Protocol Number: SMT C11005

Official Title: PhaseOut DMD: A Phase 2 Clinical Study to Assess the Activity and Safety of Utrophin Modulation with SMT C1100 in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy (SMT C11005)

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Effective Date: 24/Feb/17

Short Title: PoC Study to Assess Activity and Safety of SMT C1100 (Ezutromid) in Boys with DMD

Abstract: This is a Phase 2, open-label, study to assess the activity and safety of utrophin modulation with SMT C1100 administered twice-daily (*bid*) to paediatric male subjects with Duchenne Muscular Dystrophy (DMD).

Study SMT C11005 will enrol approximately 55 patients in three cohorts. In Cohort 1 approximately 30 patients with DMD, from UK and US sites, will receive 2.5 g SMT C1100 *bid* as a microfluidised aqueous oral suspension (F3). In Cohort 2 approximately 10 patients will receive 1 g SMT C1100 *bid* as a powder for oral suspension (F6). These 10 patients in Cohort 2 will be enrolled at US sites only. In Cohort 3, approximately 15 patients, who have previously received SMT C1100 but who are not eligible for Cohort 1 or 2, will be enrolled in a safety arm and undergo additional cardiac magnetic resonance scans and pulmonary function tests. The patients in Cohort 3 will be enrolled at UK sites only and will receive 2.5 g SMT C1100 *bid* as a microfluidised aqueous oral suspension (F3).

This study investigates the biological (pharmacokinetic/pharmacodynamic) and clinical effects of SMT C1100 in a DMD population. It also examines the long term safety profile, initially over 48 weeks but then for longer for those who agree to enter the Extension Phase (which will continue until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued). This is a proof-of-concept study and as such aims to determine if SMT C1100 acts as seen in *in vitro* and pre-clinical studies and modulates utrophin expression in muscles. This study will specifically investigate if the expected changes in utrophin have a demonstrable effect on leg muscles (determined by magnetic resonance imaging (MRI)).

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[redacted]

[redacted]

[redacted]

INVESTIGATOR SIGNATURE PAGE

I agree to conduct this Study in accordance with the requirements of this document (the Clinical Study Protocol), the Study Reference Manual and also in accordance with the following:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation of technical requirements for pharmaceuticals for human use (ICH) harmonised tripartite guideline regarding Good Clinical Practice (ICH-GCP E6 (R2) Consolidated Guidance, November 2016)
- Local laws and regulations
- Any amendments to these regulations

Investigator Name and Qualifications: _____

_____ _____

Investigator Signature Date

[Investigator Affiliation]

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15. APPENDIX 1: INDUCERS OF CYP1A1, CYP1A2 SUBSTRATES OF CYP2B6 AND BRCP 88

ABBREVIATIONS

6MWD	Six-minute walk distance
ABC	ATP-binding cassette protein
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
$AUC_{(0–t)}$	Area under the curve from time 0 to the last measureable concentration
$AUC_{(0–tau)}$	Area under the curve from time 0 to the time of the next dose
BCRP	Breast-cancer resistance protein
bid	*Bis in die* (twice-daily)
BSEP	Bile salt export pump
C4	7α-hydroxy-4-cholesten-3-one
CHF	Congestive heart failure
CK	Creatinine kinase
C_{max}	Maximum observed concentration
CRF	Case report form
CYP	Cytochrome P450
DHD I	Dihydrodiol I
DHD III	Dihydrodiol III
DMC	Data monitoring committee
DMD	Duchenne muscular dystrophy
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
ECHO	Echocardiogram
ECV	Extracellular volume
F2	Microfluidised aqueous oral suspension
F3	Microfluidised aqueous oral suspension (with xanthum gum)
F5	Aqueous oral nanosuspension
F6	Powder for oral suspension
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
GLDH	Glutamate dehydrogenase
hERG	Human ether-à-go-go-related gene
ICH	International committee on harmonization
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional review board

ITT	Intention-to-treat
LFT	Liver function test
LSLV	Last subject last visit
MATE	Multidrug and toxin extrusion protein
MDR	Multi-drug resistance gene
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRP	Multi-drug resistance associated protein
MRS	Magnetic resonance spectroscopy
NADPH	Nicotinamide adenine dinucleotide phosphate
NOAEL	No observed adverse effect level
NSAA	North Star ambulatory assessment
OATP	Organic anion-transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically based pharmacokinetics
PCF	Peak cough flow
PEF	Peak expiratory flow
PK	Pharmacokinetic
PoC	Proof of Concept
PODCI	Paediatric outcomes data collection instrument
PT	Prothrombin time
PUL	Performance of the upper limb
QTcF	QT interval, heart rate corrected using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SNIP	Sniff nasal inspiratory pressure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment Emergent Adverse Event
tid	*Ter in die* (three times daily)
t_{max}	Time of C_{max}
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal

PROTOCOL SUMMARY

Rationale

This open-label study (SMT C11005) will be the first Phase 2 study of a utrophin modulator in boys with Duchenne muscular dystrophy (DMD). Previous studies with SMT C1100 have dosed for a maximum of 2 weeks whereas this study involves initially dosing for 48 weeks and then for longer in an Extension Phase (which will continue until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued). The primary objectives of this study are to evaluate changes in leg magnetic resonance imaging (MRI) parameters over time as well as evaluate the efficacy and safety of SMT C1100 in a larger population of boys with DMD.

For Cohorts 1 and 2 this open-label proof of concept study will investigate the relationship between the SMT C1100 pharmacokinetic levels and utrophin modulation and muscle markers of regeneration as analysed in the biopsy. It will also investigate whether there is any relationship between drug concentration and change in muscle biomarkers. Further, this open-label concentration-response study will also examine whether the potentially observed utrophin modulation is correlated with improvements in markers of muscle disease progression, as indicated by leg MRI parameters (e.g., fat fraction in the leg), and/or in long term improvements in functional endpoints, such as the six-minute walk distance (6MWD). Results of this study will facilitate the design of future studies

Unfortunately, there are patients who have taken part in prior SMT C1100 studies who now do not meet the entry criteria for Cohorts 1 or 2, and are most likely to be at risk for cardio-respiratory decline due to their older age. These patients will be enrolled in this study as Cohort 3. There is increasing recognition of the effect of cardiomyopathy on morbidity and mortality in DMD, and improved strategies are needed to change the natural history of declining left ventricular systolic function and to attenuate its sequelae. There is also a need to slow down the loss of respiratory function in patients with this disease [McNally *et al.* 2015]. Therefore Cohort 3 will examine whether any potentially observed utrophin modulation improves MRI cardiac parameters (such as extracellular volume fraction (ECV), left ventricular strain, left ventricular ejection fraction, end-diastolic and end-systolic volumes (EDV), and late gadolinium enhancement of left ventricular mass) and respiratory function parameters (such as forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow (PEF)). Results from this cohort will also facilitate the design of a study in older patients.

