Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	PTC Therapeutics, Inc
	Protocol Number:	PTCEMF-GD-004
STATISTICAL ANALYSIS PLAN		

Statistical Analysis Plan

Title: A Multicenter Open Label Study on the Safety and Efficacy of Deflazacort (Emflaza®) in Subjects with Limb-Girdle Muscular Dystrophy 2I (LGMD2I)

Protocol Number: PTCEMF-GD-004

Protocol Version: 4.0 / 25-MAR-2020

SAP Version 1.0

SAP Issue Date: 28-OCT-2020

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Version	Issue Date	Section	Revision / Addition	Rationale

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APPROVALS

A Multicenter Open Label Study on the Safety and Efficacy of Deflazacort (Emflaza®) in Subjects with Limb-Girdle Muscular Dystrophy 2I (LGMD2I)

Protocol Number: PTCEMF-GD-004

Protocol Version: 4.0 / 25-MAR-2020

Version 1.0

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[redacted] Worldwide Clinical Trials

Approved by:

[redacted]

Date: 04-Nov-2020 | 09:59:58 EST

[redacted] PTC Therapeutics, Inc

[redacted]

Date: 04-Nov-2020 | 10:23:52 EST

[redacted] PTC Therapeutics, Inc

[redacted]

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[redacted] PTC Therapeutics, Inc

[redacted]

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[redacted] PTC Therapeutics, Inc

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ATC	Anatomic Therapeutic Chemical
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DEXA	Dual-Energy X-ray Absorptiometry
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ET	Early Termination
FKRP	Fukutin-related Protein Gene
FVC	Forced Vital Capacity
HR	Heart Rate
INQoL	Individualized Neuromuscular Quality of Life
IRT	Interactive Response Technology
LGMD21	Limb-Girdle Muscular Dystrophy 2I
MedDRA	Medical Dictionary of Regulated Activities
MEP	Maximal Expiratory Pressure
MIP	Maximal Inspiratory Pressure
MRI	Magnetic Resonance Imaging
NHANES III	Third Unites States National Health and Nutrition Examination Survey
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event(s)
WHO	World Health Organization

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1 INTRODUCTION

This document details the planned statistical analyses for the PTC Therapeutics, Inc. protocol "PTCEMF-GD-004" study titled "A Multicenter Open Label Study on the Safety and Efficacy of Deflazacort (Emflaza®) in Subjects with Limb-Girdle Muscular Dystrophy 2I (LGMD2I)". The proposed analyses are based on the contents of protocol version 4.0 (dated 25-March-2020).

Prior to protocol version 4.0, eligible subjects were 1:1 randomized to receive either 0.6 mg/kg/day deflazacort or matching placebo.

In protocol version 4.0, the study design was changed from a double-blinded parallel study to a single arm, open label study to evaluate the efficacy and safety of deflazacort in subjects with LGMD2I. Subjects, ≥18 years old, with LGMD2I will be enrolled in the study. Most subjects enrolled will have a screening visit and 3 additional visits (after 1, 13, and 26 weeks of treatment) and a follow-up visit (Figure 1).

Subjects that complete the screening period assessments and meet all inclusion/exclusion criteria will be enrolled at Visit 1 (baseline Visit) to a target dose of 0.6 mg/kg/day oral deflazacort.

After 26 weeks of treatment (Visit 3/5/ET), safety, efficacy, and MRI will be evaluated. At the end of the study, subjects have the following 3 options: 1) taper off deflazacort; 2) in conversation with their healthcare provider, they could switch to a commercially available version of deflazacort; or 3) in conversation with their healthcare provider, they could switch to another commercially available corticosteroid.

The follow-up visit will be a phone call about 4 weeks after the final clinic visit for subjects that complete the study and immediately start receiving commercial deflazacort or switch to another corticosteroid. The follow-up will be an office visit for subjects that are tapering off deflazacort to return study drug and for site collection of any AEs and will occur approximately 4 weeks after the final dose of deflazacort.

Subjects enrolled (and randomized to study drug) under Protocol Version 3.0 will be transitioned to Version 4.0. The sponsor will unblind the study and provide the principal investigator with a listing of their subjects' treatment assignments. The transition will proceed as follows:

Subjects Randomized to Placebo **Prior to** 01 February 2020	Subjects will have the option to be consented under Version 4.0 and immediately accelerated to the Week 26 visit and begin the open label study.
Subjects Randomized to Deflazacort **Prior to** 01 February 2020	Subjects will return to the clinic at their scheduled Week 26 Visit under Version 3.0. At the Week 26 visit, the subject will undergo Week 26 procedures and have the option to re-consent under Protocol Version 4.0 and continue for an additional 26 weeks in the open label period.
Subjects Randomized to Placebo **AFTER** 01 February 2020	Subjects will have the option to be consented under Protocol Version 4.0 and begin at the Week 26 Visit (Open-label period).
Subjects Randomized to Deflazacort **AFTER** 01 February 2020	Subjects will have the option to be consented under Protocol Version 4.0 at their Week 13 Visit. These subjects will be provided the option to re-consent to the study under Protocol Version 4.0 at Week 13 and continue until Week 26. After Week 26, the subjects will be ineligible to continue for the additional 26 weeks of open label treatment.
New subjects enrolled until 31 May 2020	Subjects will have the option to be consented under Protocol Version 4.0 and perform Baseline through Week 26 visit procedures. These subjects will be assigned deflazacort in an open-label fashion. After Week 26, the subjects will be ineligible for the additional 26 weeks of the trial.

