ULN – 10 mg/dL[2]	None	ULN – 10 mg/dL[3]	>10 mg/dL
Creatinine Enzymatic		>1 – 1.5 x baseline[4]	>1.5 – 3.0 x baseline[4]	>3.0 x baseline[4]	>6.0 x ULN
		ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	
Triglycerides		150 – 300 mg/dL	>300 – 500 mg/dL	>500 – 1,000 mg/dL	>1,000 mg/dL
Hgb	Decreased	10.0 g/dL – LLN	8.0 - <10.0 g/dL	<8.0 g/dL	
		>0 – 2 g/dL	>2 – 4 g/dL	>4 g/dL	
		(+ ULN/Baseline)[5]	(+ ULN/Baseline)[5]	(+ ULN/Baseline)[5]	
Platelet	Decreased	75,000 /mm^3 – LLN	50,000 – <75,000 /mm^3	25,000 - <50,000 /mm^3	<25,000 /mm^3
WBC	Decreased	3,000 /mm^3 – LLN	2,000 - <3,000 /mm^3	1,000 - <2,000 /mm^3	<1,000 /mm^3
		None	None	>100,000 /mm^3	
aPTT		ULN – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 x ULN	
Lymphocytes	Decreased	800 /mm3 – LLN	500 - <800 /mm^3	200 - <500 /mm^3	<200 /mm^3
		None	>4,000 – 20,000 /mm^3	>20,000 /mm^3	
Neutrophils	Decreased	1,500 /mm3 – LLN	1,000 - <1,500 /mm^3	500 - <1,000 /mm^3	<500 /mm^3

Decreased: below LLN; Otherwise, above ULN;
[1] Symptomatic, Intervention indicated
[2] without physiologic consequences
[3] with physiologic consequences
[4] Baseline is used if it is above ULN
[5] Increase from ULN/baseline: if baseline is above ULN, the increase should be above the baseline; otherwise, the increase should be above ULN.

Appendix VI. Conversion Table from Ulna Length to Height

Ulna length (cm)	32.0	31.5	31.0	30.5	30.0	29.5	29.0	28.5	28.0	27.5	27.0	26.5	26.0	25.5
Height in meters (men <65 years)	1.94	1.93	1.91	1.89	1.87	1.85	1.84	1.82	1.8	1.78	1.76	1.75	1.73	1.71

Ulna length (cm)	25.0	24.5	24.0	23.5	23.0	22.5	22.0	21.5	21.0	20.5	20.0	19.5	19.0	18.5
Height in meters (men <65 years)	1.69	1.67	1.66	1.64	1.62	1.6	1.58	1.57	1.55	1.53	1.51	1.49	1.48	1.46

ERRATA TO THE SAP

Two Sample Test statistics, delta= (m1-m2)

T-test: t=(m1-m2)/se

95% CI: delta +/- tinv(0.975, df)*se

(SAS function: p= probt(t, df) to get the p-value for the t-test.

Please note that if delta <= 0, p-value=p; if delta>0, p-value=1-p.