SMT C1100 is thought to be of potential value in treating patients with DMD and has progressed into clinical development based on knowledge of its *in vitro* properties and identified pharmacodynamic effects in animal models. *Ex vivo* human studies and *in vivo* mouse studies with SMT C1100 demonstrate that concentrations above 0.2 μM for several hours are enough for at least two-fold activation of the utrophin promoter

[Tinsley *et al*. 2011], and even lower concentrations of SMT C1100 increased *in vitro* utrophin expression in myoblasts from DMD patients. However, it is currently unknown which *in vivo* target plasma concentrations in patients would lead to activation of the utrophin promoter with subsequent increase in muscle utrophin expression and whether continuous or an intermittent stimulation of the utrophin promoter is needed to provide clinical benefit.

The development of SMT C1100 in the clinic was initially hampered by low plasma exposure and interpatient variability associated with diet (SMT C11002). SMT C1100's Phase 1 program employed multiple approaches to address early pharmacokinetic issues. Retrospective ad hoc analysis of DMD patients' food diaries identified the potential for low fat diets to affect absorption, leading to the modified diet approach that improved absorption (SMT C11003) and supported taking the microfluidised oral suspension F3 into a Phase 2 study. In previously reported studies of SMT C1100 in DMD patients (SMT C11002 and SMT C11003), results showed that SMT C1100, administered as a microfluidised formulation (F2 or F3), although having variable PK levels, was safe and well tolerated at doses up to 0.1 g/kg three times daily (*tid*) and 2.5 g twice daily (*bid*), with the 2.5 g *bid* dose considered suitable for further clinical development. Patients in Cohorts 1 and 3 of this study (SMT C11005) will receive the 2.5 g dose *bid* as a microfluidised aqueous oral suspension (F3).

In the meantime, a reformulation Phase 1b study (SMT C11004) in DMD patients demonstrated that a powder for oral suspension (F6), markedly increased exposure. In Study SMT C11004 two newly developed formulations, (a nanosuspension (F5) and a powder for oral suspension (F6)), were administered orally to determine safety and pharmacokinetics in healthy volunteers. Both formulations were found to be safe and well tolerated in the healthy volunteers though transient elevations in liver function tests were seen, the significance of which is unknown. Based on review of the safety, tolerability and pharmacokinetic data, the powder for oral suspension formulation (F6) was chosen to have its safety and pharmacokinetics investigated in DMD patients. The F6 formulation was administered to the DMD boys at doses of 0.25 g *bid*, 0.5 g *bid* and 1 g *bid*. Based upon the safety, tolerability and favourable pharmacokinetics a 1 g *bid* dose of the F6 formulation was chosen to be administered in Study SMT C11005, in a separate cohort of approximately 10 patients (Cohort 2).

PhaseOut DMD (this open label Phase 2 trial) will include both the original formulation (F3) and the new formulation (F6) each with a modified diet. Each formulation is likely to exhibit different plasma concentration ranges which together with safety and pharmacodynamic data will aid in the selection of the preferred formulation and dose for future studies. By using both the F3 and F6 formulation in this study and allowing all patients with DMD irrespective of their SMT C1100 exposure levels to participate in this study, a wide concentration response range can be investigated, which will help to identify the range of SMT C1100 plasma levels that may modulate utrophin muscle levels sufficiently to provide therapeutic benefit. This will facilitate the design of future studies.

There has been an emphasis on developing objective non-invasive markers that can be used as predictors of DMD disease severity and disease progression. The understanding of these biomarkers and their utility is still evolving but it is known that over the course of DMD, skeletal muscle is progressively replaced by fat and fibrosis, which can be measured by changes in magnetic resonance imaging (MRI). Magnetic resonance imaging measurements of inflammation and muscle adiposity are being investigated in this study as they are more objective and reproducible than measurements of muscle strength, and are less influenced by patient effort or examiner variability.

The average life-span of patients with DMD is 25–30 years [Merlini *et al,* 2015]. Currently there is no cure and only two approved treatments (one in the UK and one in the US) for a subset of ambulant boys with specific dystrophin gene mutations. The aim of SMT C1100 is to prevent continued muscle deterioration in boys with DMD by modulation of utrophin. As SMT C1100 is, theoretically, more likely to benefit those boys with adequate muscle mass and who are ambulatory, it is appropriate in this situation to enrol a young (≥5 to <10 years) male population, as patients with DMD usually become wheelchair bound between the ages of 8–12 years. However, it is also important to gather long term safety data and data on other exploratory endpoints which might be relevant for an older and less ambulant patient population. The Sponsor aims to fulfil these obligations by enrolling boys who have taken part in prior SMTC1100 studies and who now most likely do not meet the age and functional criteria of the original PhaseOut DMD study (i.e., Cohorts 1 and 2). These patients will be enrolled in Cohort 3.

Following completion of the 48 weeks of study patients in all three cohorts will be eligible to be rolled into the Extension Phase, which will continue until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued and will provide additional safety and efficacy data. Entry into this phase of the study will be optional; patients and their parents/guardians must give additional assent/consent.

Objectives

All objectives apply to all cohorts unless otherwise specified.