On 23rd July 2020, a PTC corporate decision was made to terminate the study early due to the slow recruitment and company's strategy change. This decision is not related to the safety or efficacy of the study drug. Due to the early termination, only 11 subjects were enrolled in this study.

Figure 1: Timing of assessments

Study Procedure	Screening[1]	Visit 1[2]	Safety Call	Visit 2	Visit 3[3]	Safety Call	Visit 4	Visit 5/ET[4]	Follow-up[5]	NOTES
Week (visit window)	-6 to -1 Weeks	Baseline / Week 1	Week 3 (±1 weeks)	Week 13 (±2 weeks)	Week 26 (±2 weeks)	Week 28 (±2 weeks)	Week 39 (±2 weeks)	Week 52 (±2 weeks)		
Informed Consent	X									A signed and dated informed consent must be obtained before conducting any study procedures.
Inclusion/Exclusion	X	X								
Medical/Surgical History	X	X								
Demographics	X									
FKRP Genotyping	X									Samples will be collected for sequencing of the FKRP gene to confirm the presence of a mutation. Genetic testing for FKRP will not be performed if documentation of genetic diagnosis is available at screening.
Enrollment		X								The site will conduct initial subject registration in the IRT system at Screening. At Visit 1 (baseline), eligible subjects will be assigned dose via the IRT system.
Physical Exam	X	X		X	X		X	X		
Clinical Labs (Hematology[6] and Chemistry[7])	X	X		X	X		X	X		Fasting approximately 8 hours prior to assessments.
Pregnancy Test[8]	X	X		X	X		X	X		All urine pregnancy tests taken at site will be confirmed by serum HCG. The urine pregnancy test must be negative prior to dispensation of study drug.
Height/Weight/BMI	X	X		X	X		X	X		For study inclusion, weight range must be ≥35 to ≤112.5 kg
Vitals (HR & BP)	X	X		X	X		X	X		
ECG	X			X	X			X		
Echocardiogram	X									Echocardiograms obtained within 3 months of enrollment are sufficient to obviate the screening echocardiogram.
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	

Study Procedure	Screening[1]	Visit 1[2]	Safety Call	Visit 2	Visit 3[3]	Safety Call	Visit 4	Visit 5/ET[4]	Follow-up[5]	NOTES
Week (visit window)	-6 to -1 Weeks	Baseline / Week 1	Week 3 (±1 weeks)	Week 13 (±2 weeks)	Week 26 (±2 weeks)	Week 28 (±2 weeks)	Week 39 (±2 weeks)	Week 52 (±2 weeks)		
Concomitant Medications	X	X	X	X	X	X	X	X	X	Concomitant medications information will need to be collected starting 30 days prior to first dose of study drug.
Ophthalmic Exam[9]		X			X			X		Ophthalmic exams may be scheduled within 45 days of scheduled visit to accommodate scheduling restrictions.
Lateral Spine X-ray[10]		X			X			X		
DEXA[10]		X			X			X		
Columbia Suicide Rating Scale	X	X		X	X		X	X		
PK Blood Sampling[11]		X		X						PK samples will be drawn at Visit 1 and Visit 2 (steady state) for pharmacokinetic evaluation. The following PK parameters if possible, will be calculated using noncompartmental analysis method: $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}, T_{max}, CL/F, Vz/F, λz, and $t_{½}$. Samples will be drawn at pre-dose, and 0.5, 1, 2, 4, and 6 hours post-dose at baseline and Week 13 visits.
Timed Function Tests[12]	X	X		X	X		X	X		Timed function tests will be recorded and assessed centrally in addition to the site's clinical evaluator's assessment at the visit. Timed function tests include time to up and go, time to descend 4 stairs, time to climb 4 stairs, time to run/walk 10 meters, and 2-minute walk test. Conduct details will be summarized in a manual separate from this protocol.
Hand Held Myometry[12]		X		X	X		X	X		

