NCT #NCT03783923

CLINICAL PROTOCOL

A MULTICENTER OPEN LABEL STUDY ON THE SAFETY AND EFFICACY OF DEFLAZACORT (EMFLAZA®) IN SUBJECTS WITH LIMB-GIRDLE MUSCULAR DYSTROPHY 2I (LGMD2I)

PTCEMF-GD-004

25 MARCH 2020

VERSION 4.0

PTC THERAPEUTICS, INC.

100 CORPORATE COURT

SOUTH PLAINFIELD, NJ 07080 USA

SYNOPSIS

Study Number:	PTCEMF-GD-004
Name of Investigation Product:	Deflazacort (Emflaza)
Study Title:	A Multicenter Open Label Study on the Safety and Efficacy of Deflazacort (Emflaza®) in Subjects with Limb-Girdle Muscular Dystrophy 2I (LGMD2I)
Proposed Indication	Limb-Girdle Muscular Dystrophy Type 2I
Number of Study Sites:	Approximately 5
Phase of Trial:	N/A
Study Objectives:	***Primary Study Objective*** • To evaluate the efficacy of deflazacort as measured by muscle function in subjects with Limb-Girdle Muscular Dystrophy Type 2I (LGMD2I) ***Secondary Study Objectives*** • 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 ***Exploratory Objective*** • 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
Study Endpoints	***Primary Efficacy Endpoint(s) and Evaluation(s)*** • Change from baseline in time to climb 4 stairs after 26 weeks of treatment ***Secondary Endpoints and Evaluation(s)*** • Secondary efficacy endpoints o Change from baseline in forced vital capacity (FVC) after 26 weeks of treatment o Change from baseline in 2-minute walk test after 26 weeks of treatment o Change from baseline in time to up and go after 26 weeks of treatment o Change from baseline to time to descend 4 stairs after 26 weeks of treatment o Change from baseline in time to run/walk 10 meters after 26 weeks of treatment o Change from baseline in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) after 26 weeks of treatment o 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 • 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 • Pharmacokinetic assessments at baseline and after 13 weeks of treatment ***Exploratory Endpoints*** • Change from baseline in muscular fat fraction 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
Study Population:	Subjects with LGMD2I; age ≥18 years
Sample Size	Approximately 30 subjects will receive deflazacort
Methodology/Study Design	26-week open-label period in which all subjects will receive deflazacort.
Main Inclusion Criteria	1. Genetic diagnosis of LGMD2I (confirmed mutation in the FKRP gene) 2. Male and female subjects aged ≥18 years 3. Ability to ascend 4 stairs ≥2.5 seconds and be able to complete the ascent and descent at screening and baseline 4. Ability to understand the nature of the study and the consent form and to comply with study related procedures 5. Must weigh ≥35 to ≤112.5 kg
Main Exclusion Criteria	1. Received ≥4 weeks of continuous, systemic corticosteroid therapy within 3 months of the study Screening Visit 2. Presence of significant cardiomyopathy as defined by echocardiogram (left ventricular ejection fraction <30%) at screening 3. Requires fulltime ventilator support 4. History of chronic systemic fungal or viral infections 5. History of recent bacterial infection (including tuberculosis) per discretion of the Investigator 6. Diagnosis of diabetes mellitus (controlled and/or uncontrolled) defined as HbA1c ≥6.5% (based on historical or present diagnosis) 7. History of immunosuppression or other contraindications to glucocorticosteroid therapy 8. Requires concomitant use or >1 week of drugs or substances that are moderate to strong CYP3A4 inhibitors (ie, clarithromycin, fluconazole, diltiazem, verapamil, grapefruit juice) or moderate or strong CYP3A4 inducers (ie, rifampin, efavirenz, carbamazepine, phenytoin) at baseline

	9. Participated in an interventional clinical trial within the last 3 months prior to the baseline visit 10. Unable or unwilling to comply with the contraceptive requirements of the protocol 11. Female subjects who are pregnant and/or breastfeeding 12. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neurologic, psychiatric, or allergic disease
Study Treatment:	• Oral deflazacort (target dose 0.6 mg/kg/day), may be reduced in case of tolerability issues
Duration of Treatment:	26-week open-label
Safety Monitoring	Subjects will be monitored closely for adverse events or laboratory abnormalities, or other safety assessments (ie, height, weight, vital signs, electrocardiograms, and physical examination) during the course of the study. For adverse events (AEs) or laboratory abnormalities, the Investigator should use his/her judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug therapy is appropriate. While specific monitoring, diagnostic testing, and supportive care measures must be instituted based on the clinical judgment of the Investigator, investigators are encouraged to contact the medical monitor to obtain guidance and to ascertain whether similar events are being seen at other sites. The medical monitor should be notified of any adverse event or laboratory abnormality that leads to dose interruption and should be apprised of ancillary laboratory or other diagnostic findings and the evolving data from any work-up of the initial abnormality. The medical monitor may suggest review of the case with gastroenterology, endocrinology, nephrology consultants or with other experts (either at the site or retained by PTC Therapeutics).
Serious Adverse Event Reporting	All serious adverse events (SAEs) should be reported via the SAE report form to PTC Therapeutics within 24 hours of becoming aware of the event(s).
Pharmacokinetic Sampling	Pharmacokinetic sampling will occur at the baseline and Week 13 visits.
Statistical Methods:	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. Summary statistics such as mean, standard deviation, median, minimum and maximum will be provided for the change in 4-stair climb in seconds after 26 weeks of treatment. The 95% confidence interval for the mean will be provided as well. If assuming deflazacort can prevent subjects' further progression within 6 months i.e. the mean change of 4-stair climb after 26 weeks of treatment

	is Zero 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.
Timing of Assessments	See Schedule of Events

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.

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)		
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	
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: $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, 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		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)		
Myometry[12]										
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.

PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

Study Number	PTCEMF-GD-004
Therapeutic Area	Genetic Disorders - Limb-Girdle Muscular Dystrophy Type 2I
PTC Therapeutics Substance Identifier	Deflazacort (Emflaza)
IND Number	142275
EudraCT Number	2018-004740-36
Included in clinical trials.gov Database	NCT03783923
Protocol Number	PTCEMF-GD-004
Protocol Version	4.0
Protocol Version Date	25 March 2020
Protocol Phase	N/A
Protocol Title	A Multicenter Open-Label Study on the Safety and Efficacy of Deflazacort (Emflaza®) in Subjects with Limb-Girdle Muscular Dystrophy 2I (LGMD2I)
PTC Clinical Lead	[redacted] PTC Therapeutics, Inc. 100 Corporate Court South Plainfield, NJ 07080 USA Telephone (office): [redacted] E-mail: [redacted]
PTC Medical Monitor	[redacted] PTC Therapeutics, Inc. 100 Corporate Court South Plainfield, NJ 07080 USA Telephone (office): [redacted] Email: [redacted]
PTC Biostatistician	[redacted] PTC Therapeutics, Inc. 100 Corporate Court South Plainfield, NJ 07080 USA Telephone: [redacted] E-mail: [redacted]
PTC Clinical Operations	[redacted] PTC Therapeutics, Inc. 100 Corporate Court South Plainfield, NJ 07080 USA Telephone: [redacted] Email: [redacted]

PTC THERAPEUTICS PROTOCOL APPROVAL SIGNATURES

[redacted]

Date

PTC Therapeutics, Inc.

[redacted]

Date

PTC Therapeutics, Inc.

[redacted]

Date

PTC Therapeutics, Inc.

[redacted]

Date

PTC Therapeutics, Inc.

PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

I have read the protocol document and, on behalf of my institution, agree to comply with the protocol and all applicable regulations.

Principal Investigator	**Date**

Institution: _____

Address: _____

City: _____

State/Province: _____

Country: _____

Phone: _____

Fax: _____

E-mail: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
21-desDFZ	21-desacetyl deflazacort
6MWD	6-minute walk distance
α-DG	α-dystroglycan
AE	Adverse event
AUC	Area under the concentration curve
BAP	Bone alkaline phosphatase
Beta-CTx	Beta-CrossLaps
CI	Confidence interval
CL/F	Clearance
C_{max}	Maximum concentration
CRF; (eCRF)	Case report form; electronic CRF
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DEXA	dual-energy X-ray absorptiometry
DMD	Duchene muscular dystrophy
ECG	Electrocardiogram
ET	Early termination
FKRP	Fukutin-related protein gene
FDA	Food and Drug Administration
FVC	Forced vital capacity
GCP	Good clinical practice
HbA1c	Hemoglobin A1c
HCG	Human chorionic gonadotropin
HPA	Hypothalamicpituitary-adrenal
ICH	International Council for Harmonization
IEC	Institutional Ethics Committee
IGF1	Insulin-like growth factor-1
INQoL	Individualized Neuromuscular Quality of Life
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent to treat
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LGMD	Limb-girdle muscular dystrophy
LGMD2	Limb-girdle muscular dystrophy type 2
LGMD2I	Limb-girdle muscular dystrophy type 2I
LoA	Loss of ambulation
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximal expiratory pressure
MHC	Major histocompatibility complex
MIP	Maximal inspiratory pressure
MMRM	Mixed-effect model with repeated measures
MRI	Magnetic resonance imaging
PD	Pharamcodynamic
PK	Pharmacokinetic
PT	Preferred term
PTH	Parathyroid hormone
RSI	Reference safety information
SAE	Serious adverse event
SOC	System organ class

Term	Definition
T2	Transverse relaxation time
$T_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
V_z/F	Volume of distribution
WOCBP	Women of child bearing potential
λz	(Time)-1

1 INTRODUCTION

1.1 Background

Initially described as a clinical phenotype, limb-girdle muscular dystrophies (LGMDs) are now recognized as a heterogeneous group of rare genetic myopathies with many subtypes categorized by disease, gene, and inheritance (Khadilkar 2018). The limb-girdle is the bony structure surrounding the shoulder and hip joints. LGMD usually manifests in the proximal muscles (closest to the center of the body) around the hips and shoulders and is characterized by progressive muscle wasting, resulting from replacement of muscle tissue by fibrosis and fat. LGMDs vary in severity and may affect persons at all ages. The LGMDs are classified into 2 main groups depending on the inheritance pattern: LGMD type 1 are autosomal dominant and LGMD type 2 (LGMD2) are autosomal recessive diseases.

LGMD type 2I (LGMD2I) is a subtype of the type 2 LGMD and is caused most frequently by a homozygous founder mutation (826C>A; p L276I) in the fukutin-related protein (FKRP) gene (Brockington 2001, Willis 2014, Wang 2018).

It is difficult to determine the prevalence of LGMD due to its features vary and overlap with those of other muscle disorders. The estimated prevalence of LGMD ranges from 0.07 per 100,000 to 2 per 100,000 individuals (Narayanaswami 2014, Deenen 2015, Mah 2016). LGMD2I may be one of the more common forms of LGMD (Moore 2006, Kang 2007). A small study indicated that about 4% of patients in the United States with LGMD have LGMD2I (Moore 2006). The current population in the United States is about 327,571,179; hence, up to about 400 individuals in the United States have LGMD2I. A higher prevalence of LGMD2I has been reported in northern European countries (Sveen 2006).

Common clinical symptoms of LGMD2I include proximal muscle weakness, calf hypertrophy, elevated serum creatine kinase levels, and cardiac and pulmonary involvement (Wang 2018). The clinical spectrum of LGMD2I is heterogeneous, and includes asymptomatic mutation carriers, a severe early-onset phenotype with loss of ambulation in teens as in Duchenne muscular dystrophy (DMD), and a Becker muscular dystrophy-like course with late-onset age and slow progression (de Paula 2003, Schwartz 2005). Dilated cardiomyopathy and restrictive respiratory insufficiency have been reported frequently in patients with LGMD2I (Poppe 2003, Bourteel 2009). The age at onset of LGMD2I ranged from 2 to 50 years (Boito 2005).

The pathogenesis of FKRP mutations appears primarily to be linked to the absence of glycosylation of α-dystroglycan (α-DG), an extracellular component of the dystrophin glycoprotein complex, resulting in disruption of laminin binding and instability of the dystrophin-glycoprotein complex in skeletal muscle (Brown 2004a). The dystrophin-glycoprotein complex is important for the structural stability of muscle membrane during cycles of contraction and relaxation (Muntoni 2011, Wang 2018). Phenotypic severity of LGMD2I is correlated to the degree of the reduction of α-DG (Brown 2004b).

In patients homozygous for the 826C>A missense mutation, patients generally exhibit milder and late-onset muscular dystrophy, whereas the compound heterozygous 826C>A mutation is associated with more severe and early-onset type of muscular dystrophy phenotypically related to DMD (Sveen 2006, Stensland 2011, Wang 2018). Intrafamilial variability is common and suggests other factors in addition to FKRP mutation may influence phenotype (Boito 2005, Darin 2007).

Current Treatments

No approved pharmacological treatment is currently available for LGMD2I, although aggressive supportive care including physical therapy and cardiac care is considered essential (Narayanaswami 2014).