Primary Objectives

- To investigate changes in leg MRI in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate the relationships between changes in leg MRI with plasma concentrations of SMT C1100 and its metabolites in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To assess the safety and tolerability of SMT C1100 and its metabolites in paediatric patients with DMD

Secondary Objectives

- To investigate changes in utrophin expression and muscle fibre regeneration in muscle, in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate the relationships between changes in utrophin expression and fibre regeneration in muscle and safety parameters with plasma concentrations of SMT C1100 and its metabolites in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate changes in pulmonary function tests in paediatric subjects with DMD, following treatment with SMT C1100
- To investigate the relationships between changes in pulmonary function tests with plasma concentrations of SMT C1100 and its metabolites in paediatric subjects with DMD, following treatment with SMT C1100

Exploratory Objectives

- To investigate changes in functional measures, in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between functional measures and exposure
- To investigate changes in paediatric outcomes data collection instrument (PODCI) scores in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between PODCI scores and exposure
- To investigate changes in blood biomarkers in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between blood biomarkers and exposure
- To investigate changes in cardiac MRI tests in paediatric subjects with DMD, following treatment with SMT C1100 (Cohort 3)
- To investigate the relationships between changes in cardiac MRI with plasma concentrations of SMT C1100 and its metabolites in paediatric subjects with DMD, following treatment with SMT C1100 (Cohort 3)

Endpoints

All endpoints apply to all cohorts unless otherwise specified.

Primary Endpoints

- Change from baseline to Weeks 12, 24, 36 and 48 in MRI leg muscle parameters (Cohorts 1 and 2)
- SMT C1100 and metabolite plasma concentrations at Weeks 1 (Days 1 and 7, as applicable (Cohorts 2 and 3 only)), 4, 8 (Cohorts 1 and 2 only), 12, 24, 36 and 48

- Safety data including:
  - Treatment emergent AEs

Secondary Endpoints

- Change from baseline to Week 24 or 48 in utrophin expression via muscle biopsy analysis (Cohorts 1 and 2)
- Change from baseline to Week 24 or 48 in muscle regeneration biomarkers via muscle biopsy analysis (Cohorts 1 and 2)
- Change from baseline to Weeks 12, 24, 36 and 48 (Cohorts 1 and 2) and from baseline to Weeks 1, 24 and 48 (Cohort 3) in pulmonary function tests
- Safety data including:
  - Vital signs (systolic and diastolic blood pressure and heart rate)
  - Physical examination
  - Twelve-lead electrocardiogram (ECG)
  - Echocardiogram (ECHO)
  - Pulmonary function tests:
    - Forced expiratory volume in 1 second (FEV_1)
    - Forced vital capacity (FVC)
    - Maximum inspiratory pressure (MIP)
    - Maximum expiratory pressure (MEP)
    - Peak expiratory flow (PEF)
    - Peak cough flow (PCF) (Cohort 3)
    - Sniff nasal inspiratory pressure (SNIP) (Cohort 3)
  - Safety laboratory evaluations (clinical chemistry, haematology, (all 3 Cohorts) coagulation (Cohort 2 and Cohort 3) parameters and urinalysis (all 3 Cohorts))

Exploratory Endpoints

- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in 6MWD
- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) and change measured at 6-monthly intervals for the duration of the Extension Phase in North Star Ambulatory Assessment (NSAA) global score

- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in timed function tests (10 meter run/walk, time to stand)
- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in paediatric outcomes data collection instrument (PODCI) scores
- Change from baseline to Week 12, 24, 36 and 48 for Cohorts 1 and 2 and from baseline to Week 24 and 48 for Cohort 3 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in Performance of Upper Limbs (PUL)
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) and measured at 6-monthly intervals for the duration of the Extension Phase of blood biomarkers, e.g., creatine kinase, matrix metallopeptidase 9 and other biomarkers
- Change from baseline to Week 48 (in the main phase of the study) and measured at 12-monthly intervals for the duration of the Extension Phase in cardiac MRI parameters (Cohort 3)
- Change from baseline in MRI leg muscle parameters measured at 6-monthly intervals for the duration of the Extension Phase (Cohorts 1 and 2)
- SMT C1100 and metabolite plasma concentrations measured at 6-monthly intervals for the duration of the Extension Phase
- Change from baseline in pulmonary function tests measured at 6-monthly intervals for the duration of the Extension Phase

It should be noted that patients in Cohort 3 may not be able to perform all of the functional tests at baseline. Therefore the patients included in the analyses for these tests will be test specific and based upon their baseline ability to perform the test.

Study Design

This is a Phase 2, open-label study to assess the activity and safety of utrophin modulation with SMT C1100 administered orally *bid* in ambulatory paediatric male patients with DMD. In Cohort 1, approximately 30 patients with DMD will be administered 2.5 g *bid* of SMT C1100 F3. In Cohort 2, approximately 10 patients will be administered 1 g *bid* of SMT C1100 F6. In Cohort 3, approximately 15 patients, who have previously received SMT C1100, but who are not eligible for Cohorts 1 or 2, will be administered 2.5 g *bid* of SMT C1100 F3.

Cohort 1, in which F3 will be investigated, will be conducted in a multi-centre setting in both United Kingdom (UK) and the United States of America (USA). Cohort 2, in which F6 will be investigated, will only be conducted at specific centres in the USA. Cohort 3 will only be conducted in the UK and will use the F3 formulation. All cohorts have a

Screening and Baseline Phase of up to 28 days, an open label Treatment Phase and a 30-day Safety Follow up Phase.

During the Treatment Phase, patients will be dosed by their parents/responsible-adult twice-daily with approximately 8–12 hours between breakfast and evening meal doses.

Following completion of the initial 48-weeks of the open label Treatment Phase, patients will be eligible to consider receiving SMT C1100 until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued. All patients will receive the same formulation as they had previously been receiving, twice-daily.

Study Population

Forty male patients aged ≥5 to <10 years inclusive with a diagnosis of DMD (confirmed by phenotypic and genetic evidence) who are willing to assent and whose parents/guardian consent and agree to undergo two muscle biopsies will be enrolled in either Cohort 1 or Cohort 2 of the study. Patients in Cohorts 1 and 2 must be <10 years old, able to walk 300 metres, have a consistent 6MWD (second reading within 20% of the first) and have a cardiac ECHO showing an ejection fraction of >55% and a fractional shortening of >28%.

Approximately 15 male patients with a diagnosis of DMD (confirmed by phenotypic and genetic evidence) who have previously received SMT C1100, but who are not eligible for Cohorts 1 or 2, who are willing to assent and whose parents/guardian consent will be enrolled in Cohort 3.

All patients who have completed the initial 48-week Treatment Phase will be eligible to continue into the Extension Phase which will last until SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued.