Study Procedure	Screening[1]	Visit 1[2]	Safety Call	Visit 2	Visit 3[3]	Safety Call	Visit 4	Visit 5/ET[4]	Follow-up[5]	NOTES
Week (visit window)	**-6 to -1 Weeks**	**Baseline / Week 1**	**Week 3** (±1 weeks)	**Week 13** (±2 weeks)	**Week 26** (±2 weeks)	**Week 28** (±2 weeks)	**Week 39** (±2 weeks)	**Week 52** (±2 weeks)		
Pulmonary Function Testing[12]		X			X		X	X		Pulmonary function will be evaluated by spirometry. Pulmonary function test procedures will be detailed in a manual separate from this protocol. The following pulmonary function tests will be evaluated: FVC, MIP, and MEP.
Biomarker testing (Bone Health Assays)[13]		X		X	X			X		
INQoL Questionnaire[14]		X			X			X		
MRI[12,15]		X		X	X			X		Dixon MRI and T2 MRI will evaluate muscular fat fraction and inflammation, respectively, of selected lower limb muscles. Details will be further elucidated in an MRI manual separate from this protocol.
Study Drug Administration										
Dispense Drug via IRT		X		X	X		X			
Unused Drug Return/ Compliance				X	X		X	X	X[5]	

Abbreviations: AE, adverse event; BP, blood pressure; BMI, body mass index; DEXA; dual-energy X-ray absorptiometry; ECG, electrocardiogram; ET, early termination; FKRP, fukutin-related protein gene; FVC, forced vital capacity; HCG; human chorionic gonadotropin; HR, heart rate; INQoL, Individualized Neuromuscular Quality of Life; IRT, Interactive Response Technology; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MRI, magnetic resonance imaging; PD, pharmacodynamic; PK, pharmacokinetic; SAE, serious adverse event

Note: See also Section 3.4 for explanation of the transition from Protocol Version 3.0 to Version 4.0.

1 Screening procedures must take place within 42 days of baseline visit (Visit 1). No study-related procedures should be performed prior to the signature of the informed consent document(s).

2 Any screening procedure completed within and including 7 days of Visit 1, with the exception of the time to climb 4 stairs, can serve as baseline and does not need to be repeated at Visit 1. The time to climb 4 stairs must always be performed twice at the baseline visit and all other visits. The second 4 stair climb test should be done a minimum of 5 minutes after the prior test, or any other physical activity. The baseline visit may be split into two consecutive days.

3 At Visit 3, subjects initially randomized to deflazacort will continue deflazacort treatment while subjects originally randomized to placebo will initiate deflazacort treatment at a target dose of 0.6 mg/kg/day. For placebo subjects, all assessments will be performed prior to first dose of deflazacort (See also Section 3.4 for explanation of the transition from Protocol Version 3.0 to Version 4.0).

[4] At Visit 5/ET, subjects/Investigators who elect to discontinue corticosteroid therapy altogether will need to taper off deflazacort. If it is determined by the Investigator that any subject will discontinue the study, all early termination visit procedures should be completed and the final visit should be captured as early termination (ET) in an electronic case report form (eCRF). If it is determined that a subject will discontinue the study in between visits, the subject should return at earliest convenience for an early termination visit, following completion of any required study medication assessments. For subjects who terminated early/ discontinued from the study and are tapering off deflazacort, a follow-up visit will occur approximately 4 weeks after the final study drug dose. In case of discontinuation due to an AE, the AE should be followed up by the investigator until it is resolved, or the investigator assesses it as chronic or stable.

[5] The follow-up visit will be a phone call approximately 4 weeks after Visit 5 for subjects that complete the study and immediately start receiving commercial deflazacort or another corticosteroid. The follow-up will be an office visit for subjects that are tapering off deflazacort to return study drug and for site collection of any AEs and will occur 4-weeks after last dose of study drug.

[6] Hematology assessments include hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration, mean platelet volume, red blood cell distribution width, neutrophils (% and absolute), total lymphocytes (% and absolute), monocytes (% and absolute), eosinophils (% and absolute), basophils (% and absolute), and platelets.

[7] Chemistry assessments include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (urea), creatinine, uric acid, protein (total), albumin, bilirubin (total), aspartate transaminase, alanine transaminase, gamma glutamyl transpeptidase, alkaline phosphatase, lactase dehydrogenase, glucose (fasting), hemoglobin A1c, calcium, phosphate, magnesium, creatine kinase, cholesterol, high density lipoproteins, low density lipoproteins (calculated), and triglycerides.

[8] Only for women of child-bearing potential.

[9] Ophthalmological examination includes a glaucoma assessment, cataract assessment, and intraocular pressure measurement.

[10] If possible, both X-ray and DEXA should be performed; however, only an X-ray or DEXA is acceptable if the other technology is not available or prohibited per local ethical/regulatory decree.

[11] The pre-dose blood draw will be taken within 2 hours before dosing. For timepoints up to 2-hours post dose, a window of ± 10 minute will be allowed for blood collection. From 4 hours to 6 hours post samples, a window of ± 30 minutes will be allowed.