1.2 Deflazacort (Emflaza)

Deflazacort (Emflaza®) is a corticosteroid used as an anti-inflammatory and immunosuppressive agent. Pharmacologically, it is an inactive ester pro-drug which is metabolized rapidly to the active drug 21-desacetyl-deflazacort (21-desDFZ), which acts through the glucocorticoid receptor to exert its anti-inflammatory and immunosuppressive effects. Deflazacort has an extensive exposure history as an approved drug in many countries outside of the United States. The side effect profile of deflazacort in patients with DMD aged ≥5 years is well characterized and consistent with that of the corticosteroid class of drugs.

On February 9, 2017, deflazacort was approved by the U.S. Food and Drug Administration (FDA) as a treatment for patients aged ≥5 years with DMD and as a treatment for patients ≥2 years with DMD on June 7, 2019 (https://www.emflaza.com/).

PTC Therapeutics has decided to initially investigate the use of deflazacort in LGMD by focusing on its affects in LGMD2I. The choice of LGMD2I was based upon the fact that several case reports have indicated benefit of corticosteroid use in this subtype of LGMD and other muscular dystrophies (Angelini 2007, Darin 2007, Lin 2007, Svahn 2015, Wang 2018). PTC Therapeutics has also taken into consideration advice from clinical experts who treat patients with LGMD, including LGMD2I.

Multiple lines of evidence indicate that the use of deflazacort may show treatment benefit in LGMD2I. Several clinical and preclinical studies found that the immune system is involved in the pathology of LGMD2I and that corticosteroid therapy was associated with clinical benefit (see Section 3.2 for greater description) (Darin 2007, Lin 2007, Svahn 2015, Wang 2018).

1.3 Benefit/Risk Profile

Currently, treatment options for LGMD2I are limited. LGMD2I is a devastating disease and patients with this form of muscular dystrophy are at high risk for developing respiratory failure and cardiomyopathy (Narayanaswami 2014). Respiratory failure constitutes a major comorbidity, interfering with daytime cognitive function and negatively affecting quality of life (Narayanaswami 2014). In addition, ventilatory and oropharyngeal weakness can threaten survival through the risk of upper airway obstruction and/or bellows failure (Narayanaswami 2014).

Deflazacort carries the risks common to all corticosteroids, including immune suppression, decreased bone density, and endocrine insufficiency (see Emflaza® [deflazacort] Prescribing Information).

No definitive therapies are available for LGMD2I, and only a few clinical studies have assessed therapies for the treatment of LGMD2I (Narayanaswami 2014). To date no randomized, controlled clinical studies have been performed that evaluate treatment effect of corticosteroids in this patient population. Several case study reports suggest that corticosteroid therapy may improve the symptoms of the disease and possibly delay disease progression (Darin 2007, Svahn 2015, Wang 2018). In addition, preclinical studies in a LGMD2I mouse model found prednisolone treatment improved muscle pathology with significant reduction in muscle degeneration and enhanced functionality of α-DG (Wu 2016).

Given the limited treatment options to slow the deterioration of muscle function in LGMD2I and findings from preclinical studies and case reports, it is reasonable to consider the use of deflazacort in treating patients with LGMD2I. Moreover, deflazacort has well established efficacy in DMD, and has been shown to delay DMD disease progression in patients (Bello 2015, McDonald 2018). The safety profile of corticosteroids is well established in multiple indications, and safety concerns can be managed through monitoring, including bone health (as assessed by incidence of fracture and dual energy X-ray absorption [DEXA]) scans. Hence, the potential benefits of this study outweigh the potential risks to study subjects.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

1. To evaluate the efficacy of deflazacort as measured by muscle function in subjects with LGMD2I

2.1.2 Secondary Objectives

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

2.1.3 Exploratory Objective

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

2.2 Endpoints

2.2.1 Primary Endpoint

The primary efficacy endpoint is:

1. Change from baseline in time to climb 4 stairs after 26 weeks of treatment

2.2.2 Secondary Endpoints

1. Secondary efficacy endpoints
    a. Change from baseline in forced vital capacity (FVC) after 26 weeks of treatment
    b. Change from baseline in 2-minute walk test after 26 weeks of treatment
    c. Change from baseline in time to up and go after 26 weeks of treatment
    d. Change from baseline to time to descent 4 stairs after 26 weeks of treatment
    e. Change from baseline in time to run/walk 10 meters after 26 weeks of treatment
    f. Change from baseline in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) after 26 weeks of treatment
    g. Change from baseline in hand-held myometry after 26 weeks of treatment
    h. Change from baseline in global T2 relaxation time of selected upper and lower limb muscles after 26 weeks of treatment
2. Safety profile characterized by type, frequency, severity, timing, and relationship to study drug of any adverse events (AEs), laboratory abnormalities, electrocardiogram (ECG) abnormalities, ophthalmologic abnormalities, DEXA to evaluate bone density, and/or X-ray to assess spine fracture
3. Pharmacokinetic assessments at baseline and after 13 weeks of treatment

2.2.3 Exploratory Endpoints

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

3 STUDY DESIGN

3.1 Overall Design

Study PTCEMF-GD-004 is a prospective, open label study designed to evaluate the safety and efficacy of deflazacort in subjects with LGMD2I.

Approximately, 30 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: see section 3.4). A follow-up visit will be a phone call approximately 4 weeks after the final study visit 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. At Week 3, a member of the site staff will follow-up with the subject to assess safety.

At the Screening Visit inclusion/exclusion criteria, demographics and medical/surgical history will be assessed (see Table 6, Schedule of Events for details). In addition, genotyping to confirm a subject carries a mutation in the FKRP gene may be performed for subjects lacking documentation of the FKRP mutation. All subjects must sign an informed consent prior to any study procedures being conducted.

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.

Note: Doses are described as target doses, resulting from the possibility of variation of ±20% from the target dose due to the available tablet strengths and changes in subject weight.

Study medication will be assigned according to the subject's weight. Three weight bands will be utilized and automatically assigned via an Interactive Response Technology (IRT) system. Unless an occurrence of an AE requires otherwise, the investigator is encouraged to maintain the same dose through the first 13 weeks of treatment due to safety or tolerability considerations; the dose can be changed to the next lower weight-band if needed (see Section 6.1.2.1 for weight band chart).

Screening procedures must occur within 6 weeks (42 days) prior to the baseline visit (Visit 1). Any screening procedures completed within and including 7 days of Visit 1, except for 4-stair climb, can serve as baseline and do not have to be repeated at Visit 1. At baseline and all other visits, the 4-stair climb will be performed twice. The second 4 stair climb 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.

At the baseline visit, all baseline procedures must be performed, and the pre-dose PK sample must be drawn prior to the first dose of study medication. Study medication will then be administered, and the remainder of the PK samples drawn according to the PK draw schedule (ie, 0.5, 1, 2, 4, and 6 hours post-dose). Baseline efficacy, MRI, and safety will also be assessed. The baseline visit can be conducted over two consecutive days.

A member of the site staff will follow-up with the subject 3 weeks from the baseline visit to assess safety.

Subjects will return to the site after 13 weeks (Visit 2/4) for safety, efficacy, PK, and MRI assessments. At Visit 2, the daily dose of study drug will be administered following the pre-dose PK blood draw.

For the remaining visits, study drug will be administered at home on the day of the in-clinic visit.

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. If it is determined that a subject will discontinue the study in between visits, the subject should return at the earliest convenience for an early termination visit, following completion of any required study medication assessments. Subjects who terminated early/ discontinued from the study and are tapering off deflazacort will be followed until the tapering is complete, and a follow-up visit will occur about 4 weeks after termination. 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.

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 final dose of deflazacort.

3.2 Scientific Rationale for Study Design

This study is designed to evaluate the efficacy and safety of deflazacort in the treatment of patients with LGMD2I.

At present, no therapies have clearly been demonstrated to slow progression of muscle weakness for LGMDs. A limited number of case reports and small studies have assessed the use of corticosteroid treatment in LGMD, and have shown some potential benefit of corticosteroid use in patients with certain subtypes of LGMD including LGMD2C, LGMD2D, LGMD2E; and LGMD2I, LGMD2L, LGMD2M (Pegoraro 1993, Angelini 1998, Godfrey 2006, Darin 2007, Baumeister 2009, Wong-Kisiel 2010, Nigro 2014, Svahn 2015, Carotti 2017, Wang 2018). Mouse models have also shown benefit of corticosteroid treatment in certain LGMDs (Wu 2016, Quattrocelli 2017).

Several case reports have suggested the positive benefit of long-term corticosteroid therapy in patients with LGMD2I (Darin 2007, Lin 2007, Svahn 2015, Wang 2018). These studies also suggest that a treatment effect should be observable within a 26-week period.

- Darin et al. (2007) found LGMD2I was associated with inflammation with up-regulation of major histocompatibility complex (MHC) class 1 in muscle biopsies of 2 patients with LGMD2I (Darin 2007). In both patients, after 4 to 6 months of treatment with prednisolone (initiated daily dose of 0.35 mg/kg/day) significant improvement in muscle strength and motor function were observed.

  - The first patient (age 16 years), prior to prednisolone treatment, could only walk short distances indoors without support and had great difficulty rising from a chair. After 6 months of treatment, no further deterioration in muscle function was observed, and the patient showed improvement in muscle strength, motor function, and time tests that were maintained over time. The patient remained on corticosteroid therapy >4 years. Over this time the dose of corticosteroid ranged from 0.32 to 0.37 mg/kg/day.
  - The second patient (age 10 years), prior to prednisolone treatment initiation, had great difficulty rising from the ground after a fall and rising from a chair, and could only do these tasks with support. Following 4 months of treatment, the patient could rise from the floor easier and without support and could swim and stand on 1 leg for a longer period of time. The prednisolone therapy was decreased over time. The treatment effects were stable until 2 years after onset of treatment, which was associated with reduction of the prednisolone dosage to 0.17 mg/kg/day. The patient remained on corticosteroid therapy >4 years.

- Lin et al. (2007) identified a female patient (age 2 years and 3 months) with LGMD2I who had progressive shoulder and pelvic muscle weakness and became unable to walk (Lin 2007). The patient was treated with prednisolone (20 mg/day). The corticosteroid therapy was associated with improvement of the clinical and pathological symptoms of the disease. Her muscle weakness gradually improved within 3 months and she was again ambulant at the age of 2 years and 6 months and could run and dance for the following 5 years.
- Svahn et al. (2015) described a woman (age 20 years) with LGMD2I clinical findings suggestive of an inflammatory myopathy who showed significant clinical improvement using corticosteroid, azathioprine, and intravenous immunoglobulin treatments (Svahn 2015). Oral prednisolone was started at a daily dose of 50 mg resulting in a reduction in myalgia, which was subsequently tapered to 25 mg/day due to adverse side effects of tremor and drowsiness. Over approximately a year, prednisolone was tapered to 12 mg/day. A stable clinical improvement in walking distance of 2000 meters was seen with therapy and the patient was able to go back to work.
- Wang et al. (2018) identified 2 patients from unrelated families with LGMD2I (Wang 2018). One patient (age 15 years) developed progressive proximal muscle weakness of the lower leg at age 6 years and by age 10 had difficulty climbing stairs. The patient had mild inflammatory involvement within the endomysial connective tissues by muscle biopsy. The patient was treated with prednisolone (0.75 mg/kg/day). At a second visit 8 months following the start of therapy, the patient showed no further deterioration in muscle strength or 6-minute walk distance (6MWD) compared with prior to therapy.

PTC Therapeutics has decided to initially investigate the use of deflazacort in LGMD by focusing on its affects in LGMD2I. The choice of LGMD2I was based upon the fact that several case reports have indicated benefit of corticosteroid use in this subtype of LGMD and other muscular dystrophies (Angelini 2007, Darin 2007, Lin 2007, Svahn 2015, Wang 2018). PTC Therapeutics has also taken into consideration advice from clinical experts who treat patients with LGMD, including LGMD2I.

Several lines of clinical and preclinical evidence indicate that the use of deflazacort may show treatment benefit in LGMD2I. A number of case study reports have demonstrated good clinical responses to corticosteroid therapy in patients with LGMD2I. Darin et al (2007) reported that muscle strength and motor function were significantly improved in two patients with LGMD2I after prednisolone treatment for 4 to 6 months (Darin 2007). They also reported that the immune system was involved in the pathology of LGMD2I based on muscle biopsies showing inflammation with up-regulation of MHC class 1. Svahn et al (2015) described a patient with LGMD2I who had clinical findings suggestive of an inflammatory myopathy who showed significant clinical improvement using corticosteroid, azathioprine and intravenous immunoglobulin treatments (Svahn 2015). Wang et al. (2018) identified a member of a family with mild inflammatory involvement within the endomysial connective tissues by muscle biopsy that was determined to result from LGMD2I (Wang 2018). They found that following prednisolone therapy no further deterioration in muscle strength was observed in this patient. Moreover, corticosteroid treatment was associated with lack of deterioration in 6MWD, compared with 6MWD prior to therapy.