Study Assessments

Time and Events Table

Cohorts 1 and 2 ONLY

Phase	Screening Phase	Baseline Phase	Treatment Phase – Cohorts 1 and 2								Early termination visit	End of study visit
Day(D)/Week(W)	up to D-28	to D-1	W1/ Day 1	W1/ Day 7[l,o]	W4 + 1 w[o]	W8 + 1 w[o]	W12 +/-2 w	W24 +/-2 w	W36 +/-2 w	W48 +/-2 w		W52 +/- 2 w
Informed consent and assent	X											
Resident at site		X						X		X		X
Demographic data	X											
Medical history	X											
Inclusion/exclusion criteria	X											
Nutritionist appointment	X											
Vital signs	X	X	X				X	X	X	X	X	X
Physical examination	X	X					X	X	X	X	X	X
12-lead electrocardiogram	X	X	X[h]				X[g]	X[h]	X[g]	X[h]	X	X
Echocardiogram	X							X		X	X [a]	X
Pulmonary assessments [b]	X						X	X	X	X	X [a]	X
Haematology, clinical chemistry and urinalysis	X	X[c]					X	X	X	X	X	X
Coagulation tests[l]	X	X[c]		X			X	X	X	X	X	X
Liver function tests, including glutamate dehydrogenase; amylase and lipase	X	X	X	X[l]	X	X	X	X	X	X	X	X
C4 and FGF19	X		X[j]					X[j]		X[j]		X
MRI - leg	X						X	X	X	X	X [d]	
NSAA		X					X	X	X	X	X	X
10 metre run/walk		X					X	X	X	X	X	X
Six minute walk distance/test	X	X					X	X	X	X	X	X
Muscle Biopsy [e]		X						X		X	X	
PODCI		X					X	X	X	X	X	X
PUL [n]		X					X	X	X	X	X	X
Blood biomarkers [f]		X	X[f]		X	X	X	X	X	X	X	X

Phase	Screening Phase	Baseline Phase	Treatment Phase – Cohorts 1 and 2								Early termination visit	End of study visit
Day(D)/Week(W)	up to D-28 to D-1		W1/ Day 1	W1/ Day 7[l,o]	W4 + 1 w[o]	W8 + 1 w[o]	W12 +/-2 w	W24 +/-2 w	W36 +/-2 w	W48 +/-2 w		W52 +/- 2 w
SMT C1100 parent and metabolites pharmacokinetic sampling			X[i]	X[l,m]	X[k]	X[i]	X[i]	X[k]	X[i]	X[k]	X	X
SMT C1100 *bid* dosing			X	X	X	X	X	X	X	X		
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X

If multiple assessments are at the same time point, it is appreciated that some deviation in timing will be necessary. A ±15 minute window is acceptable with pharmacokinetic samples being performed as close to scheduled time point as possible. Please see the study manual for more information on timing.

a. If not performed in the last 12 weeks.
b. Pulmonary assessments include forced expiratory volume in 1 second, peak expiratory flow, forced vital capacity, maximum inspiratory pressure and maximum expiratory pressure
c. These need not be repeated at Day -1 if they have been performed within 7 days of Day 1. All samples should be collected in a fasting condition
d. If not performed in the last 6 weeks.
e. A maximum of two muscle biopsies will be taken one of which will be at baseline. The patients will be assigned as to when they will receive the second muscle biopsy procedure. The first 8 patients in Cohort 1 will have a biopsy at 24 weeks and the remaining 22 patients will be alternately assigned between the 24 week and the 48 week time points. The first 6 patients in Cohort 2 will have a biopsy at 24 weeks and the remaining 4 patients will have theirs at the 48 week time point. If the patient has not performed their second biopsy prior to their early termination from the study, at the Sponsor's discretion, it may be performed at their Early Termination visit.
f. Plasma biomarkers include creatine kinase, matrix metalloproteinase 9, and others, as well as quantification of changes of proteins. Note: creatinine kinase and MMP-9 will not be collected at Week 1.
g. ECG to be performed 4 hours post AM dose.
h. ECGs to be performed pre-AM dose and 0.5, 2, 4 and 6 h post-AM dose OR pre-PM dose and 0.5, 2 and 4 h post-PM dose.
i. Each patient will have three PK samples taken at pre-AM dose and, 3 and 6 h post-AM dose
j. Samples to be collected pre-AM dose, 3 h post- AM dose, pre-PM dose and 4 h post-PM dose; At Week 1, only AM samples apply
k. Each patient will have three PK samples taken at pre-PM dose and 4 and 10 h (+ up to 4 hours but before the next AM dose) after the PM dose.
l. Cohort 2 only.
m. One PK sample collected at 4 hours post-AM dose.
n. Where a biopsy is performed at the same visit this procedure should be performed prior to the biopsy.
o. Laboratory assessments may be conducted by the sponsor-provided home nursing vendor on Day 7 (Cohort 2 only) and Weeks 4 and 8 (Cohorts 1 and 2).

Time and Events Table

Cohort 3 ONLY

	Screening Phase	Treatment Phase Cohort 3							Early termination visit	End of study visit
	D-28 to D-1	W1/Day 1	W1/Day 7[i]	W4 + 1[i] w	W12 +/-2 w	W24 +/-2 w	W36 +/-2 w	W48 +/-2 w		W52 +/- 2 w
Informed consent and assent	X									
Demographic data	X									
Medical history	X									
Inclusion/exclusion criteria	X									
Nutritionist appointment	X									
Vital signs	X	X			X	X	X	X	X	X
Physical examination	X				X	X	X	X	X	X
12-lead electrocardiogram	X				X[d]	X[d]	X[d]	X[d]	X	X
Cardiac magnetic resonance imaging	X							X	X[g]	
Pulmonary assessments [a]	X	X	X			X		X	X	X
Haematology, coagulation, clinical chemistry & urinalysis	X	X	X		X	X	X	X	X	X
Liver function tests, including glutamate dehydrogenase; amylase and lipase	X		X	X	X	X	X	X	X	X
C4 and FGF19	X					X[f]		X[f]		X
NSAA	X					X		X	X	X
10 metre run/walk	X					X		X	X	X
Six minute walk distance/test	X					X		X	X	X
PODCI	X					X		X	X	X
PUL[b]	X					X		X	X	X
Blood biomarker separate sample [c]	X	X		X		X		X	X	X