[12] Efficacy and PD assessments will be performed post-daily-dose at each clinic visit, except for the baseline visit (Visit 1). At screening and baseline visits, the ability to ascend 4 stairs must be ≥2.5 and ≤8 seconds. In addition, the 4-stair climb will be performed twice at each visit. The second test should be done a minimum of 5 minutes after the prior test (or any other physical activity). The two 4-stair climb results must be within 20% of one another. If they are not the Medical Monitor should be contacted.

[13] Biomarker testing (bone health assays) include bone alkaline phosphatase (BAP), Beta-CrossLaps (Beta-CTx), insulin-like growth factor-1 (IGF1), parathyroid hormone (PTH) intact, aldosterone, and vitamin D (Serum 25-hydroxyvitamin D3).

[14] INQoL will be performed before the first dose at baseline and after 26 weeks of treatment, when possible.

[15] Dixon MRI and T2 MRI will be conducted at a subset of sites that have been pre-qualified by a central imaging vendor to perform this assessment. To be pre-qualified, a site must have access to whole-body scanner and appropriate personnel and must have been trained on the procedure for data acquisition. MRI data will be analyzed centrally.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of deflazacort as measured by muscle function in subjects with Limb-Girdle Muscular Dystrophy Type 2I (LGMD2I).

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the effects of deflazacort on pulmonary function in subjects with LGMD2I.
- To evaluate the pharmacokinetic (PK) profile of deflazacort in subjects with LGMD2I.
- To evaluate safety of deflazacort in subjects with LGMD2I.

2.3 Exploratory Objectives

The exploratory objectives are

- To evaluate the predictive value of global T2 MRI as a measure of efficacy of deflazacort in subjects with LGMD2I.
- To evaluate quality of life by the Individualized Neuromuscular Quality of Life (INQoL) questionnaire in subjects with LGMD2I

3 ENDPOINTS

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in time to climb 4 stairs for subjects with LGMD2I after 26 weeks of treatment for subjects who received at least one dose of deflazacort.

3.2 Secondary Efficacy Endpoints

The secondary endpoints are

- Change from baseline in forced vital capacity (FVC) after 26 weeks of treatment
- Change from baseline in 2-minute walk test after 26 weeks of treatment
- Change from baseline in time to up and go after 26 weeks of treatment

- Change from baseline to time to descent 4 stairs after 26 weeks of treatment
- Change from baseline in time to run/walk 10 meters after 26 weeks of treatment
- Change from baseline in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) after 26 weeks of treatment
- Change from baseline in hand-held myometry after 26 weeks of treatment
- Change from baseline in global T2 relaxation time of selected upper and lower limb muscles after 26 weeks of treatment

3.3 Exploratory Efficacy Endpoints

- Change from baseline in muscular fat using Dixon magnetic resonance imaging of selected lower limb muscles after 26 weeks of treatment
- Change from baseline in the INQoL questionnaire in subjects with LGMD2I after 26 weeks of treatment

3.4 Safety Endpoints

Safety profile characterized by type frequency, severity, timing, and relationship to study drug of any adverse events, laboratory abnormalities, electrocardiogram (ECG) abnormalities, ophthalmologic abnormalities, dual-energy X-ray absorptiometry (DEXA) to evaluate bone density and/ or X-ray to assess spine fracture.

3.5 Pharmacokinetic Endpoints

Pharmacokinetic assessments at baseline and after 13 weeks of treatment. PK analyses will be discussed in a separate SAP.

4 SAMPLE SIZE

This is a single arm, open label study to evaluate the efficacy and safety of deflazacort in subjects with LGMD2I. The primary endpoint is the change in 4-stair climb in seconds after 26 weeks of treatment.

Sample size is based on assuming the deflazacort can prevent subjects' further progression within 6 months i.e. the mean change of 4-stair climb after 26 weeks of treatment is 0 second and the standard deviation of the change is 0.7, with a total of 30 subjects, the 95% confidence will be from -0.25 to 0.25 seconds.

5 RANDOMIZATION

Subjects enrolled under protocol v3.0 were 1:1 randomized to get placebo or deflazacort. After protocol v4.0, the study became an open label study and all subjects received deflazacort.

6 STATISTICAL ANALYSES

Subjects will be pooled in all efficacy and safety analyses regardless of the protocol version they enrolled. No summary tables will be provided for the events or assessments occurred during the placebo period for subjects who enrolled prior to protocol version 4.0 and randomized to placebo group. All events or assessments occurred during the placebo period will be presented in the by-subject listings only.

Subjects who took at least one dose of deflazacort will be pooled in the safety and efficacy summaries. Safety and efficacy listings will be provided including the events and measurements occurred during placebo period.