Preclinical studies support the use of deflazacort in the treatment of LGMD2I. Murine models of LGMD2I have shown that corticosteroid treatment is associated with a reduction in the fibroinflammatory process and increases in the proportion of functionally glycosylated α-DG (Wu 2016, Quattrocelli 2017). Wu et al. (2016) generated a mouse model for LGMD2I that contains a P448L mutation and exhibits a typical muscular dystrophy phenotype observed in most LGMD2I muscle, including a significant reduction in functional glycosylation of α-DG in muscles and mild cardiac muscle pathology without an apparent involvement of the central nervous system (Wu 2016). Skeletal muscles of this mouse model undergo progressive degeneration, particularly in the diaphragm, although the life span of the mice can by >16 months. Wu et al. found that P448L-mutant mice administered 2 mg/kg daily or 5 mg/kg daily or twice weekly of prednisolone for 3 months compared with saline treated controls showed increased muscle strength as measured by forelimb and hindlimb grip strength, although this did not reach statistical significance. They also found that both daily and twice weekly 5 mg/kg prednisolone showed clear improvement in muscle pathology with a significant reduction in degenerating fibers compared with controls. In addition, treatment with 5 mg/kg of prednisolone both daily or twice a week greatly reduced inflammation, with almost elimination of focal accumulation of infiltrates, and a significant reduction in the number of hypertrophic fibers (>80 µm in diameter) compared with saline treated controls was also observed.

The use of corticosteroids for the treatment of LGMD2I is further supported by the findings that steroids improved FKRP-mediated muscular dystrophy in a zebrafish model of LGMD2I (Serafini 2018). Serafini et al. generated a LGMD2I model in zebrafish by expression of a FKRP transgene that contained the human *fkrp (L276I)* open reading frame under a heat-shock promoter in fish that did not have a functional *fkrp* gene (ie, *fkrp-/fkrp-*) (Serafini 2018). Zebrafish expressing the transgene had overall pathology consistent with LGMD2I (Serafini 2018). Using the LGMD2I zebrafish model, Serafini et al. performed an unbiased double-blind screen of the FDA-approved Prestwick compound library (Version 2). Out of the 1,120 total compounds in the library, 20 unique compounds were identified that ameliorated FKRP-dependent pathologies, with steroids being one of the most common group (Serafini 2018).

Deflazacort has been shown to have clinical benefit in other muscular dystrophies. In Duchenne muscular dystrophy DMD, deflazacort treatment tended to result in a greater delay in milestone transitions compared with prednisolone/prednisone therapy (Bello 2015, McDonald 2018). In the Cooperative International Neuromuscular Research Group Duchenne Natural History Study, deflazacort had a >2-year-later median age of loss of ambulation (LoA) (13.9 vs. 11.2 years, respectively) and a significantly lower yearly risk of LoA (Cox regression, 0.498 vs. 0.294; P<0.001) than prednisolone/prednisone (Bello 2015). Deflazacort was also associated with a greater delay in loss of the ability to rise from supine and of hand-to-mouth function compared with prednisolone/prednisone (P values ≤0.0114) (Bello 2015). Deflazacort has also been found to show benefit in patients with LGDM2E. A case report of two siblings with homozygous β-sarcoglycan gene mutation (S114F), consistent with LGMD2E, underwent a course of deflazacort (Wong-Kisiel 2010). At 22 months of drug therapy, both patients had stable or improved strength testing. Despite the severe phenotype, deflazacort had a beneficial effect on slowing disease progression in LGMD2E, similar to that seen in DMD.

The decision to evaluate deflazacort for the treatment of LGMD2I is based on the prior clinical evidence of the benefit of corticosteroid use in LGMD2I and other muscular dystrophies, and the potential for greater efficacy and tolerability observed with deflazacort compared with prednisolone/prednisone.

Common deflazacort-related AEs in DMD

The safety of deflazacort has been studied in semi-chronic to chronic studies in both adults and children. Deflazacort-associated AEs are consistent with known AEs of the glucocorticoid class, including weight gain, cushingoid features, insulin resistance, diabetes, behavioral side-effects, osteopenia, risk of fractures, and cataracts (Table 1) (Emflaza [deflazacort] Prescribing Information , Matthews 2016, Calcort 6 mg Tablet SmPC 2018). The common AEs across approved indication of deflazacort in Europe and the United States can be found in the prescribing information (Emflaza [deflazacort] Prescribing Information , Calcort 6 mg Tablet SmPC 2018).

Of note, in 1 study deflazacort was associated with less cushingoid face than prednisone (P value = 0.0385; (Griggs 2016)). A beneficial difference in weight gain versus other glucocorticoids is seen early in treatment with deflazacort and is maintained for up to 1 year. This lessened weight gain is important in this patient population since diminished strength from the disease is worsened by weight gain (Griggs 2016).

Table 1. Incidence of TEAEs in Deflazacort and Placebo Treatment Arms in DMD Subjects

Preferred Term	Deflazacort 0.9 mg/kg/day (N=93) n (%)	Placebo (N=61) n (%)
Number of subjects with at least 1 TEAE	76 (81.7)	46 (75.4)
Cushingoid	41 (44.1)	5 (8.2)
Erythema	19 (20.4)	3 (4.9)
Hirsutism	24 (25.8)	1 (1.6)
Weight increased	21 (22.6)	3 (4.9)
Headache	17 (18.3)	12 (19.7)
Nasopharyngitis	21 (22.6)	3 (4.9)
Central obesity	17 (18.3)	2 (3.3)
Increased appetite	11 (11.8)	1 (1.6)
Pollakiuria	12 (12.9)	1 (1.6)
Abdominal pain upper	9 (9.7)	4 (6.6)
Upper respiratory tract infection	10 (10.8)	5 (8.2)
Constipation	7 (7.5)	3 (4.9)
Influenza	4 (4.3)	2 (3.3)
Cough	7 (7.5)	3 (4.9)
Abnormal behaviour	7 (7.5)	3 (4.9)
Rash	5 (5.4)	3 (4.9)
Skin striae	4 (4.3)	0 (0.0)
Acne	4 (4.3)	1 (1.6)
Nausea	4 (4.3)	2 (3.3)
Vomiting	2 (2.2)	4 (6.6)
Ear infection	2 (2.2)	1 (1.6)
Diarrhoea	4 (4.3)	4 (6.6)
Abasia	0 (0.0)	8 (13.1)
Fall	2 (2.2)	1 (1.6)
Appetite disorder	0 (0.0)	1 (1.6)

Abbreviations: DMD, Duchenne muscular dystrophy; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of individuals in a study; n, number of subjects; TEAE, treatment-emergent adverse events
Note: Percentages are n/N*100. At each level of summarization, a subject is counted only once. MedDRA version 17.0 has been used for the coding of adverse events.
Source: 120-Day Safety Update Table 18 (modified)

Benefit/risk

Study PTCEMF-GD-004 will evaluate the use of deflazacort in adult patients with LGMD2I. Deflazacort has been successively used to treat diseases not only in adults but also in vulnerable pediatric populations, including DMD, juvenile chronic arthritis, nephrotic syndrome, and bronchial asthma. The safety concerns related to deflazacort use are well known and can be managed through appropriate medical monitoring. Given the findings of case reports that suggest corticosteroid use may reduce disease progression in patients with LGMD2I, the potential benefits of the treatment outweigh the anticipated risks of the drug.

Study assessments

In this study, muscle function following deflazacort or placebo therapy will be evaluated using a number of tests that assessed different aspects of muscle function, such as peak physical activity

(timed-function tests), endurance (2-minute walk test), muscle strength (myometry), and pulmonary function (FVC, MIP, and MEP).

The PK of deflazacort will be investigated to evaluate the exposure of the drug in subjects with LGMD2I; a population in which this assessment has not been previously performed. This information may help to determine the relationship of drug exposure with the efficacy and safety of the drug in this patient population. The following PK parameters will be calculated using noncompartmental analysis method: $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, C_{max}, T_{max}, CL/F, Vz/F, λz, and t½.

Magnetic resonance imaging (specifically Dixon MRI and global T2) are noninvasive methods that will be used to measure changes in muscular fat fraction and water content, respectively, of the muscle following deflazacort treatment. These methods have been shown to detect therapeutic effects of corticosteroids in reducing inflammatory processes in skeletal muscle of boys with DMD (Arpan 2014, Hathout 2016a). The advantage of the use of these potential biomarkers is that they are anticipated to be independent of muscle function, such as the ability to walk (Hathout 2016a).

The INQoL questionnaire, developed by Vincent et al. (2007), consists of 45 questions within 10 sections, 4 sections focus on the impact of key muscle disease symptoms (weakness, locking [ie, myotonia], pain, and fatigue), 5 sections focus on the impact of muscle disease on particular areas of life (activities, independence, social relationships, emotions, and body image), and 1 section asks about the positive and negative effects of treatment, reflecting the trade-off between the positive and negative effects of treatment now and in the future (Vincent 2007).
The life domains that emerged correspond to the broad domains believed to make up the QoL spectrum (physical, psychological, and social functioning). The questionnaire is structured to allow for variations in the individual characteristics that influence quality of life.
Participants respond using a 7-point Likert scale.
The final score is presented as a percentage of the maximum detrimental impact; therefore, a higher percentage indicates a greater impact and lower QoL.
In the original study, INQoL was validated through 252 completed questionnaires, including adult patients with LGMD. More than 60% of all respondents reported an impact on the life areas included in the questionnaire.
This scale has been used in LGMD studies (Peric 2018), where mental domains were less impaired than physical, and the presence of cardiomyopathy correlated with a worse QoL.
This scale has been translated in several languages and validated for English in several countries.

3.3 Justification of Dose

The subjects will receive a 0.6 mg/kg daily dose of deflazacort. This dose is lower than the recommended dose of 0.9 mg/kg/day for DMD. Based on the higher body weight of the subjects in this trial (age ≥18 years) compared with DMD patients, the lower dose of 0.6 mg/kg/day is justified in order to reduce tolerability issues and corresponds to the equivalent prednisone dose (0.5 mg/kg/day) used in LGMD2I based on anecdotal reports. The study of Darin et al. found that initial treatment of prednisolone at doses ranging from 0.032 to 0.37 mg/kg/day improved symptoms of LGMD2I in 2 patients (Darin 2007).

Nevertheless, the 0.9 mg/kg/day dose serves as benchmark for the following discussion. A clinical study in DMD subjects (N=24; age 4 to 16 years) (MP-104-CL-005) found administration of

deflazacort 0.9 mg/kg/day did not result in accumulation of 21-desDFZ after 7 days of oral dosing in children or adolescents; exposures to 21-desDFZ after oral administration of deflazacort to children and adolescents with DMD on Day 1 were similar to exposures measured on Day 8. The dose-normalized exposure parameters and the dose-dependent parameters (clearance and volume of distribution) were consistent between children and adolescents. Multiple oral doses of deflazacort 0.9 mg/kg/day were safe and well tolerated by children (ages 4 up to 12 years) and adolescent (ages 12 to 16, inclusive) subjects with DMD. These results support the evaluation of the lower dose of 0.6 mg/kg/day for this indication.

Sufficient data exists for the safety of the proposed dosing in females and the study requires stringent contraceptive measures for both males and females in the absence of adequate reproductive toxicity studies.

3.4 Subject Transition Procedures: Version 3.0 to Version 4.0

The sponsor will unblind the study and provide the principal investigator a listing of their subjects' treatment assignments. Subjects enrolled (and randomized to study medication) under Protocol Version 3.0 will be transitioned to Version 4.0 according to the following procedure:

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.

Subjects may continue to be screened under Protocol Version 4.0 procedures until the close of screening on May 31, 2020.

3.5 Study Completion

The study will end when the last subject completes the follow-up visit.

4 STUDY POPULATION

The target population for this study is subjects, ≥18 years of age with LGMD2I.

4.1 Overview

4.2 Inclusion Criteria

1. Genetic diagnosis of LGMD2I (confirmed mutation in the FKRP gene)
2. Male and female subjects aged ≥18 years
3. Ability to ascend 4 stairs ≥2.5 seconds and be able to complete the ascent and descent both at screening and baseline
4. Ability to understand the nature of the study and the consent form and to comply with study related procedures
5. Must weigh ≥35 to ≤112.5 kg

4.3 Exclusion Criteria

1. Received ≥4 weeks of continuous, systemic corticosteroid therapy within 3 months of study the Screening Visit.
2. Presence of significant cardiomyopathy as defined by echocardiogram (left ventricular ejection fraction <30%) at screening
3. Requires fulltime ventilator support
4. History of chronic systemic fungal or viral infections
5. History of recent bacterial infection (including tuberculosis) per discretion of the Investigator
6. Diagnosis of diabetes mellitus (controlled and/or uncontrolled) defined as HbA1c ≥6.5% (based on historical or present diagnosis)
7. History of immunosuppression or other contraindications to glucocorticosteroid therapy
8. Requires concomitant use or >1 week of drugs or substances that are moderate to strong CYP3A4 inhibitors (ie, clarithromycin, fluconazole, diltiazem, verapamil, grapefruit juice) or moderate or strong CYP3A4 inducers (ie, rifampin, efavirenz, carbamazepine, phenytoin) at baseline.
9. Participated in an interventional clinical trial within the last 3 months prior to the baseline visit
10. Unable or unwilling to comply with the contraceptive requirements of the protocol
11. Female subjects who are pregnant and/or breastfeeding

12. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neurologic, psychiatric, or allergic disease

4.4 Screen Failures

Any subject that does not meet inclusion or exclusion criteria within the defined screening window prior to randomization, will be considered a screen failure. Screen failures can be rescreened after consultation with the Medical Monitor.