	Screening Phase	Treatment Phase Cohort 3							Early termination visit	End of study visit
	D-28 to D-1	W1/Day 1	W1/Day 7[i]	W4 + 1[i] w	W12 +/-2 w	W24 +/-2 w	W36 +/-2 w	W48 +/-2 w		W52 +/- 2 w
SMTC1100 parent & metabolites sparse pharmacokinetic sampling[e]		X	X[h]	X	X	X	X	X	X	X
SMT C1100 *bid* dosing		X	X	X	X	X	X	X		
Adverse event recording	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X

If multiple assessments are at the same time point, it is appreciated that some deviation in timing will be necessary. A ±15 minute window is acceptable with pharmacokinetic samples being performed as close to scheduled time point as possible. Please see the study manual for more information on timing.

a. Pulmonary assessments include forced expiratory volume in 1 second, peak expiratory flow, forced vital capacity, maximum inspiratory pressure, maximum expiratory pressure, peak cough flow and sniff nasal inspiratory pressure.
b. Where a biopsy is performed at the same visit this procedure should be performed prior to the biopsy.
c. Plasma biomarkers include creatine kinase, matrix metalloproteinase 9, and others, as well as quantification of changes of proteins. Note: creatinine kinase and MMP-9 will not be collected at Week 1.
d. ECGs to be performed pre-AM dose and 0.5, 2, 4 and 6 h post-AM dose
e. Each patient will have three PK samples taken at pre-AM dose and, 3 and 6 h post-AM dose
f. Samples to be collected pre-AM dose, 3 h post- AM dose, pre-PM dose and 4 h post-PM dose; At Week 1, only AM samples apply
g. If not performed in the last 6 weeks.
h. One PK sample collected at 4 h post-am dose.
i. Laboratory assessments may be conducted by the sponsor-provided home nursing vendor on Day 7 and Week 4.

Time and Events Table

Extension phase

	Entry Phase/ Baseline Phase	Treatment Phase Cohorts 1, 2 and 3 To be repeated at the time points below in each year of the treatment phase until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued.				Early termination visit	Approval/ Discontinuation
	W48 of original Phase Out DMD[h]	12 W +/-2 w[g]	24 W +/-2 w	36 W +/-2 w[g]	48 W +/- 2 w		Approval +/- 2 w
Informed consent and assent	X						
Vital signs	X	X	X	X	X	X	X
Physical examination	X		X		X	X	X
12-lead electrocardiogram	X[a]		X[b]		X[b]	X[b]	X[b]
Echocardiogram	X		X[i]		X[i]	X	X
Pulmonary assessments [c]	X		X		X	X	X
Haematology, clinical chemistry, coagulation parameters [f], and urinalysis	X	X	X	X	X	X	X
Liver function tests, including glutamate, dehydrogenase, amylase, and lipase	X	X	X	X	X	X	X
Leg MRI (Cohort 1 and 2 only)	X		X		X	X	
Cardiac MRI (Cohort 3 only)	X				X	X	
NSAA	X		X		X	X	X
10 metre run/walk,	X		X		X	X	X
Six minute walk distance/test	X		X		X	X	X
PODCI, EQ-5D,UL- PROM,	X		X		X	X	X
PUL	X		X		X	X	X
Blood biomarkers [d.]	X		X		X	X	X
SMT C1100 parent and metabolites PK	X		X[e]		X[e]	X	X
SMT C1100 *bid* dosing	X	X	X	X	X		
Adverse event recording	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X

If multiple assessments are at the same time point, it is appreciated that some deviation in timing will be necessary. A ±15 minute window is acceptable with pharmacokinetic samples being performed as close to scheduled time point as possible. Please see the study manual for more information on timing.

a. ECG at 0.5,2,4 and 6 h after am dose
b. ECG at a single time point 4 hours after dosing
c. Pulmonary assessments include forced expiratory volume in 1 second, peak expiratory flow, forced vital capacity, maximum inspiratory pressure and maximum expiratory pressure
d. Plasma biomarkers include creatine kinase, matrix metalloproteinase 9, and others, as well as quantification of changes of proteins. Note: creatine kinase and MMP-9 will not be collected at Week 1.
e. Each patient will have single PK samples taken at 4 h post-AM dose
f. Coagulation parameters for Cohort 2 and Cohort 3 only.
g. If only the procedures in this column are being performed at a visit then the visit may be performed at the study site or samples may be collected by the study appointed home nursing vendor with AE and concomitant medication checks being performed in a documented telephone call.
h. The Week 48 visit of PhaseOut DMD is counted as the baseline visit for the extension phase. These procedures do not need to be repeated.

1. INTRODUCTION

1.1. Background

Duchenne muscular dystrophy (DMD) is a progressive, lethal muscle wasting disease characterised by a generalised weakness and progressive loss of muscle strength; ultimately, cardiac and respiratory difficulties present, leading to death [Mercuri *et al*, 2013]. Duchenne muscular dystrophy is an X-linked recessive disorder with a global estimated incidence of approximately 1 in 3500 live male births caused by mutations or deletions in the dystrophin gene [Mammen *et al,* 2015]. Dystrophin provides a link between the actin cytoskeleton and the dystrophin protein complex group of proteins that are anchored in the cell membrane so enabling stabilisation of the membrane during contraction and relaxation [Cirak *et al*, 2012]. A lack of functional dystrophin results in structural and functional changes in muscle fibres, whereby repeated cycles of muscle necrosis and regeneration lead to the eventual replacement of muscle by adipose and connective tissue. Currently there is no effective treatment for DMD [Kharra *et al*, 2014]. Various strategies developed to alleviate the symptoms include steroid treatment [Ricotti *et al*, 2013], anti-inflammatory agents [Serra *et al*, 2012], and growth hormone and myostatin inhibitors [Zatz *et al*, 1986; Bogdanovich *et al*, 2002]. More recently, the majority of nonclinical and clinical investigational studies have examined gene therapy approaches, that focus on restoring the deficient dystrophin in the muscle fibres [Bowles *et al*, 2012; Falzarano*et al*, 2014].

The potential for utrophin to act as a functional replacement for dystrophin has been recognised for some time [Sonnemann *et al*, 2009]. The utrophin gene is the autosomal homologue of dystrophin and utrophin and dystrophin share similar structural organisational motifs and binding properties. Summit is developing SMT C1100, which is the first in a new pharmacological class of small molecules that act to increase transcription of utrophin. Summit has demonstrated that SMT C1100 increases levels of utrophin ribonucleic acid (RNA) and protein in human and mouse cells. This increase in utrophin protein has been shown in dystrophin-deficient muscle cells taken from DMD patients and confirmed in vivo in a mouse model (mdx) [Tinsley *et al*, 2011].