6.1 Analysis Populations

Subjects excluded from the analysis sets and the reason for their exclusion will be presented in the by-subject listings only.

6.1.1 Enrolled Population

The Enrolled population includes all informed-consented subjects who meet all inclusion and exclusion criteria.

6.1.2 Full / Safety Population

The Full and Safety Populations consist of all enrolled subjects who received at least one dose of deflazacort.

6.1.3 Pharmacokinetic Population

The pharmacokinetic (PK) population includes all enrolled subjects who received at least 1 dose of deflazacort and had at least one PK profile.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Age

Age at time of informed consent as collected on the CRF will be used to represent age of subject in the study.

6.2.2 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

6.2.3 Baseline

Baseline is defined as the last non-missing observation (either scheduled, unscheduled, or repeated) prior to the first dose of deflazacort.

The time to climb 4 stairs: it is performed twice at each visit. The maximum value prior to the first dose of deflazacort will be considered as baseline.

6.2.4 Data handling

The details for data handling will be provided in Appendix 1. Calculation of duration, imputation of missing or partial start and stop dates of adverse events and concomitant medications and handling of inexact values are described.

6.2.5 Individualized Neuromuscular Quality of Life (INQoL)

The calculation of the INQoL questionnaire scores is detailed in Appendix 2.

6.2.6 Study Visits

Nominal visits will be used as the analysis visits for subjects who were randomized to deflazacort under protocol version 3.0 or enrolled under protocol version 4.0.

For subjects who were randomized to placebo under protocol version 3.0 and then reconsented to receive deflazacort under protocol version 4.0, the nominal visits will be remapped to have the start of the open label visit as the first analysis visit. For example:

Nominal visit for placebo subjects	Analysis visit
V1	
V2	
V3 (Start of open label)	V1
V4	V2

V5	V3
…	…

All summaries will be based on analysis visits. Assessment taken under unscheduled visits or nominal visits during the placebo period for subjects who randomized to placebo group will be presented in the subject listings only.

6.2.7 Change from Baseline

Change from baseline for any variable at a given visit will be calculated by subtracting the baseline value (last non-missing scheduled, unscheduled or repeat value before the first dose of deflazacort) of the variable from the value of the variable at the given visit. If there is no baseline or screening value, then the change from baseline will be missing.

6.3 Conventions

All data listings, summaries, figures, and statistical analyses will be generated using SAS version 9.4 or higher[1].

Summary displays based on the Enrolled Population will have Overall as the column header. In all summary tables, all subjects who received at least one dose of deflazacort will be pooled regardless of the protocol versions they were enrolled, and the treatment column will be displayed as Deflazacort. Deflazacort treated subjects will be pooled in all safety summaries across all deflazacort treated periods.

The following defined study period will be presented in the by-subject listings only:

- Placebo period: The observations before entering to open label for subjects randomized to placebo under protocol version 3.0.

Listings will be sorted in the following order parameter, subject and visit (sorted in chronological order – earliest to latest) unless otherwise stated. The appropriate study period will be included in the listings.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. For the primary and secondary efficacy endpoints, the lower and upper 95% confidence limits for the mean will be provided.

Categorical variables will be summarized by percentage and frequency counts. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown.

6.3.1 Decimal Places

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) 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 raw data. Percentages will be displayed with one decimal place.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects, who entered the study under protocol v3.0, who entered the study under protocol v4.0, who entered the open label, were randomized under protocol v3.0, who were transitioned to the open label by previous treatment received and overall, who received at least 1 dose of study drug and who are in each analysis set will be summarized for the Enrolled Population.
- The number of subjects screened, and the number of subjects who had screening failed. The number of subjects who prematurely discontinued study drug and the discontinuation reason will be tabulated for the Safety Population.

6.5 Protocol Deviations

Protocol deviations including those related to COVID-19 will be presented in the subject listings only.

6.6 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be summarized for the Safety Population. Demographic data, age in years at informed consent, sex, race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White), as well as height in cm, weight in kg, body mass index (BMI) in kg/m^2 at screening and duration of clinical symptom and left ventricular ejection fraction (%) from Echocardiogram and FKRP Genotyping will be summarized. Where patients have checked more than one box for race, they will be presented in the demography summary as “Multiple Race”. The listing will document all selected races.

6.7 Medical History

Medical history conditions will be presented for the Safety Population. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA, version 23.1) primary system organ class and preferred term.

Medical history will be presented in the by-subject listings only.

6.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHODrug Global B3 version Sep 2020) into Anatomical-Therapeutic-Chemical (ATC) classification codes.

Medications will be classified as prior medications, and/or concomitant medications. Any medication used prior to the first dose of deflazacort will be classified as prior medication and those used on or after first dose of deflazacort date until the date of last dose of deflazacort will be classified as concomitant medications. Medications used prior to the first dose and continued during deflazacort treatment will be considered as both prior and concomitant medication.