5 ENROLLMENT PROCEDURES

5.1 Source and Number of Subjects

Approximately 30 subjects will be enrolled. Subjects will be recruited via existing LGMD2I populations at investigative sites and/or referrals.

5.2 Screening

The Investigator must inform each study subject of the nature of the study, explain the potential risks, and obtain written informed consent from the legal guardian and/or study candidate (as required by local regulations) prior to performing any study-related screening procedures.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Investigational Product(s) Administration

The investigational medicinal to be used in this study is oral deflazacort, 0.6 mg/kg/day.

6.1.1 Investigational Product Description

6.1.1.1 Deflazacort

Deflazacort will be provided as 6 mg, 18 mg, or 36 mg tablets for oral administration once daily. The drug substance and drug product are manufactured under current good manufacturing practice conditions.

Each tablet contains deflazacort and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and pre-gelatinized corn starch.

6.1.2 Dosing and Administration

Deflazacort will be assigned via an IRT system according to the subject's weight at baseline. Subjects will be assigned deflazacort 0.6 mg/kg/day and will continue on the assigned weight based dose through 26 weeks. Any subject assigned to placebo prior to the Version 4.0 amendment will be switched to deflazacort as described above.

Study drug will be taken by the subject orally, at home (except on days where the subject is instructed to take the dose in clinic), in a single, daily, morning dose. If the subject is unable to swallow the tablet whole, tablets may be crushed in between two spoons or using a tablet crusher

and stirred into soft food (eg, applesauce, pudding) and ingested immediately. Subject must be instructed not to split the tablet(s) and subjects are instructed not to chew the study drug. Tablets may be taken with or without water and with or without food.

6.1.2.1 Weight Bands

Study participants will be assigned the appropriate, weight-based dosing band (excursions from the target weight permitted out to approximately 20%, greater or less, than target based on available tablet strengths) (Table 2):

Table 2. Weight-based Dosing Summary

0.6 mg/kg/day

Dose (mg)	Target Weight (in Kg)	Weight Band (in Kg)	Dosing Combination
24	40.0	35 - 49.9	6mg + 18mg
36	60.0	50 -74.9	36 mg
54	90.0	75 - 112.5	36mg + 18mg

6.1.2.2 Safety Criteria for Adjustment or Stopping Dosing

Unless an occurrence of an AE requires otherwise, the investigator is encouraged to maintain the same dose through the first 13 weeks of treatment due to the potential to confound the PK, safety, and efficacy evaluations. Dose adjustments are permitted as follows:

1. In order to maintain the weight-based dose of 0.6 mg/kg/day of deflazacort, if the subject has experienced weight gain that places them in the next higher weight band, the dose may be increased accordingly. If the subject has experienced an AE as described below, the Investigator may elect not to increase the dose despite weight gain.

2. At the discretion of the Investigator, the dose may be decreased to that of the next lower weight band in response to an AE. See recommendations below.

3. At the end of the study, subjects will switch from the study medication to an appropriate dose of a commercially available deflazacort or any other available corticosteroid. If the subject/Investigator does not wish to continue corticosteroid use, the dose of deflazacort must be reduced per Section 7.1 procedures.

Discontinuation of deflazacort during Period 1 of the study should be avoided unless clinically necessary. In the case of the development of predictable, deflazacort-related adverse effects, appropriate supportive care should be provided such that dosage can be maintained. Specific, standard of care recommendations for precautionary interventions for specific corticosteroid-related AEs are given below.

Acne

In the event of bothersome acne that may be attributable to deflazacort, the following interventions are recommended:

1. The subject should be encouraged to use appropriate conventional therapy for acne

2. If conventional therapy does not provide an adequate response, the dosage should not be increased to adjust for increases in body weight.

3. If the acne is so severe that it cannot be managed with appropriate anti-acne measures, dosage reductions can be made down to the next lower weight band of the dosing arm assigned.

Behavior Changes

Where behavior changes are disruptive to family/school life, the following interventions are recommended:

1. The subject should be encouraged to seek behavioral support from a qualified behavioral specialist.

2. If the subject is already receiving behavioral advice under the guidance of a behavioral specialist, the dosage should not be increased to adjust for increases in body weight. Consideration can be given to administering the corticosteroid dose at night instead of in the morning.

3. If there is no improvement despite behavioral advice under the guidance of a behavioral specialist, dosage reductions can be made down to the next lower weight band of the dosing arm assigned.

4 If the severe behavioral problems continue to cause unacceptable disruption to school/work/family life necessitating cessation of deflazacort, Section 7.1 procedures should be followed.

Bone Fractures Due to Osteoporosis

Subjects who experience limb fractures should have fixation as directed by an orthopedic surgeon. Subjects who develop vertebral fractures can be treated with bisphosphonates (eg, pamidronate, 0.5 to 1 mg/kg/day intravenous for 3 days every 4 months). Subjects should not have a dosage adjustment due to the occurrence of fractures.

Cataracts

The development of cataracts should prompt referral to an ophthalmologist for evaluation. Subjects should not have a dosage adjustment due to the occurrence of cataracts.

Cushingoid Appearance

If the subject develops a Cushingoid appearance, that is unacceptable to the subject, the following actions are recommended:

1. Reassurance and support should be provided. Counseling from a qualified behavioral specialist should be considered.

2. If the Cushingoid appearance remains unacceptable to the subject, the dosage should not be increased to adjust for increases in body weight.

3. If the Cushingoid appearance remains unacceptable to the subject, a dose reduction can be made down to the next lower weight band of the dosing arm assigned.

4. Every attempt should be made to avoid stopping deflazacort solely for Cushingoid appearance; however, should cushingoid appearance become unacceptable to the subject necessitating cessation of deflazacort, Section 7.1 procedures should be followed

Gastrointestinal Irritation

In the event of the development of symptoms consistent with esophagitis, gastritis, or duodenitis, the following interventions are recommended:

1. Treatment with supportive care (H_2 antagonists, proton pump inhibitors, antacids) should be initiated and dosage should not be increased to adjust for increases in body weight.

2. If symptoms persist for ≥6 weeks despite supportive care (H_2 antagonists, proton pump inhibitors, antacids), a gastroenterology consultation should be encouraged.

3. If symptoms persist despite continued supportive care (H_2 antagonists, proton pump inhibitors, antacids) and gastroenterology evaluation, dose reduction can be made down to the next lower weight band of the dosing arm assigned.

4. If the gastroenterologist recommends discontinuation of deflazacort for frank gastrointestinal ulceration, bleeding, etc, Section 7.1 procedures should be followed.

Hyperglycemia or Glycosuria

Evidence of fasting hyperglycemia or ≥1+ glycosuria persisting for ≥6 weeks should prompt the following interventions:

1. Monitor hemoglobin average blood sugar concentrations (A1c) to evaluate for evidence of chronic hyperglycemia.

2. If hyperglycemia or glucosuria is only episodic and chronic hyperglycemia is not present by hemoglobin A1c, deflazacort should not be increased to adjust for increases in body weight.

3. If chronic hyperglycemia is present by hemoglobin A1c, consultation should be arranged with an endocrinologist regarding diagnostic evaluation and potential intervention for hyperglycemia.

4. If hyperglycemia persists and dose reduction is warranted, reduction can be made down to the next lower weight band of the dosing arm assigned.

5. If the endocrinologist recommends deflazacort discontinuation, Section 7.1 procedures should be followed.

Hypertension

Evidence of substantial hypertension (blood pressure elevation systolic BP ≥140 mmHg and or diastolic BP ≥90 mmHg) persisting for ≥6 weeks should prompt the following interventions:

1. Dietary recommendations (weight reduction/sodium reduction) should be considered.
2. Dosage should not be increased to adjust for increases in body weight.
3. If substantial hypertension persists, appropriate blood pressure management (eg, diuretics, beta blockers, calcium channel blockers) can be considered.
4. If hypertension persists despite continued antihypertensive therapy, dose reduction can be made down to the next lower weight band of the dosing arm assigned.
5. If hypertension persists despite continued antihypertensive support and dosage reductions, Section 7.1 procedures should be followed.

Infections Potentially Related to Corticosteroid-Mediated Immunosuppression

Unusual opportunistic infections or unusual responses to infection potentially consistent with corticosteroid-mediated immunosuppression should prompt the following interventions:

1. Consultation with an infectious disease expert should be obtained.
2. If infections cannot be managed with appropriate antibiotic prophylaxis or treatment, dosage should not be increased to adjust for increases in body weight.
3. If infections still cannot be managed with appropriate antibiotic prophylaxis or treatment, a dose reduction can be made down to the next lower weight band of the dosing arm assigned.
4. If infections are clinically severe and/or persistent despite dosage reductions, Section 7.1 procedures should be followed.

Weight Gain

In the event of a body weight increase that is unacceptable to the subject, the following interventions are recommended:

1. Reassurance and support should be provided. Counseling from a nutritionist should be considered.
2. Should weight increase continue to be unacceptable, dosage should not be increased to adjust for increases in body weight.
3. If the body weight increase remains unacceptable to the subject, a dose reduction can be made down to the next lower weight band of the dosing arm assigned.
4. Every attempt should be made to avoid stopping deflazacort solely for weight gain; however, if the subject demands that deflazacort be stopped, Section 7.1 procedures should be followed.

6.1.3 Return of Study Drug

Subjects should return all remaining/unused study drug to the study site at each onsite study visit. The Study Drug Administration Record (accountability log) will serve as the source document for drug supply to the subjects and will document the return of unused drug for compliance assessments. Unused study drug must be returned to PTC Therapeutics or its designee. Records documenting the date of study drug shipping, and amount shipped should be kept in the Investigator site study file.

6.1.4 Overdose or Inadvertent Exposure Precautions

Treatment of acute overdose is based on clinical judgement, which may include immediate gastric lavage or emesis followed by supportive and symptomatic therapy. If non-study subjects (eg, sibling, parent) ingests the medication, a prompt call to the Medical Monitor is required to discuss appropriate care.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Drug will be supplied to the investigative site via courier from a depot. Sites will have an initial shipment sent prior to the first subject randomizing and resupplied automatically throughout the study. The Investigator must ensure that all study drug supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator, through the IRT system, must maintain full accountability of the study drug from receipt to destruction. The IRT will maintain information such as the receipt of all study drug shipped by the Sponsor (or their representative), including but not limited to the date received, lot number(s), retest date(s), amount received, and the disposition of all study drug. Current dispensing records will also be maintained through the IRT system, including the date, amount, kit and lot(s) of study drug dispensed and the subject receiving the drug.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Deflazacort tablets (6 mg, 18 mg and 36 mg) will be used for this study. The tablets are white, and either round or ovular in shape depending on the strength of the tablet (6 mg and 18 mg tablets are round, 36 mg tablets are ovular). Tablets will be packaged in weekly blister cards. Weekly blister cards will be packaged into visit cartons. Tablets needed for appropriate taper dose will be available and packaged in bottles. The blister cards, visit cartons, and bottles will be labeled in accordance with participating country regulatory requirements and certified language text translation.

6.2.3 Storage and Stability

Deflazacort should be stored at controlled room temperature. Detailed storage requirements should be as described in country-specific prescribing information.

6.3 Measures to Minimize Bias: Randomization and Blinding

Study medication will be administered in an open-label fashion.

6.4 Study Intervention and Compliance

Subjects will receive properly labeled blister cards with the daily dose assignment broken out by week. Each subject will be instructed to take all tablets on a daily basis that correspond to the day of the week. Dosing should begin corresponding to the day of the week Visit 1 took place (eg, if Visit 1 occurs on a Wednesday, the subject should be instructed to begin treatment by administering tablets from the blister card column associated with Wednesday). On the initial pack, the subject should not take tablets from preceding days of the week (eg, in the previous example, Sunday, Monday, Tuesday). These would be returned as unused supplies at the following visit. Study drug will be administered at home with the exception of Visit 1 and Visit 2 where the dose will be taken after the pre-dose PK sample has been collected (Visit 1 and Visit 2). Subjects must return empty blister cards and unused supplies at each study visit and in the event of an early termination for compliance assessments.

Home dosing will be monitored via review of returned study medication packaging and subject interview.

6.5 Concomitant Therapy

All medications taken by subjects 30 days prior to the first dose of study drug and through the follow-up visit will be recorded.

All medications (prescription and over the counter), vitamin and mineral supplements, and herbs taken during the study will be documented on the concomitant medication electronic case report form (eCRF). Information recorded will include: start and stop dates, dose and route of administration, and indication.