The mdx mouse is a genetic surrogate of the human DMD condition although it presents with a relatively mild histopathological and clinical phenotype. Summit showed that SMT C1100 dosed to mdx mice at 50 mg/kg/day reduced a number of the pathological effects of dystrophin deficiency [Tinsley *et al*. 2011]. Treatment resulted in reduced muscle pathology (regeneration, fibrosis, inflammation), better muscle physiology (leading to an increase in overall strength) and an ability to resist fatigue after forced exercise. The significant clinical advantage of utrophin modulation over other approaches is that the therapy may be beneficial to all DMD patients, regardless of the type of dystrophin mutation.

SMT C1100 has been shown to be safe and well tolerated in the following studies: nonclinical toxicology studies up to 39 weeks of treatment in three species; a Phase 1 study in healthy volunteers for up to 10 days of treatment with 0.2 g/kg *bis in die* (*bid*) [Tinsley *et al*, 2015] and 3 studies with DMD paediatric patients.

Study SMT C11002 was an open-label, non-randomised, Phase 1 study consisting of three groups of DMD paediatric patients. Each group received SMT C1100 for up to 11 days treatment, with doses up to 0.1 g/kg *ter in die* (*tid*) with a microfluidised formulation (F2).

In study SMT C11003 (a Phase 1b placebo-controlled study) patients with DMD completed three 14-Day dosing periods during which they received SMT C1100 (F3) 1.25 g *bid*, SMT C1100 (F3) 2.5 g *bid* and placebo *bid* in a cross-over dose ascending manner. Single and multiple oral doses of 1.25 g and 2.5 g *bid* were safe and well tolerated in these paediatric DMD patients. A balanced diet improved the bioavailability of SMT C1100 (F3), particularly after the evening 2.5 g dose. As before the pharmacokinetics of SMT C1100 (F3) were characterised by prolonged absorption and high between-patient variability in systemic exposure, and evidence of diurnal variation.

Study SMT C11004 was an open-label, non-randomised, Phase 1 study consisting of two parts. Part A, a single-centre study in healthy adult male subjects and Part B a multicenter study in male paediatric patients with DMD, conducted at five centres in the United Kingdom. In Part A SMT C1100 was given as an oral nanosuspension (F5) and a powder for oral suspension (F6). In healthy adults, exposures of SMT C1100 were higher when SMT C1100 was dosed as F6 formulation compared to the F5 formulation. For instance, comparing the exposures obtained at the end of the dosing period (Day 5 [PM]); the exposure with the 4 g *bid* F6 formulation (2279 ng/mL and 10890 ng*h/mL for C_{max} and AUC, respectively) compared to 6 g *bid* with the nanosuspension (371.5 ng/mL and 2844 ng*h/mL for C_{max} and AUC, respectively), were 9.2 and 5.7-fold higher on a dose normalized basis for C_{max} and AUC, respectively. In Part B, F6 was given to each patient for 7 days in each of three treatment periods, with escalating doses (0.25g, 0.5g and 1g) of F6 administered *bid*. There was a minimum of a 7 day washout period between each treatment period.

In Study SMT C11004 SMT C1100 was generally well tolerated with only one serious adverse event (SAE) being reported (high liver function tests (primarily elevated conjugated bilirubin) in a patient with DMD). Due to this SAE, patients will undergo additional monitoring for liver abnormalities in this study.

The PhaseOut DMD study involving a second cohort of patients dosed with F6 aims to provide further information on the safety and pharmacokinetics of the F6 formulation, and corresponding higher SMT C1100 exposure, over a longer time period.

1.1.1. Name and Description of the Investigational Medicinal Product

The investigational medicinal product (IMP) used in Cohort 1 and Cohort 3 of this study is an oral microfluidised aqueous suspension of SMT C1100, 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (also known as formulation F3).

The IMP used in Cohort 2 of this study is a powder for oral suspension of SMT C1100, 5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole (also known as formulation F6).

[redacted]

[redacted]

1.1.3. Summary of Clinical Studies in the Duchenne Muscular Dystrophy Population

In an open-label Phase 1b study (SMT C11002), SMT C1100 was administered orally as a microfluidised aqueous suspension (F2) to assess the safety, tolerability and pharmacokinetics of single and multiple doses in paediatric patients with DMD. Group A's treatment consisted of oral doses of SMT C1100 0.05 g/kg given once on Day 1, *bid* on Days 2–10 and once on Day 11. Group B's treatment consisted of oral doses of SMT C1100 0.1 g/kg given once on Day 1, *bid* on Days 2–10, and once on Day 11. Group C's

treatment consisted of oral doses of SMT C1100 0.1 g/kg given once on Day 1, *tid* on Days 2–10, and once on Day 11. Overall, multiple doses of SMT C1100 were safe and well tolerated at dose levels up to 0.1 g/kg *tid*, with the most frequent adverse event (AE) being pale stools. Patients in SMT C11002 were requested to take their doses within 10 minutes of food; however, there was no standardisation of meals consumed prior to dosing. It was therefore unknown what contribution the differences in food intake prior to dosing had on the extent of SMT C1100 exposure and between-patient variability.

Following single and multiple oral administrations, SMT C1100 was rapidly absorbed with time of maximum concentration (t_{max}) being attained within approximately 1–6 hours in all patients. SMT C1100 exhibited biphasic elimination with an apparent dose-independent terminal elimination half-life ($t_{1/2}$), with mean $t_{1/2}$ ranging from approximately 5–10 hours. Similarly to results seen in study SMT C11001 (conducted in healthy adults), single and multiple oral dose pharmacokinetics of SMT C1100 in male paediatric patients with DMD demonstrated large variability between patients and provided no evidence that increasing dose or differing dosing regimen had an impact on exposure. There was high between-patient variability (geometric coefficient of variation of 78–248%) in $AUC_{(0–tlast)}$, area under the concentration curve from time 0 to the time of next dose ($AUC_{(0–tau)}$) and $C_{max.}$ The comparison of doses and regimens was hindered by this large variability and the presence of only four patients per group. Observed exposures were lower than anticipated with only a single patient receiving *bid* dosing achieving target exposures. Following 11 days of *bid* dosing, SMT C1100 exposure was significantly reduced, with systemic exposure (assessed by $AUC_{(0–tau)}$) being approximately 56–65% lower on Day 11 compared to Day 1. A time-dependent reduction in exposure was observed in study SMT C11001, albeit not to the same magnitude (23–40% reduction) suggesting that SMT C1100 is subject to autoinduction, although AhR-mediated induction of CYP1A was not evident from *in vitro* evaluation.