Prior and concomitant medications will be presented in the by-subject listings only.

6.9 Exposure to Study Drug

Deflazacort treatment duration (days) is defined as the date of last deflazacort dose before tapering – the date of first deflazacort dose +1. The deflazacort treatment duration will not consider breaks in therapy.

Exposure will be summarized in all deflazacort treated subjects across all deflazacort treated periods using Safety Population.

Placebo treatment duration (days) is defined as the date of last placebo dose – the date of first placebo dose +1. Placebo treatment duration will only be presented in the by-subject listings.

6.10 Efficacy Analyses

All efficacy analyses of data will be performed using the Full Population. All data will be summarized at scheduled visits. All data, including unscheduled visit data, will be presented in the by-subject listings.

Efficacy will be summarized by visit for the period treated with deflazacort.

The data collected before start of deflazacort for subjects receiving placebo under protocol version 3.0 will be included in the by-subject listings only.

6.10.1 Analysis of Primary Endpoint

The actual value and the change from baseline in 4-stair climb time, measured in seconds will be summarized descriptively (number of non-missing observations (n), mean, standard deviation, minimum, median, and maximum) at each assessment visit for the Full Population. The time to climb 4 stairs is performed twice at each visit. The maximum value at each visit will be used for summary and analysis purposes.

In addition, the 95% confidence interval for the mean change from baseline after 26 weeks of deflazacort treatment will be provided.

A waterfall plot of the change in 4- stair climb time at Week 26 will be provided.

6.10.2 Analysis of Secondary Endpoints

The following secondary endpoints will be summarized similar to the primary endpoint by study visits for the actual value and the change from baseline.

- Forced vital capacity (FVC)
- 2-minute walk test
- Time to up and go
- Time to descent 4 stairs
- Time to run/walk 10 meters
- Maximal inspiratory pressure (MIP)
- Maximal expiratory pressure (MEP)
- Hand-held myometry

For all endpoints with repeated measurements, the maximum value at each visit will be used for summary and analysis purposes.

Similar as the primary endpoint, summary statistics such as n, mean, standard deviation, median, minimum and maximum, and the 95% confidence interval for the mean change at Week 26 will be provided for all secondary endpoints.

6.10.3 Exploratory Analysis

INQoL questionnaire results will be presented in the by-subject listing only.

6.11 Pharmacokinetic Analyses

PK analyses will be discussed in a separate SAP.

6.12 Safety Analyses

The safety analyses will be presented for the Safety Population.

The adverse events and other safety summaries will be reported across all deflazacort treated periods. The adverse events occurred during placebo period for subject randomized to placebo under protocol version 3.0 will not be summarized and will only be included in by-subject listings.

6.12.1 Adverse Events

Adverse events (AEs) will be classified as pre-treatment adverse event, treatment-emergent adverse event (TEAE) and post-treatment adverse event. Pre-treatment AE is defined as the AE occurring prior to the start of the deflazacort treatment.

TEAE is defined as the AE occurring or worsening on or after the first deflazacort dose and up to 30 days after the last deflazacort dose. Post-treatment AE is defined as the AE occurring after 30 days of the last deflazacort dose.

If a subject experience the same preferred term multiple times, the event will be counted only once and by the greatest severity.

TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1).

A treatment-related AE is defined as an AE as being possibly or probably related to the study drug. If an AE has a missing relationship it is assumed to be related to the study drug for analysis purposes.

An overall TEAE summary table will be provided with following information:

- The number of subjects with at least one TEAE
- The number of subjects with at least one treatment related TEAE
- The number of subjects with at least one Grade 3 or Grade 4 TEAE
- The number of subjects with a Grade 5 TEAE (Fatal)
- The number of subjects with at least one SAE
- The number of subjects with at least one TEAE leading to treatment discontinuation

- The number of subjects with at least one TEAE leading to dose reduction or interruption

In addition, the All TEAE by SOC and PT summary tables will be provided.

Detailed listings by subject of all AEs (pre-treatment AEs, TEAEs, related TEAEs, serious TEAEs, TEAEs leading to early termination of the study and TEAEs leading to death) will be provided. In addition, listings of SAE, treatment related TEAE, TEAE leading to treatment discontinuation, TEAE leading to dose reduction/interruption, and Grade 3/4/5 TEAEs will be provided as well.

6.12.2 Laboratory Data

Listings of clinical laboratory data with abnormal flags will be provided by subject, visit, and laboratory parameters. In addition, clinically significant laboratory measurements recorded throughout the study and serum pregnancy results will also be presented in the by subject listing.

6.12.3 Vital Signs

Assessments of vital signs including height, weight, BMI, diastolic blood pressure, pulse rate and systolic blood pressure will be presented in the by-subject listings only.