The Investigator is encouraged to consult the PTC medical monitor or designee with questions relating to specific drugs and their potential for interactions with deflazacort.

6.5.1 Rescue Medication

There is no defined rescue medication for this study. Medication prescribed to mitigate the known adverse effects of deflazacort are not considered rescue medications.

6.5.2 Prohibited Medications

Subjects receiving corticosteroids, including deflazacort, and concomitant therapy with neuromuscular blocking drugs (eg, pancuronium) may be at increased risk of developing an acute myopathy .

Subjects should not receive live or attenuated vaccines during the study.

Additionally, the continuous, concomitant use of strong CYP3A4 inhibitors and inducers are prohibited during the study (Table 3 and Table 4). If the use of any of the medications listed below (or another, unlisted CYP3A inhibitor/inducer) becomes medically necessary, the PI must discuss management and further study eligibility with the medical monitor.

Table 3. CYP3A Inhibitors

Strong Inhibitors ≥5-fold increase in AUC or >80% decrease in CL/F	Moderate inhibitors ≥2 but <5-fold increase in AUC or 50-80% decrease in CL/F	Weak inhibitors ≥1.25 but <2-fold increase in AUC or 20-50% decrease in CL/F
boceprevir	aprepitant	chlorzoxazone
cobicstat	cimetidine	cilostazol
clarithromycin	ciprofloxacin	fosaprepitant
conivaptan	clotrimazole	istradefylline
danoprevir/ritonavir	crizotinib	ivacaftor
diltiazem	cyclosporine	lomitapide
elvitegravir/ritonavir	dronedarone	ranitidine
grapefruit juice	erythromycin	ranolazine
idelalisib	fluconazole	tacrolimus
indinavir/ritonavir	fluvoxamine	ticagrelor
itraconazole ketoconazole	imatinib	
lopinavir/ritonavir	tofisopam	
nefazodone	verapamil	
nelfinavir		
paritaprevir/ritonavir/ombitasvir		
posaconazole		
ritonavir		
saquinavir/ritonavir		
telaprevir		
tipranavir/ritonavir		
troleandomycin		
voriconazole		

Abbreviations: AUC, area under the concentration-time curve; CL/F, clearance.

Table 4. CYP3A Inducers

Strong Inducers ≥80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
carbamazepine enzalutamide	bosentan	armodafinil
mitotane	efavirenz	rufinamide
phenytoin	etravirine	
rifampin	modafinil	
St. John's wort		

Abbreviations: AUC, area under the concentration-time curve

7 INVESTIGATIONAL PRODUCT DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Medication

If the subject is discontinued from the study medication, the following 3 options are available: 1) taper off deflazacort; 2) in conversation with their healthcare provider, they could switch to a commercially available generic version of deflazacort; or 3) in conversation with their healthcare provider, they could switch to other commercially available corticosteroids.

Long term administration of deflazacort may lead to suppression of the hypothalamicpituitary-adrenal (HPA) axis. Rapid reduction or abrupt withdrawal of therapy that has been prolonged or at high doses can cause secondary adrenal insufficiency (suppression of the HPA axis), and steroid withdrawal or deprivation syndrome. Recovery from suppression of the HPA axis after discontinuing deflazacort can be prolonged (possibly 6 to 12 months) and may vary based on doses, dosing schedules and duration of deflazacort therapy. Since there is a great deal of individual variability in susceptibility to suppression of the HPA axis after chronic use of exogenous corticosteroids, it is not possible to predict with confidence which subjects will be affected. Deflazacort should not be stopped suddenly. Therefore, general tapering recommendations are provided; however, investigators may taper according to their standard of care and clinical judgement. If there is no standard tapering practice at the site, the following taper practice based on the PJ Nicholhof Protocol (Kinnett 2017) is advised (Table 5):

1. Using the 6 mg tablet strengths from the available taper bottle, begin by giving a 20% to 25% lower dose for two weeks
2. Repeat step 1 and continue to lower the dose by 20% to 25% original dose until near physiologic dose (~0.1 mg/kg)
3. If necessary, substitute deflazacort with short acting form of a corticosteroid (ie, hydrocortisone (0.3 mg/kg/day)
4. Stop corticosteroids and observe for signs of adrenal crisis

Table 5. Taper paradigm per weight band

Weight Band (mg)	0.6 mg/kg Target Weight	1st Reduction *(~.45 mg/kg)	2nd Reduction *(~0.3 mg/kg)	3rd Reduction *(~0.15 mg/kg)	Consider Short Acting Corticosteroid
24	40 kg	18 mg	12 mg	6 mg	Stop Deflazacort
36	60 kg	30 mg	18 mg	12 mg	Stop Deflazacort
54	90 kg	42 mg	30 mg	18 mg	Stop Deflazacort

*Approximate mg/kg calculations based on the weight requirement to achieve exactly 0.6 mg/kg dose. 20% fluctuation (higher and lower weight) is inherent in each weight band and should be considered when applying the tapering paradigm.

7.2 Participant Discontinuation/Withdrawal from the Study

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. 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. The PTC medical monitor should be informed via e-mail of when a subject discontinues study treatment. 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.

Reasons for discontinuation may be for any of the following reasons:

1. The subject requests to be discontinued from the study
2. The occurrence of a clinically significant worsening of disease status or change in a laboratory parameter that may place the subject at risk
3. Upon consultation with the PTC Therapeutics medical monitor, the Investigator may withdraw the subject from deflazacort treatment, if, in the Investigator's clinical judgment, it is not in the subject's best interest to continue.
4. The occurrence of a serious AE
5. The occurrence of a protocol violation, if it interferes with the safety of a subject or data integrity
6. The Sponsor or Investigator terminates the study

7.3 Lost to Follow-up

Subjects are considered lost to follow-up if the subject does not return to the clinic and attempts to contact the subject were unsuccessful. Efforts must be made on the part of the site to avoid any subject being lost to follow-up during the study. Before subjects are considered lost to follow-up, a minimum of 2 documented telephone contact attempts and 1 certified letter within 6 weeks of the most recent planned study visit must be sent in efforts to contact the subject. After being considered lost to follow-up, a subject's status may be changed if the subject makes contact at a later time provided the trial is ongoing.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Schedule of Events and Study Procedures

Table 6 summarizes schedule of study procedures and assessments.

Table 6. Schedule of Events

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		

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)		
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	
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: $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, 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

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)		
										test. Conduct details will be summarized in a manual separate from this protocol.
Hand Held Myometry[12]		X		X	X		X	X		
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.

8.2 Efficacy Assessments

For the efficacy assessments of pulmonary function, timed function tests, and hand held myometry, each site will have at least one and preferably two trained clinical evaluators who are qualified physical therapists and who will have undergone standardized training. They must be certified as capable of performing all clinical assessments as specified for this study. Their strength measures, results of lung function tests and timed function tests must match those of the trainer within set acceptability parameters that are detailed in the clinical evaluator manual. Other efforts to reduce variability, include making every effort to have each subject assessed by the same clinical evaluator for each type of assessment throughout the entire study. Assessments must be conducted in the same order at each visit as stated in the clinical evaluator manual and at approximately the same time of day throughout the study. Clinical evaluators will not have access to prior test results to avoid bias based on knowledge of previous data.

Clinical assessments conducted by the physical therapists will be monitored for quality control by an expert team of physical therapists. Videos will be uploaded to a cloud based secure storage facility for centralized review. Clinical evaluator performance will be documented by a report which is sent to the evaluators and stored in the site files as well as within the secure cloud-based facility. Informed consent for video review will be obtained from the subject.

8.3 Pharmacokinetic Assessments

Blood samples (at least 1 mL per sample) will be collected for determination of 21-desacetyl deflazacort and 6β-hydroxy-21-desacetyl deflazacort. Pharmacokinetic sample collection, processing, storage, and shipment will be performed according to instructions outlined in the PK laboratory manual separate from this protocol. 21-desacetyl deflazacort and 6β-hydroxy-21-desacetyl deflazacort plasma concentrations will be determined by the bioanalytical group of Celerion, Lincoln, Nebraska, USA, using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification of the LC-MS/MS method for simultaneous determination of 21-desacetyl deflazacort and 6β-hydroxy-21-desacetyl deflazacort is 1.0 and 0.5 ng/mL respectively.

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 minutes will be allowed for blood collection. From 4 hours to 6 hours post samples, a window of ± 30 minutes will be allowed.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of an adverse events

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered related to the drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a study subject who is administered study drug in this study.

For this protocol, untoward medical occurrences that should be reported as AEs include the following:

1. All AEs during the course of treatment with study drug administration
2. All AEs resulting from medication misuse, abuse, withdrawal, or overdose, of study drug
3. All AEs resulting from medication errors such as dispensing or administration error outside of what is described in the protocol
4. Apparently unrelated illnesses, including worsening of a preexisting illness
5. Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.
6. Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
7. Laboratory or ECG abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring and should not be reported as AEs.
8. A preexisting condition (eg, allergic rhinitis) must be noted on the appropriate eCRF for Visit 1 but should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that occurs during the treatment with study drug should be reported as the AE and the resulting appendectomy should be recorded in the source documents and eCRF. If a surgical procedure was planned prior to entry into the study, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an AE. Note that, as described in Section 8.4.2 any hospitalization occurring as the consequence of an AE during the study period should be reported as an serious adverse event (SAE).

Each AE is to be classified as serious or non-serious by the Investigator using medical and scientific judgment.

8.4.2 Definition of a serious adverse events

An SAE is an untoward medical occurrence or effect associated with the use of a study drug at any dose, regardless of whether it is considered by the Investigator to be related to the study drug, which results in one of the following:

1. Results in death. This includes all deaths on treatment or within 30 days after last study drug administration, including deaths due to disease progression. Any death occurring later than 30 days following the last dose need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported AE should be the event that caused the death. In addition, any AE resulting in death that occurs subsequent to the AE reporting period and that the Investigator assesses as possibly related to the study drug should also be reported as serious.

2. Is life-threatening. This refers to an event in which the subject was at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.

3. Requires hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or treatment-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Treatments in the emergency room for procedures such as hydration that do not require admitting the subject to the hospital and observational durations in the emergency room for less than 24 hours do not fall into this category.

4. Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions, not related to cancer.

5. Any other medically important event that the Investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. These are AEs that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether an AE is serious based on above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

6. A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death, or congenital anomaly (including that in an aborted fetus).

Note that any SAEs occurring within 30 days after last study drug administration (end of study) should be reported to the sponsor if the Investigator becomes aware of them.

8.4.3 Unexpected Adverse Events

The Investigator Brochure contains the Reference Safety Information (RSI) which will be used for assessing expectedness. If an event is not listed in the RSI, it should be considered unexpected or if the AE occurs at a greater severity, specificity or frequency, it should be considered unexpected.

8.4.4 Eliciting adverse event information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs at each scheduled clinic visit after study drug administration or during any telephone contact with the subject. The type of question asked should be open-ended, for example, "*How have you been feeling*?" or a similar type of query.

8.4.5 Recording Serious and Non-serious Adverse Events

All AEs (both serious and non-serious) that occur in subjects during the AE reporting period must be recorded, whether or not the event is considered drug related. In addition, any known untoward event that occurs subsequent to the AE reporting period that the Investigator assesses as possibly related to the investigational drug/product should also be recorded as an AE.

All AEs are to be recorded in the source documents and on the eCRF using concise medical terminology; whenever possible, terms contained in the Medical Dictionary for Regulatory Activities (MedDRA) should be employed. In addition, the following information should be recorded:

1. Indication of whether the event is serious or non-serious (see Section 8.4.2)
2. Relationship to study drug (see Section 8.4.2)
3. Severity of the event (see Section 8.4.7)
4. Onset date
5. Resolution date, or date of death
6. Action taken
7. Outcome of the event

Classification of the event as serious or non-serious determines the reporting procedures to be followed.

8.4.6 Describing adverse event relationship to study drug

The Investigator should provide an assessment of the relationship of the AE to the study drug, ie, whether there is a reasonable possibility that the study drug caused the AE, using the considerations outlined in Table 7.

Table 7. Relationship of Study Drug to Adverse Event Relationship

Relationship	Description
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; improvement upon withdrawal of the drug; recurrence upon rechallenge with the drug; lack of alternative explanations for the event.
Possible	A clinical event occurring coincident with administration of the study drug and which may or may not be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal or rechallenge may be lacking.
Unlikely	A clinical event with a temporal relationship to the study drug exposure that does not preclude causality but for which there is a clear alternate cause that is more likely to have caused the adverse event than study drug. Such alternatives include a concomitantly administered drug, the subject's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug, lack of a temporal association with study drug administration, lack of association of the event with study drug withdrawal or rechallenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors.

8.4.7 Grading of Severity of Adverse Event

The severity of AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (refer to the Study Manual). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the Investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 8.

Table 8. Grading of Adverse Event Severity Grade

	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life
Grade 5	Fatal	Sign or symptom results in death

8.4.8 Adverse Event Reporting

Investigator site reporting requirements for AEs are summarized in Table 9.