In Study SMT C11002, the pharmacokinetic analysis of metabolites DHD I and DHD III obtained from an exploratory assay, revealed broadly similar disposition (t_{max} and $t_{1/2}$) to that of the parent drug. Both metabolites were markedly more abundant than SMT C1100 in plasma, with mean metabolite ratios appearing to be independent of dose. On Day 1, mean metabolite ratios ranged from 10.8–36.0 and 20.6–58.5 for DHD I and DHD III, respectively. Following multiple dosing, metabolite ratios were higher, ranging from 46.6–74.2 and 63.2–112 for DHD I and DHD III, respectively. As the exposure of DHD I and DHD III at 0.1 g/kg *bid* and *tid* doses was similar between Days 1 and 11, these data indicate that the increase in metabolite ratios are a reflection of a reduction in exposure to SMT C1100 over time.

Although DHD I levels in Study SMT C11002 were within the levels seen in the animal toxicology studies, the DHD III levels for some patients exceeded those seen in the female rat toxicology study. However, a battery of *in vitro* assessments did not identify

any unique safety concern for DHD III relative to SMT C1100 or DHD I and there were no adverse effects in patients that might be related to any of the off-target effects identified *in vitro* for SMT C1100, DHD I or DHD III.

Study SMT C11003 was a Phase 1b placebo-controlled, multi-centre, randomised, double-blind dose escalation study to evaluate the pharmacokinetics and safety of SMT C1100 in patients with DMD who were following a balanced diet and consumed 100 mL full-fat (whole) milk immediately after dosing with F3. Twelve patients were enrolled in this study and patients completed three 14-Day dosing periods during which they received SMT C1100 1.25 g *bid*, SMT C1100 2.5 g *bid* and placebo *bid* in a cross-over dose ascending manner.

Single and multiple oral doses of 1.25 g and 2.5 g *bid* were safe and well tolerated in paediatric DMD patients. A balanced diet improved the bioavailability of SMT C1100, particularly after the evening 2.5 g dose. As before the pharmacokinetics of SMT C1100 were characterised by prolonged absorption and high between-patient variability in systemic exposure, and evidence of diurnal variation. Systemic exposure of DHD I and DHD III were markedly higher than that of SMT C1100, with no dose or time dependency in metabolite ratios.

At both dose levels, there were no severe AEs, no study discontinuations due to an AE, and no serious AEs reported during the study. The majority of AEs were mild gastrointestinal disorders which resolved without treatment. The most frequently reported TEAE was pale stools and thus consistent with TEAEs in previous clinical studies. The only other drug-related TEAEs reported with SMT C1100 were diarrhoea, pain in the upper abdomen and constipation. The reporting of these TEAEs for patients administered active drug was similar to that reported during treatment with placebo.

In the Investigator's opinion there were no clinically important findings for clinical laboratory evaluations, vital signs, 12-lead ECGs, or physical examinations performed during the study.

SMT C11004 was an open-label, nonrandomised, Phase 1 study consisting of two parts. Part A was a single-centre study in healthy adult male subjects where 2 formulations of SMT C1100 were investigated (an oral nanosuspension (F5) and a powder for oral suspension (F6)). Part B was a multicenter study in male paediatric patients with DMD conducted at five centres in the United Kingdom where only the F6 formulation was investigated.

In Part A, one subject who received SMT C1100 F6 formulation at 4 g *bid* discontinued due to a TEAE of upper abdominal pain that was considered related to study drug by the investigator. All 16 subjects reported TEAEs, the majority of which were mild. 'Discoloured faeces' was the most frequently-reported TEAE. Headache and nausea were

the other drug-related TEAEs reported with the nanosuspension and Change of Bowel Habit, Abdominal Discomfort, Faeces Pale, Abdominal Pain, Diarrhoea, Dyspepsia and Nausea reported for the powder for oral suspension formulation. Transient increases in liver-related laboratory tests were observed during the dosing period, though no subject satisfied any of Hy's criteria and values returned to baseline after dosing had stopped.

In Part B seven of the eight patients experienced at least one TEAE with all but one event being considered mild or moderate by the Investigator. There was one SAE of elevated liver function test abnormalities with the 0.25 g *bid*, dose, the cause of which is unknown. The patient himself was clinically well but nevertheless discontinued from the study after a positive rechallenge in Period 2. Laboratory values for this patient returned to the normal range at the 2-week follow up. One additional patient discontinued on Day 7 after his AM dose in the 1 g *bid* dose period for an AE of abdominal pain. The majority of the AEs were gastrointestinal in nature with diarrhoea being the most frequently reported event; interestingly, pale faeces were reported only during dosing with 0.5 g *bid*.

With respect to the pharmacokinetic profile with DMD patients, overall there was an increase in steady state C_{max} and $AUC_{0–24}$ with increasing dose which was greater than dose proportional with the two higher dose levels (0.5 and 1g *bid*), however there was little to no accumulation with repeated dosing. There was dose proportionality between the 0.25 g *bid* and 0.5 g *bid* dose levels. At the two highest dose levels mean (geometric) C_{max} was above levels that *in vitro* increased utrophin production, with the highest geometric mean C_{max} over 24 hours being 390 ng/mL at the 1 g *bid* dose level, at steady state.

Further information can be found in the Investigator's Brochure [Investigator's Brochure 2016] for SMT C1100.

1.1.4. Study Conduct

This study will be conducted in accordance with the requirements of this document (the Clinical Study Protocol), the Study Reference Manual and also in accordance with the following:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonization harmonized tripartite guideline regarding Good Clinical Practice (ICH-GCP; E6 (R2) Consolidated Guidance, November 2016)
- Local laws and regulations
- Any amendments to these regulations

1.2. Rationale

This open-label study (SMT C11005) will be the first Phase 2 study of a utrophin modulator in boys with DMD.