6.12.4 Electrocardiogram Data

ECG parameter results including overall interpretation, heart rate, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval and RR interval will be presented in the by-subject listings only.

6.12.5 Physical Examination

Physical examination results will be presented in the by-subject listing only.

6.12.6 Ophthalmology Examination

Ophthalmology Examination results will be presented in the by-subject listings only.

6.12.7 Bone Density

Bone density as assessed by dual-energy X-ray absorptiometry (DEXA) will be summarized with raw scores and normalized scores for total hip bone mineral density (BMD), total body BMD and lumbar spine BMD. The normalized scores will be calculated based on Third United States National Health and Nutrition Examination Survey (NHANES III[3]) data and adjusted by gender.

First, the means and the standard deviations (SDs) will be calculated for each gender using NHANES III DEXA data as the reference means and SDs. Then the normalized z-score[2] will be derived using the following formula:

$$\text{Normalized score} = \frac{\text{Measured BMD} - \text{Mean BMD of gender matched reference group}}{\text{SD of gender matched reference group}}$$

Raw scores, normalized scores, and change from baseline in raw scores and normalized scores will be summarized by analysis visits.

Since not all subjects will have DEXA or X-ray assessed due to the availability or the local ethical regulation, the summary tables of DEXA or X-ray will be based on the Safety Population who had performed the assessments.

7 INTERIM ANALYSIS

No interim analyses are planned for this study.

8 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

Due to the early termination of the study (decision made 23rd July 2020), only 11 subjects were enrolled in the study with limited information. Medical History, Concomitant medications, Exploratory Efficacy Endpoints (except fat fraction), Laboratory results, Vital Signs, ECG, Physical Examination and Ophthalmology examination information will be presented only in listings instead of summary tables. In addition, Dixon MRI and T2 MRI endpoints is not collected and will not be summarized or listed.

10 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. Carey JJ, Delaney MF. T-Scores and Z-scores. In: Clinical Reviews in Bone and Mineral Metabolism, 10 November 2009. p.113-121
3. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [Accessed: 20 August 2020][https://wwwn.cdc.gov/Nchs/Nhanes/Dxa/Dxa.aspx]

11 APPENDIX 1: DATA HANDLING

Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of deflazacort.

- date of event – date of first dose of deflzacort + 1, for events on or after first dose
- date of event – date of first dose of deflazacort, for events before first dose

Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

Missing / Partial Start / Stop Date of Adverse Events (AE) and Concomitant Medications

Generally, if the adverse event (AE) or medication stop date is completely missing, no imputation will be done. AE will be considered as treatment emergent adverse event (TEAE) and medication will be considered as concomitant.

Missing and partial start and stop dates will be imputed for analysis purposes as follows.

Partial or missing start date will be imputed as follows:

- Missing day only
  - If the month and year are the same as the year and month of the first deflazacort date, then the first dosing date will be assigned to the missing field.
  - If the partial date (year and month) is prior to the first deflazacort date (year and month), then the last day of the month will be assigned to the missing field.
  - If the partial date (year and months) is after the first deflazacort date (year and month), then the first day of the month will be assigned to the missing field.
- Missing month only
  - The day will be treated as missing and both month and day will be imputed according to the imputations rules for missing day and month.
- Missing day and month

  - If the year is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing field.
  - If the year is prior to the year of the first dosing date, then December 31 will be assigned to the missing field.
  - If the year is after the year of the first dosing date, then January 1st will be assigned to the missing field.
- Missing year
  - No Imputation will be done.
  - The AE will be considered as TEAE if the end date is missing or after the first dosing date.
  - The medication will be considered as both prior and concomitant if the end date is missing or after the first dosing date.

If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by stop date.

Partial or missing stop date will be imputed as follows:

- Missing day only
  - If the month and year are the same as the year and month of the last deflazacort date, then the last dosing date will be assigned to the missing field.
  - If the partial date (year and month) is prior to the last deflazacort date (year and month), then the last day of the month will be assigned to the missing field.
  - If the partial date (year and months) is after the last deflazacort date (year and month), then the first day of the month will be assigned to the missing field.
- Missing month only
  - The day will be treated as missing and both month and day will be imputed according to the imputations rules for missing day and month.
- Missing day and month
  - If the year is the same as the year of the last dosing date, then the last dosing date will be assigned to the missing field.
  - If the year is prior to the year of the last dosing date, then December 31 will be assigned to the missing field.

  - If the year is after the year of the last dosing date, then January 1st will be assigned to the missing field.

- Missing year
  - No Imputation will be done.
  - If both start and stop date of an AE are missing, the AE will be considered as TEAE
  - If both start and stop date of a medication are missing, the medication will be considered as both prior and concomitant medication.

If the start date is non-missing and the imputed stop date is before the start date, the stop date will be imputed by start date.

Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

12 APPENDIX 2: SUBSCALE SCORES AND TOTAL SCORES FOR INQOL QUESTIONNAIRE

Subscale scores and total scores for INQoL questionnaire will be calculated with the following rules.

Dimensions	Subscales	Number of Items	Cluster of Items
Section 1: Symptoms	Weakness	3	1 a, b, c
	Pain	3	2 a, b, c
	Feeling Tired	3	3 a, b, c
	Locking	3	4 a, b, c
	Droopy eyelids	3	5 a, b, c
	Double vision	3	6 a, b, c
	Swallowing	3	7 a, b, c
Section 2: Life domains	Activities	5	1 AI, II, III 1 BI, II
	Independence	3	2 A, 2 BI, 2 BII
	Social relationship	10	3 AI, II, III, IV 3 BI, II, III, IV, V, VI
	Emotions	6	4 AI, II, III, IV 4 BI, II
	Body image	3	5 A, 5 BI, II
Section 3: Treatment Effects	Perceived treatment effects	3	1 AI, III 1 BI, III
	Expected treatment effects	3	1 AII, III 1 BII, III
Quality of life		14	Items from section B for questions on section 2.

Calculating individual scores:

1. **Weakness score** = (a+b+c) / 19 X 100

2. **Pain score** = (a+b+c) / 19 X 100
3. **Feeling tired score** = (a+b+c) / 19 X 100
4. **Muscle locking score** = (a+b+c) / 19 X 100
5. **Droopy eyelids score** = (a+b+c) / 19 X 100
6. **Double vision score** = (a+b+c) / 19 X 100
7. **Swallowing score** = (a+b+c) / 19 X 100
8. **Activities score** = [4 X (AI+AII+AIII)] + [3 X (BI+BII)] / 108 X 100

   If not working due to condition item -> AIII=6

   If retired/unemployed/work in home (not as a result of condition)

   -> [6 X (AI+AII)] + [3 X (BI+BII)] / 108 X 100
9. **Independence score** = [12 X A] + [3 X (BI+BII)] / 108 X 100
10. **Social relationships** = [3 X (AI+AII+AIII+AIV)] + [BI+II+III+IV+V+VI] / 108 X 100

    If partner/spouse item (AI) not applicable:

    -> [4 X (AII+AIII+AIV)] + [BI+II+III+IV+V+VI] / 108 X 100
11. **Emotions score** = [3 X (AI+AII+AIII+AIV)] + [3 X (BI+BII)] / 108 X 100
12. **Body Image score** = [12 X (A)] + [3 X (BI+BII)] / 108 X 100
13. **Perceived treatment effect score =**[(AI+AIII)-(BI+BIII)]/12 X 100
14. **Expected treatment effect score =**[(AII+AIII)-(BII+BIII)]/12 X 100
15. **Qol score**: Add scores of items in section B for questions on section 2 (with correction i.e. 3X (BI + B2) for Quns 1,2,4&5 and BI+II+III+IV+V+VI for Qun 3), divide total score by 180 and multiply by 100 (to achieve percentage score)

Handling missing observations:

<u>Section 1:</u>

Q1-7

1A-4A If missing and rest of symptom qun missing (i.e. part B) -> score zero

1B-4B a. If missing, score "1"

b. If missing, impute previous value (part a)

c. If missing, score "0"

Section 2:

Q1

1 A. If an item missing, sum completed items, and multiply by 6 if two items completed and 12 if only one item has been completed (to get score out of 72)

(N.B. "Work activities" item: if not working due to condition score "6" and count as a completed item).

EXAMPLE: If "Leisure activities" is missing, add values of "Daily activities" & "Work Activities". Multiply this by 6.

BI. If missing, impute average of completed "activities" items (from 5A)

BII. If missing, score as "0"

Q2

2 A. if missing, score as "0"

BI. If missing, impute value from 2A

BII. If missing, score as "0"

Q3

3 A. If item missing, sum the completed items and multiply by 4 if three completed items, 6 if two completed items & 12 if one completed item

BI. If missing, impute average of 3a items

i) Relationship with spouse/partner &

ii) Relationship with other family members

BII. If missing, score as "0"

BIII. If missing, impute value from "Friends" (3AII) item

BIV. If missing, score as "0"

BV. If missing, impute value from "Other people" (3AIV) item

BVI. If missing, score as "0"

Q4

4 A. If item missing, sum the completed items and multiply by 4 if three completed items, 6 if two completed items and 12 if one completed item

BI. If missing, impute average of items completed in 4A

BII. If missing, score as "0"

Q5

A. If missing, score as "0"

BI. If missing, impute value from 5A

BII. If missing, score as "0"

Section 3:

Q1

1A I. If missing, score as "0"

II. If missing, score as "0"

III. If missing, score as "0"

1B I. If missing, score as "0"

II. If missing, score as "0"

III. If missing, score as "0"

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