Table 9. Investigator Site Requirements for Reporting Adverse Events

Event	Recorded on the eCRF	Reported on the SAE Report Form to PTC Pharmacovigilance Within 24 Hours of Awareness
Serious AE	All	All
Non-Serious AE	All	None
Exposure to the study drug during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

Abbreviations: AE, adverse event; eCRF, electronic case report form; SAE, serious adverse event

All AEs should be followed up by the Investigator until they are resolved, or the Investigator assesses them as chronic or stable. The Investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, the PTC Therapeutics Pharmacovigilance Department or designee should be informed via e-mail or fax. A subject withdrawn from the study because of an AE must be followed by the Investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. Follow-up may need to continue after the subject has discontinued from the study, and additional investigations may be requested by the PTC Therapeutics medical monitoring team.

The first day of AE reporting will coincide with the date of signing of informed consent and including a minimum of 30 calendar days after the last administration of study drug.

8.4.9 Serious Adverse Event Reporting

All SAEs should be reported via the SAE report form to PTC Therapeutics within 24 hours of becoming aware of the event(s). In addition, the AE portion of the eCRF must also be completed.

The SAE report form should be signed by the Investigator; however, if the Investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE report form must be faxed or e-mailed to the PTC Therapeutics Pharmacovigilance Department or designee and to the site Institutional Review Board/Institutional Ethics Committee (IRB/IEC) (if required by local regulations) within 24 hours.

Follow-up information to the SAE should be clearly documented as “follow-up” in the SAE report form and must also be faxed or e-mailed to the same party. All follow-up SAE report forms for the event must be signed by the Investigator. Any source documents (eg, progress notes, nurses’ notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor should be redacted so that the subject’s name, address, and other personal identity information are obscured. Only the subject’s study number and initials are to be provided (in regions where the provision of such information is permitted). The information in the AE portion of the eCRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (for example, if a subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the AE.

The PTC Therapeutics Pharmacovigilance Department contact information for reporting SAEs is provided below. This information is also provided in the Study Manual and in the SAE report form.

PTC Therapeutics Safety Department
Attention: Pharmacovigilance
E-mail: [redacted]
Facsimile: [redacted]

8.4.10 Contraception

Women of child bearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (eg, hysterectomy, bilateral tubal ligation, bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. Women who are WOCBP and are using an active method of birth control, are practicing abstinence or where the partner is sterile (eg, vasectomy), are considered to be WOCBP.

WOCBP must use 2 forms of effective contraception simultaneously for the duration of study participation in a manner such that risk of failure is minimized. Periodic and/or temporary abstinence such as declaration of abstinence during study participation or fertility awareness-based methods to prevent pregnancy (including but not limited to symptothermal and ovulation estimation by either calendar day or salivary/cervical secretions) are not considered effective methods of birth control; however, true (absolute) sexual abstinence (ie, in line with the preferred and usual lifestyle of the subject) may be permitted. Effective methods of birth control approved for use in this study are:

1. Implants (eg, Norplant® system)
2. Injectable (eg, Depo-Provera®)
3. Transdermal patch
4. Combined oral contraceptives
5. Barrier methods (condoms and diaphragm with spermicide) – note: double barrier method is required if no other methods of birth control are in use
6. Intrauterine devices (eg, ParaGard®, Mirena®)

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation. During the trial, all WOCBP will be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

8.4.11 Reporting Pregnancy

PTC Therapeutics should be notified in the event that a female subject in the study, or a female partner of a male subject in the study, becomes pregnant on-study or within 30 days of the last administration of study drug must be reported on a Pregnancy Notification Form (see Study Manual for details).

This must be done whether or not an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

Written consent is required prior to collecting and reporting any information on a female partner of a male subject in the study.

If possible, the Investigator should follow the subject, or the pregnant female partner of a male subject, until completion of the pregnancy and notify the PTC Therapeutics medical monitor of the outcome within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial Pregnancy Notification Form via the Pregnancy Outcome Form (see the Study Manual for details).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should follow the procedures for reporting SAEs, ie, report the event to the PTC Therapeutics Safety Department or designee and follow-up by submission of appropriate AE eCRFs (see Section 8.4.9).

8.4.12 PTC Therapeutics Adverse Event Reporting Requirement

As the sponsor of the study, PTC Therapeutics is responsible for reporting certain safety information, particularly SAEs and subject deaths related to participation in the study, to each investigator in an expedited manner. If notification of an AE requiring expedited reporting to investigators is received, PTC Therapeutics or its designated representative will contact each investigational site participating in this study by e-mail, fax, and/or overnight mail such that the Investigator can promptly notify the site IRB/IEC per their local requirements. The initial expedited safety report will be provided as required according to local regulations (eg, within 15 days) after the earliest date PTC Therapeutics or an agent of PTC Therapeutics (eg, a site monitor) becomes aware of an AE. This awareness date is the date the regulatory reporting clock begins, and the date is considered Day 0.

8.4.13 Safety Monitoring

Subjects will be monitored closely for adverse events or laboratory abnormalities, or other safety assessments (ie, height, weight, vital signs, electrocardiograms, and physical examination) during the course of the study.

For adverse events or laboratory abnormalities, the Investigator should use his/her judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug therapy is appropriate.

While specific monitoring, diagnostic testing, and supportive care measures must be instituted based on the clinical judgment of the Investigator, investigators are encouraged to contact the medical monitor to obtain guidance and to ascertain whether similar events are being seen at other sites. The medical monitor should be notified of any adverse event or laboratory abnormality that leads to dose interruption and should be apprised of ancillary laboratory or other diagnostic findings and the evolving data from any work-up of the initial abnormality. The medical monitor may suggest review of the case with gastroenterology, endocrinology, nephrology consultants or with other experts (either at the site or retained by PTC Therapeutics).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis

No hypothesis will be tested in this study.

9.2 Sample Size Determination

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. Summary statistics such as mean, standard deviation, median, minimum and maximum will be provided for the change in 4-stair climb in seconds after 26 weeks of treatment. The 95% confidence interval for the mean will be provided as well.

If 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 Zero 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.

9.3 Population for Analyses

9.3.1 Full/Safety Population

The Full/Safety population includes all enrolled subjects who receive at least one dose of deflazacort.

9.3.2 Pharmacokinetic Population

The pharmacokinetic population includes all enrolled subjects who received at least 1 dose of study drug and had sufficient concentration-time data for the calculation of PK parameters.

9.4 General Statistical Considerations

Continuous variables will be summarized using the number of non-missing observations (N), mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using count and percentage.

By-patient listings will be created for each case report form (CRF) module.

9.5 Specific Statistical Analyses

9.5.1 Study Conduct

All protocol deviations will be listed and summarized.

9.5.2 Subject Disposition

The disposition of subjects will be summarized, including the number of subjects screened, the number of screen failures, the reason of screening failure, the number of subjects enrolled, the number of enrolled subjects who received at least 1 dose of study drug. The number of subjects who prematurely discontinued study drug and the discontinuation reason will be tabulated.

9.5.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics of subjects will be summarized descriptively based on Full/Safety Population.

9.5.4 Study Treatment and Extent of Exposure

All analyses of treatment exposure will be conducted using the safety population. Duration of treatment exposure, and treatment compliance, will be summarized by actual treatment received in the safety population. The dose modifications and modification reasons will be listed and summarized as well.

9.5.5 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary currently in effect into Anatomical-Therapeutic-Chemical classification codes. The types and the dates of concomitant medications will be listed and summarized.

9.5.6 Analyses of Primary Endpoints

The primary efficacy endpoint (change in 4-stair climb in seconds) will be summarized the number of non-missing observations (N), mean, standard deviation, minimum, median, and maximum. The 95% confidence interval for the mean change after 26 weeks of treatment will be provided as well.
Analyses of Secondary Endpoints for Efficacy

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 will be provided for all secondary endpoints.

9.5.7 Analyses of Secondary Endpoints for Safety

Safety results will be summarized in safety population.

The baseline value is defined as the last non-missing value prior to the first dose.

9.5.7.1 Adverse Events

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

Adverse events will be coded using the most recent version of MedDRA. The severity of AEs will be graded by investigators according to the CTCAE, Version 5.0 whenever possible.

The frequency of subjects experiencing a specific adverse event will be tabulated by system organ class (SOC) and preferred term (PT). AE leading to study medication discontinuation, AE leading to dose reduction/interruption, AE related to study medication, AE leading to death, AEs with CTCAE Grade 3 or higher, and SAE will be tabulated and summarized by treatment by SOC and PT.

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

9.5.7.2 Laboratory Abnormalities

The severity of laboratory abnormalities will be graded using the CTCAE whenever possible.

Descriptive statistics will be used to summarize the laboratory results and the change from baseline by visit . Shift tables from baseline to worst severity grade observed during the treatment will be displayed . The number and percentage of subjects experiencing a specific laboratory abnormality will be tabulated as well. Other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings of clinical laboratory data with abnormal flags will be provided by subject, visit, and test.

9.5.7.3 Other Safety Assessments

Height, weight, body mass index, vital signs (heart rate and blood pressure), ECG, and physical examination data analyses will be descriptive in nature, and the data will be summarized by visit.

9.5.8 Analyses of Secondary Endpoints for Pharmacokinetics

Pharmacokinetic assessments: 21-desacetyl deflazacort and 6β-hydroxy-21-desacetyl deflazacort plasma concentrations collected prior to the morning dose will be summarized. The relationship between 21-desacetyl deflazacort and 6β-hydroxy-21-desacetyl deflazacort plasma concentrations and selected efficacy and safety outcomes will be explored. Results will be compared with PK data from previous studies. PK parameters will be calculated using noncompartmental analysis method: $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, C_{max}, T_{max}, CL/F, Vz/F, λz, and t½.

9.5.9 Exploratory Endpoints

Exploratory endpoints will be listed or summarized descriptively as appropriate.

9.5.10 Subgroup Analyses

No subgroup analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation (ICH) GCP guidance documents and all relevant local law and applicable regulatory requirements.

PTC Therapeutics will ensure notification to all competent authorities, ethics committees, and local authorities of any substantial protocol amendment according to relevant local law and applicable regulatory requirements. PTC Therapeutics will inform the competent authorities, ethics committees, and local authorities about non-substantial amendments according to relevant local law and applicable regulatory requirements. PTC Therapeutics must receive approval from the applicable competent authorities, ethics committees, and local authorities before implementing the substantial amendment.

10.1.1 Institutional Review Board/Independent Ethics Committee

Prior to enrollment of subjects into the study, as required by the FDA and other regulatory authorities, the protocol and informed consent document will be reviewed and approved by an appropriate IRB/IEC. The Investigator will assure that approval of the study protocol will be obtained from the IRB/IEC and that all aspects of the IRB/IEC review will be conducted in accordance with current regulations. Amendments to the protocol will be subject to the same IRB/IEC review requirements as the original protocol. Only changes necessary to eliminate apparent immediate hazards to subjects may be initiated prior to IRB/IEC approval. In that event, the Investigator must notify the IRB/IEC and PTC Therapeutics in writing within 5 working days after implementation. The investigator will also promptly notify the IRB/IEC of any serious, unexpected adverse events, or any other information that may affect the safe use of the drug during the course of the study.

A letter documenting the IRB/IEC approval and a list of the names and titles of the IRB/IEC members must be received by PTC Therapeutics prior to the initiation of the study. All correspondence with the IRB/IEC should be retained in the Investigator's study file.

The Investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to PTC Therapeutics or CRO designee. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB/IEC and to PTC Therapeutics or CRO designee. This report should include the dates of initiation and completion of the study, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of subjects evaluated, the number of subjects who discontinued (and the reasons for discontinuation), the number of subjects who completed the study, and the results of the study, including a description of any adverse events. PTC Therapeutics or CRO designee will assist the Investigator in the preparation of this report, as needed.

10.1.2 Informed Consent Process

The Investigator will assure that informed consent will be obtained from each subject and/or legal guardian prior to study entry and that the informed consent will be obtained in accordance with current regulations.

The Investigator or sub-investigator will give each subject and/or legal guardian full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent/ document will be provided to each subject and/or legal guardian in a language in which the subject or legal guardian is fluent. This information must be provided to the subject or legal guardian prior to undertaking any study-related procedure. Adequate time should be provided for the subject and/or legal guardian to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the subject and/or legal guardian may have about the study. The subject and/or legal guardian should be able to ask additional questions as and when needed during the conduct of the study. The subject's and/or legal guardian signature on the informed consent form should be obtained at the Investigator site in the presence of the Investigator or a qualified representative (eg, sub-investigator).

Each subject or legal guardian will be given a copy of the signed consent form. The original signed informed consent forms will be retained by the Investigator with the study records.

The written subject information must not be changed without prior approval by PTC Therapeutics and the IRB/IEC.

10.1.3 Study Discontinuation and Closure

PTC Therapeutics reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The Investigator, after consultation with the PTC Therapeutics medical monitor, reserves the right to discontinue the study at the Investigator site for safety reasons at any time.

After a decision to terminate the study, investigators must contact all subjects who are continuing their participation in the study and must do so within a time-period set by PTC Therapeutics. As directed by PTC Therapeutics, all study materials must be collected, and all electronic data entry forms completed to the greatest extent possible.

10.1.4 Confidentiality and Privacy

Research records will be collected and stored in a manner that protects the confidentiality of subject information. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs, paper CRFs, or other records provided to or retained by PTC Therapeutics (or its authorized designee). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by blanking out the subject's name and replacing the name with the subject's study identification number on any record provided to or retained by PTC Therapeutics. The informed consent form must include appropriate statements explaining these requirements.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and the IRB/IEC will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and the IRB/IEC. By signing this protocol, the Investigator affirms to PTC Therapeutics that the Investigator will maintain, in confidence, information furnished by PTC Therapeutics and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

10.1.5 Clinical Monitoring

In accordance with 21 CFR Part 312.56 and/or relevant ICH guidelines, PTC Therapeutics or a designee will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide PTC Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, applicable FDA and other relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this study. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by PTC Therapeutics. The Investigator/institution guarantees direct access to source documents by PTC Therapeutics and appropriate regulatory authorities.

It is important that the Investigator and relevant institutional personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.1.6 Quality Assurance and Quality Control

To ensure compliance with GCP and all applicable regulatory requirements, PTC, PTC's representatives, a regulatory authority or and Institutional Review board may conduct a quality assurance audit. Reasons for quality assurance audit may include but are not limited to: random selection, geographic proximity, suspected GCP violation, high enrolling site, recurring protocol deviations, etc. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Council on Harmonisation, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.1.7 Data Handling and Record Keeping

To enable evaluations and/or audits from regulatory authorities or PTC Therapeutics, the Investigator agrees to keep accurate and complete records, including the identity of all participating subjects (sufficient information to link eCRFs and clinic records/source documents), all original signed informed consent forms, electronic copies (ie, CD-ROM, USB, etc) or paper copies of the data that have been captured in the electronic data capture for each subject (eCRFs), and detailed records of study drug disposition. All records and documents pertaining to the study will be maintained by the Investigator until notification is received from PTC Therapeutics that the records no longer need to be retained.

The Investigator must obtain written permission from PTC Therapeutics before disposing of any records. The Investigator will promptly notify PTC Therapeutics in the event of accidental loss or destruction of any study records. If the Investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to PTC Therapeutics as applicable.

10.1.8 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to:

1. Failure to adhere to study exclusion and inclusion criteria
2. Failure to comply with dispensing or dosing requirements
3. Use of medications that are specifically prohibited in the protocol
4. Missed or out-of-window visits
5. Drug dosing not administered within the time frame specified in the protocol
6. Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc - either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
7. Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, or failure to obtain IRB approvals for the protocol and ICF revisions

Significant deviations are any deviations that impact subject eligibility (ie, protocol inclusion/exclusion violations), subject safety or a subject's ability to continue in the clinical trial.

At the outset of the study, a process for defining and handling protocol deviations will be established with the CRO. This will include determining which deviations will be designated significant; thus, requiring immediate notification to the PTC Therapeutics medical monitor and the sponsor.

Prospective deviations (eg, protocol waivers) are prohibited per PTC policy.

The Investigator is responsible for seeing that any known protocol deviations are recorded handled as agreed.

10.1.9 Publication and Data Sharing Policy

The information developed during the conduct of this clinical study is considered confidential by PTC Therapeutics. This information may be disclosed as deemed necessary by PTC Therapeutics.

PTC Therapeutics intends that the data from this study will be presented and published. The PTC Therapeutics staff under the direction of the PTC Therapeutics Chief Medical Officer or designee in collaboration with the Investigator will be responsible for writing presentations and manuscripts for publication. Investigators will not be allowed to publish or present the data from this study without prior agreement with PTC Therapeutics.

The Investigator is obliged to provide the sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Data from all sites participating in the study will be pooled and analyzed by the sponsor or the sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the Investigator may publish or present the results generated at his or her site.

The Investigator will provide the sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The sponsor shall inform the Investigator in writing of any changes or deletions in such presentation or publication required to protect the sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the Investigator may proceed with the presentation or submission for publication unless the sponsor has notified the institution or the Investigator in writing that such proposed publication or presentation discloses the sponsor's confidential and proprietary technical information. Further, upon the request of the sponsor, the Investigator will delay the publication or presentation for an additional 90 days to permit the sponsor to take necessary actions to protect its intellectual property interests.

10.2 Additional Considerations

10.2.1 Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 and with requirements of the International Committee of Medical Journal Editors as a condition of consideration for publication of study results, PTC Therapeutics will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov and EudraCT websites and that information at the websites relating to study design and conduct are appropriately updated during the course of the study. In order to facilitate this process, investigators will need to supply PTC Therapeutics with appropriate contact information for investigator site personnel.

10.2.2 Communications with Regulatory Authorities

PTC Therapeutics will assume responsibility for regulatory interactions with regulatory authorities (eg, the FDA, the European Medicines Agency, and/or others). In this regard, PTC Therapeutics will maintain an IND for deflazacort in support of the study. In fulfilling this responsibility, PTC Therapeutics (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, FDA form 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. PTC Therapeutics (or a designee) will also assume responsibility for adverse event reporting to regulatory authorities as described in Section 8.4.12.

10.3 Protocol Amendment History

Version 1: 13 December 2018

Version 2: 28 February 2019

The overall reason for Version 2: The overall reasons for Version 2 were to include DEXA as an additional safety assessment in subjects with LGMD2I. In addition, several editorial changes were made to clarify and correct the text.

Item No.	Protocol Section	Version 2/Update	Reason/ Rationale
1	Protocol	“Patient(s)” was revised to “subject(s)” when referring to this protocol. “Pill(s)” was revised to “tablet(s)”. The following terms were deleted: caregiver(s) (except Sections 6.1.2, 6.1.4, and 7.3), assent, parent(s), legally acceptable representative Editorial revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity.	Update
2	Protocol	The title of the protocol was edited to read: “A Multicenter Randomized Placebo-Controlled Phase 3 Study on the Safety and Efficacy of Deflazacort (Emflaza®) in Subjects with Limb-Girdle Muscular Dystrophy 2I (LGMD2I)”	Update
3	Synopsis	The title of the protocol in the synopsis was corrected and now reads: “A Multicenter Randomized Placebo-Controlled Phase 3	Update

Item No.	Protocol Section	Version 2/Update	Reason/ Rationale
		Study on the Safety and Efficacy of Deflazacort (Emflaza®) in Subjects with Limb-Girdle Muscular Dystrophy 2I (LGMD2I)"	
4	Synopsis	Secondary Endpoints were edited to include DEXA as part of safety assessment (secondary endpoint) to evaluate bone density. Exploratory endpoints were edited to indicate that change from baseline in muscular fat fraction and inflammation of selected lower limb muscles will be evaluated at Week 26. Inclusion criteria #5 was edited to read: "Must weigh ≥35 to ≤112.5 kg" Exclusion criteria #5 was edited to read: "History of recent bacterial infection (including tuberculosis) per discretion of the Investigator" Exclusion criteria #9 was edited to indicate a person is excluded from the study if they participated in an interventional study within 3-months prior to baseline of study PTCEMF-GD-004 (Study 004). The #9 exclusion criteria now reads: "Participated in an interventional clinical trial within the last 3 months prior the Baseline Visit" Statistical Methods was edited to read: "Primary analysis will be performed using the ITT population from all scheduled visits."	Update
5	Protocol Identifiers and Study Personnel	The Clinical trials.gov number has been added. That is NCT03783923	Update
6	Synopsis and Section 8.1 - Schedule of Events	A follow-up phone call for collecting AEs was added to the Schedule of Events table. DEXA has been added to the Schedule of Events. The "notes" for Height/Weight/BMI was edited to read "For study inclusion, weight range must be ≥35 to ≤112.5 kg". The "notes" for MRI was edited to indicate qMRI and T2 MRI will evaluate muscular fat fraction and inflammation, respectively, of selected lower limb muscles. Footnote #2 of the Schedule of Events was edited to include the fact that the assessment of time to climb 4 stairs must always be repeated at the baseline visit and now reads: "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 repeated 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." Footnote #3 was added to describe Visit 3 procedures when switching from the double-blind to open-label phase of the protocol. Footnote #4 was edited to more fully describe the early termination visit. It describes the follow-up for subjects that are remaining on corticosteroid therapy and for those tapering off of deflazacort. Footnote #5 was edited to more clearly define the follow-up visit/phone call for those subjects that complete the study and immediately start receiving commercial deflazacort or another corticosteriod. It will be an office for subjects tapering off deflazacort	Update

Item No.	Protocol Section	Version 2/Update	Reason/ Rationale
		to return study drug and for site collection of any AEs and will occur 4-weeks after last dose of study drug. Footnote #7 was edited to indicate that 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. Footnote #9 was edited to indicate efficacy and PD assessment 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 4-stair climb 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.	
7	2.2.2	DEXA has been added as part of safety assessment (secondary endpoint) to evaluate bone density.	Update
8	2.2.3	Exploratory endpoints were edited to indicate that change from baseline in muscular fat fraction and inflammation will be evaluated from selected lower limb muscles at Week 26.	Update
9	3.1	Text was added that describes the follow-up visit. Text was edited to indicate genotyping may be performed to confirm a subject carries a mutation in the FKRP gene if they are lacking documentation of an FKRP mutation. Text was added to indicate that safety, efficacy, and PD will be evaluated at Visit 3 (Week 26). Placebo subjects will have all assessments performed prior to first dose of deflazacort. A description of Visit 4 (Week 39), Visit 5/ET and the Follow-up Visit/phone call has been added. Figure 1 was revised to better portray the follow-up Visit/phone call.	Update
10	4.2	Inclusion criterial #2 was edited to read: “Male and female subjects aged ≥18 years” Inclusion criteria #5 was edited to read: “Must weigh ≥35 to ≤112.5 kg”	Update
11	4.3	Exclusion criteria #5 was edited to read: “History of recent bacterial infection (including tuberculosis) per discretion of the Investigator” Exclusion criteria #9 was edited to indicate a person is excluded from the study if they participated in an interventional study within 3-months prior to baseline of study PTCEMF-GD-004 (Study 004). The #9 exclusion criteria now reads: “Participated in an interventional clinical trial within the last 3 months prior the Baseline Visit”	Update
12	6.1.2	Text was edited to read specify that in Period 2 dose adjustments are permitted in case of tolerability issues at the discretion of the Investigator but only after discussion with the PTC Therapeutics medical monitor, as described in Section 6.1.2.2 of the protocol. Text was edited to clarity that subjects must be instructed not to split the tablet(s) and subjects are instructed not to chew the study drug.	Update
13	7.2	A description of the how patients who terminate early/discontinue from the study will be followed-up has been added.	Update

Item No.	Protocol Section	Version 2/Update	Reason/ Rationale
14	9.5.10	Text was edited to read: “Results will be compared with PK data from previous studies. PK parameters will be calculated using noncompartmental analysis method: AUC(0-t), AUC(0-inf), Cmax, Tmax, CL/F, Vz/F, λz, and t½.	Update

Version 3: 26 September 2019

The overall reason for Version 3: The overall reasons for Version 3 were to address regulatory feedback and to provide updates, including adding an exploratory objective and endpoint, to add study visits, to clarify options for subjects at the end of the study and if their blind is broken, and to clarify statistical analysis for the key secondary endpoints. In addition, several editorial changes were made to clarify and correct the text.

Item No.	Protocol Section	Version 3/Update	Reason/ Rationale
1	Protocol	Document date/version were updated. Editorial revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. Additionally, table numbers and cross references to tables were updated based on the new Table 1 that was added.	Update
2	Synopsis	An Exploratory Objective and an Exploratory Endpoint was added to include the Individualized Neuromuscular Quality of Life (INQoL) questionnaire in subjects with limb-girdle muscular dystrophy 2I (LGMD2I). Inclusion criteria #3 was edited to clarify the number of seconds the subject has to ascend the stairs. Exclusion criteria #6 was edited to clarify the criteria for diabetes mellitus.	Update
3	Synopsis and Section 8.1 - Schedule of Events	The Schedule of Events table was edited to include a Safety Call at Week 28, to clarify the clinical laboratory assessments, to add Study Procedures for Biomarker testing (Bone Health Assays) and the INQoL Questionnaire, to clarify the Ophthalmological examination, to clarify the number of seconds the subject has to ascend the stairs, and to add visits for ECGs, AE/SAE monitoring, and concomitant medications. Edits to the table include updates to the footnotes and the numbering of the footnotes.	Update
4	1.2	Text was added to include the date the U.S. Food and Drug Administration (FDA) approved deflazacort as a treatment for patients ≥2 years with DMD.	Update
5	2.1.3	An Exploratory Objective was added to include the INQoL questionnaire in subjects with LGMD2I.	Update
6	2.2.3	An Exploratory Endpoint was added to include the INQoL questionnaire in subjects with LGMD2I.	Update
7	3.1	Text was added/edited to include the Week 28 Safety Call, to clarify dose adjustments, and to clarify the options for subjects at the end of the study. The Week 28 Safety Call was also added to Figure 1.	Update
8	3.2	Text and table were added/edited to describes the benefit/risk profile for the use of deflazacort in subjects with LGMD2I. Text was added to describe the INQoL questionnaire.	Update
9	4.2	Inclusion criteria #3 was edited to clarify the number of seconds the subject has to ascend the stairs.	Update
10	4.3	Exclusion criteria #6 was edited to clarify the criteria for diabetes mellitus.	Update
11	6.1.2.2	Text regarding dose adjustments has been modified for clarity.	Update

Item No.	Protocol Section	Version 3/Update	Reason/ Rationale
		The following text was deleted “provided the subject has completed the Week 13 visit” from Acne, Behavior Changes, Cushingoid Appearance, Gastrointestinal Irritation, Hyperglycemia or Glycosuria, Hypertension, Infections Potentially Related to Corticosteroid-Mediated Immunosuppression, and the Weight gain sections. Text in the Hypertension section regarding substantial hypertension was modified for clarity. In the subsection of Weight Gain, “child/family” was changed to “subject” and “/family” was deleted for clarity.	
12	6.3	Text was added/edited to clarify the options for subjects whose blind has been broken.	Update
13	6.5	In the Concomitant Therapy section, “study” was changed to “follow-up visit” for all medication taken by subjects 30 days prior to the first dose of study drug	Update
14	6.5.2	Text was added to clarify that subjects should not receive live or attenuated vaccines during the study.	Update
15	7.1	Text added/edited to clarify the options for subjects who discontinue study drug.	Update
16	8.2	The following sentence was deleted “Each evaluator will be expected to demonstrate reliability and competence by assessing a volunteer subject with LGMD2I in accordance with the clinical evaluator manual.”	Update
17	8.4.2	The following sentence was deleted “An event need not be reported as an SAE if it exclusively represents a relapse or an expected change or progression of the baseline cancer.”	Update
18	9.5.7	Text was added/deleted to clarify the statistical analysis for the key secondary endpoints.	Update
19	10.1	Text was added to clarify the regulatory, ethical, and study oversight considerations.	Update
20	11	List was updated to add sources to the references list.	Update
21	10.3	Added Protocol Version History.	Update

Version 4: 24 March 2020

The overall reason for Version 4: The overall reason for Version 4 was the closure of the study. The protocol was amended to allow continuation of treatment for those subjects already on study and to allow further enrollment up to approximately 30 subjects.

Item No.	Protocol Section	Version 4/Update	Reason/ Rationale
1	Protocol	Document date/version were updated. Editorial revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The study title was updated to reflect that the study is now an open-label study.	Update
2	Synopsis	The number of study sites and planned subjects was reduced and all mention of placebo treatment was removed. The synopsis was aligned with all changes mentioned below.	Update
3	2.1.3	Pharmacodynamic biomarkers were removed from the exploratory objectives and replaced by MRI	Update
4	2.2	The “key” designation was removed from secondary endpoints, the exploratory endpoints were updated to include Dixon MRI, and the endpoint regarding T2 mapping was moved from Exploratory to Secondary.	Update
5	3.1	The study design was updated to remove randomization and a placebo-controlled period and to reduce the number of study sites, subjects, and visits.	Update
6	3.4	Section added to explain transition from Protocol Version 3.0 to Version 4.0.	Update
7	4.2	Inclusion criterion #3 was amended to read “Ability to ascend 4 stairs in ≥2.5 seconds and be able to complete the ascent and descent at screening and baseline.”	Update
8	5.1	The number of planned subjects was reduced from 100 to 30.	Update
9	6	Randomization to placebo was removed.	Update
10	9	The statistical analyses were updated to remove the comparison against placebo.	Update

11 REFERENCES

Angelini C. The role of corticosteroids in muscular dystrophy: a critical appraisal. Muscle Nerve. 2007;36(4):424-435.

Angelini C, Fanin M, Menegazzo E, Freda MP, Duggan DJ, Hoffman EP. Homozygous alpha-sarcoglycan mutation in two siblings: one asymptomatic and one steroid-responsive mild limb-girdle muscular dystrophy patient. Muscle Nerve. 1998;21(6):769-775.

Arpan I, Willcocks RJ, Forbes SC, Finkel RS, Lott DJ, Rooney WD, et al. Examination of effects of corticosteroids on skeletal muscles of boys with DMD using MRI and MRS. Neurology. 2014;83(11):974-980.

Baumeister SK, Todorovic S, Milic-Rasic V, Dekomien G, Lochmuller H, Walter MC. Eosinophilic myositis as presenting symptom in gamma-sarcoglycanopathy. Neuromuscul Disord. 2009;19(2):167-171.

Bello L, Gordish-Dressman H, Morgenroth LP, Henricson EK, Duong T, Hoffman EP, et al. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology. 2015;85(12):1048-1055.

Boito CA, Melacini P, Vianello A, Prandini P, Gavassini BF, Bagattin A, et al. Clinical and molecular characterization of patients with limb-girdle muscular dystrophy type 2I. Arch Neurol. 2005;62(12):1894-1899.

Bourteel H, Vermersch P, Cuisset JM, Maurage CA, Laforet P, Richard P, et al. Clinical and mutational spectrum of limb-girdle muscular dystrophy type 2I in 11 French patients. J Neurol Neurosurg Psychiatry. 2009;80(12):1405-1408.

Brockington M, Yuva Y, Prandini P, Brown SC, Torelli S, Benson MA, et al. Mutations in the fukutin-related protein gene (FKRP) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C. Hum Mol Genet. 2001;10(25):2851-2859.

Brown SC, Torelli S, Brockington M, Yuva Y, Jimenez C, Feng L, et al. Abnormalities in alpha-dystroglycan expression in MDC1C and LGMD2I muscular dystrophies. Am J Pathol. 2004a;164(2):727-737.

Brown SC, Torelli S, Brockington M, Yuva Y, Jimenez C, Feng L, et al. Abnormalities in α-Dystroglycan Expression in MDC1C and LGMD2I Muscular Dystrophies. The American Journal of Pathology. 2004b;164(2):727-737.

Calcort 6 mg Tablet SmPC. Approved Summary of Medicinal Product Characteristics (SmPC), Calcort 6 mg Tablet, United Kingdom, updated 03 May 2018.

Carotti M, Fecchio C, Sandonà D. Emerging therapeutic strategies for sarcoglycanopathy. Expert Opinion on Orphan Drugs. 2017;5(5):381-396.

Darin N, Kroksmark AK, Ahlander AC, Moslemi AR, Oldfors A, Tulinius M. Inflammation and response to steroid treatment in limb-girdle muscular dystrophy 2I. Eur J Paediatr Neurol. 2007;11(6):353-357.

de Paula F, Vieira N, Starling A, Yamamoto LU, Lima B, de Cassia Pavanello R, et al. Asymptomatic carriers for homozygous novel mutations in the FKRP gene: the other end of the spectrum. Eur J Hum Genet. 2003;11(12):923-930.

Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature. J Neuromuscul Dis. 2015;2(1):73-85.

Emflaza [deflazacort] Prescribing Information. Retrieved August 28, 2018, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208684s000,208685s000lbl.pdf.

Godfrey C, Escolar D, Brockington M, Clement EM, Mein R, Jimenez-Mallebrera C, et al. Fukutin gene mutations in steroid-responsive limb girdle muscular dystrophy. Ann Neurol. 2006;60(5):603-610.

Griggs RC, Miller JP, Greenberg CR, Fehlings DL, Pestronk A, Mendell JR, et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. Neurology. 2016;87(20):2123-2131.

Hathout Y, Seol H, Han MH, Zhang A, Brown KJ, Hoffman EP. Clinical utility of serum biomarkers in Duchenne muscular dystrophy. Clin Proteomics. 2016a;13:9.

Kang PB, Feener CA, Estrella E, Thorne M, White AJ, Darras BT, et al. LGMD2I in a North American population. BMC Musculoskeletal Disorders. 2007;8:115-115.

Khadilkar SV, Patel BA, Lalkaka JA. Making sense of the clinical spectrum of limb girdle muscular dystrophies. Pract Neurol. 2018;18(3):201-210.

Kinnett K, Noritz G. The PJ Nicholoff Steroid Protocol for Duchenne and Becker Muscular Dystrophy and Adrenal Suppression. PLoS Curr. 2017;9.

Lin YC, Murakami T, Hayashi YK, Nishino I, Nonaka I, Yuo CY, et al. A novel FKRP gene mutation in a Taiwanese patient with limb-girdle muscular dystrophy 2I. Brain Dev. 2007;29(4):234-238.

Mah JK, Korngut L, Fiest KM, Dykeman J, Day LJ, Pringsheim T, et al. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. Can J Neurol Sci. 2016;43(1):163-177.

Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2016(5):Cd003725.

McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, 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. 2018;391(10119):451-461.

Moore SA, Shilling CJ, Westra S, Wall C, Wicklund MP, Stolle C, et al. Limb-Girdle Muscular Dystrophy in the United States. Journal of Neuropathology & Experimental Neurology. 2006;65(10):995-1003.

Muntoni F, Torelli S, Wells DJ, Brown SC. Muscular dystrophies due to glycosylation defects: diagnosis and therapeutic strategies. Curr Opin Neurol. 2011;24(5):437-442.

Narayanaswami P, Weiss M, Selcen D, David W, Raynor E, Carter G, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline

development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology. 2014;83(16):1453-1463.

Nigro V, Savarese M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. Acta Myol. 2014;33(1):1-12.

Pegoraro E, Hoffman EP. Limb-Girdle Muscular Dystrophy Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews((R)). Seattle (WA): University of Washington, Seattle

University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.

Peric M, Peric S, Stevanovic J. Quality of life in adult patients with limb-girdle muscular dystrophies. A Neurol Belg. 2018;118:243-250.

Poppe M, Cree L, Bourke J, Eagle M, Anderson LV, Birchall D, et al. The phenotype of limb-girdle muscular dystrophy type 2I. Neurology. 2003;60(8):1246-1251.

Quattrocelli M, Salamone IM, Page PG, Warner JL, Demonbreun AR, McNally EM. Intermittent glucocorticoid dosing improves muscle repair and function in mice with limb-girdle muscular dystrophy. The American journal of pathology. 2017;187(11):2520-2535.

Schwartz M, Hertz JM, Sveen ML, Vissing J. LGMD2I presenting with a characteristic Duchenne or Becker muscular dystrophy phenotype. Neurology. 2005;64(9):1635-1637.

Serafini PR, Feyder MJ, Hightower RM, Garcia-Perez D, Vieira NM, Lek A, et al. A limb-girdle muscular dystrophy 2I model of muscular dystrophy identifies corrective drug compounds for dystroglycanopathies. JCI Insight. 2018;3(18).

Stensland E, Lindal S, Jonsrud C, Torbergsen T, Bindoff LA, Rasmussen M, et al. Prevalence, mutation spectrum and phenotypic variability in Norwegian patients with Limb Girdle Muscular Dystrophy 2I. Neuromuscul Disord. 2011;21(1):41-46.

Svahn J, Streichenberger N, Benveniste O, Menassa R, Michel L, Fayolle H, et al. Significant response to immune therapies in a case of subacute necrotizing myopathy and FKRP mutations. Neuromuscul Disord. 2015;25(11):865-868.

Sveen ML, Schwartz M, Vissing J. High prevalence and phenotype-genotype correlations of limb girdle muscular dystrophy type 2I in Denmark. Ann Neurol. 2006;59(5):808-815.

Vincent K, Carr A, Walburn J, Scott D, Rose M. Construction and validation of a quality of life questionnaire for neuromuscular disease (INQoL). Neurology. 2007;68:1051-1057.

Wang DN, Wang ZQ, Chen YQ, Xu GR, Lin MT, Wang N. Limb-girdle muscular dystrophy type 2I: two Chinese families and a review in Asian patients. Int J Neurosci. 2018;128(3):199-207.

Willis TA, Hollingsworth KG, Coombs A, Sveen ML, Andersen S, Stojkovic T, et al. Quantitative magnetic resonance imaging in limb-girdle muscular dystrophy 2I: a multinational cross-sectional study. PLoS One. 2014;9(2):e90377.

Wong-Kisiel LC, Kuntz NL. Two siblings with limb-girdle muscular dystrophy type 2E responsive to deflazacort. Neuromuscul Disord. 2010;20(2):122-124.

Wu B, Shah SN, Lu P, Richardson SM, Bollinger LE, Blaeser A, et al. Glucocorticoid Steroid and Alendronate Treatment Alleviates Dystrophic Phenotype with Enhanced Functional Glycosylation of alpha-Dystroglycan in Mouse Model of Limb-Girdle Muscular Dystrophy with FKRPP448L Mutation. Am J Pathol. 2016;186(6):1635-1648.