The decision to progress into clinical development was taken after SMT C1100 demonstrated significant disease-modifying potential for DMD in non-clinical efficacy studies. SMT C1100 has been shown to increase utrophin RNA and protein and reduce muscle damage, *in vivo,* in the mdx mouse model of DMD disease [Tinsley *et al*, 2011]. *In vitro* assays with human myotubes or human DMD cells treated with SMT C1100 demonstrated a 25% increase in utrophin messenger RNA and a 100% increase in utrophin protein, respectively, leading to an estimated EC_{50} of 0.2 micromolar (67 ng/mL) in the *in vitro* myotube assay and an EC_{50} level of 33.7 ng/mL in the *in vitro* DMD myoblast assay.

A key question for all utrophin modulator studies relates to how much utrophin is necessary to slow down the muscle degeneration of DMD boys. There is likely to be a level of protein that is sufficient to maintain proper membrane organisation and function, and prevent the degenerative process. However, lower levels of utrophin could slow down the rate of muscle fibre degeneration which would still be of significant benefit to DMD boys. The same question is being investigated for dystrophin. Godfrey *et al* have shown that a low (15% homogeneous dystrophin) expression is sufficient to protect against eccentric contraction-induced injury in mdx [Godfrey *et al*, 2015]. Strikingly, changes in muscle strength were proportional to dystrophin expression levels. These data appear to define the dystrophin restoration levels required to slow down or prevent disease progression and improve overall muscle function once a dystrophic environment has been established in the mdx mouse model. Analysis of dystrophin levels in Becker patients with dystrophin truncations, which mimic the protein the exon skipping drug hopes to create, suggests levels significantly lower than normal levels will provide significant benefit. One publication suggests that threshold rather than dose–effect relationship of dystrophin levels determines disease severity. This threshold could be around 10% of normal dystrophin levels (at least for the exon 45–47 deletion), which has important implications for therapeutic approaches that aim to restore dystrophin [Van den Bergen *et al*, 2014]. A second publication showed that dystrophin protein levels in Becker patients (who express the same internally deleted dystrophin as could be induced by exon skipping therapies) are mostly associated with mild phenotypes and that these patients express dystrophin at a high enough level (at least 40% of control) to provide a functional benefit [Anthony *et al*, 2011].

Previous studies with SMT C1100 have dosed for a maximum of 2 weeks whereas this study will involve initially dosing for 48 weeks, but potentially dosing for longer periods of time (until SMT C1100 is approved in the relevant countries or development of SMT C1100 is

discontinued). The primary objectives of this study are to evaluate changes in leg magnetic resonance imaging (MRI) parameters over time as well as evaluate the efficacy and safety of long term dosing with SMT C1100 in a larger population of boys with DMD. This study will investigate the relationship between the SMT C1100 pharmacokinetic levels and utrophin modulation and muscle markers of regeneration. It will also investigate whether a relationship exists between utrophin modulation and muscle markers of regeneration. Further, this open-label concentration-response study will also examine whether the potentially observed utrophin modulation does indeed lead to improvements in markers of muscle disease progression as indicated by the MRI fat fraction in leg muscles or in long term improvements in functional endpoints such as the six-minute walk distance (6MWD). Results of this study will enable the design of a pivotal study.

Following completion of the 48 weeks of study, patients in all three cohorts will be eligible to be rolled into the Extension Phase, which will continue until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued, and will provide additional safety and efficacy data. Entry into this phase of the study will be optional; patients and their parents/guardians must give additional assent/consent.

Currently there is no cure for all boys with DMD although two treatments (one in the US and one in EU) are available for subset of ambulant boys with specific dystrophin gene mutation. The average life- span of patients with DMD is 25–30 years [Merlini *et al*, 2015]. SMT C1100 aims to prevent continued muscle deterioration in boys with DMD. It is theoretically most likely to benefit those boys with adequate muscle mass and those who are ambulatory. Thus it is appropriate to enrol a younger (≥5 to <10 years) DMD population in Cohorts 1 and 2 as patients usually become wheelchair bound between the ages of 8–12 years [Uzark et al, 2012]. However, based on the natural history data, we expect there will be patients who have taken part in prior SMT C1100 studies who now do not meet the entry criteria for Cohorts 1 and 2 and are most likely to be a risk for cardio-respiratory decline. These patients will be enrolled in this study in Cohort 3 and have cardiac and respiratory end points measured, providing essential data for the safety database and allowing the assessment of endpoints relevant in an advancing patient population.

In a previously reported study of SMT C1100 in DMD patients (SMT C11002), results showed that SMT C1100 was safe and well tolerated at doses up to 0.1 g/kg *tid* as a microfluidised aqueous suspension (F2). However, patients had variable plasma concentrations of SMT C1100 with only two of the patients achieving concentrations similar to those seen in a fed study with healthy adult volunteers (SMT C11001). Retrospective dietary data collection suggested that boys in SMT C11002 with DMD followed a low fat diet.

Consequently it was hypothesised that SMT C1100 exposure could be improved by dietary manipulation. In study SMT C11003, patients with DMD were requested to take their doses with 100 mL full-fat milk and follow a balanced diet. The data from SMT C11003 supported the hypothesis demonstrating improved exposure of SMT C1100. As discussed above, these concentrations have been shown, *in vitro,* in both human myotubes and DMD myoblasts, to upregulate utrophin. Patients who were involved in both the SMT C11002 and SMT C11003 studies showed increased exposure when they took SMT C1100 with milk in the SMT C11003 study compared to the SMT C11002 study where milk was not required to be consumed with SMT C1100. Results in Study SMT C11004 showed that the F6 formulation of SMT C1100 had significantly improved pharmacokinetic properties with higher C_{max} and AUC's achieved (greater than six-fold increase in maximum SMT C1100 plasma levels), and was safe and well tolerated at doses up to the maximum dose used, 1 g *bid*. Consequently this formulation and dose will also be investigated in a small number of patients in Study SMT C11005.

By allowing all patients with DMD, irrespective of SMT C1100 levels, to participate in this study, we aim to address some of the questions about appropriate utrophin levels for benefit as even low plasma levels of SMT C1100 may modulate utrophin muscle levels enough to be of some clinical benefit.

With the low SMT C1100 exposure partly mitigated by asking patients with DMD to follow a balanced diet and consume 100 mL milk with SMT C1100 and with the development of formulation (F6), the next stage of SMT C1100 development is SMT C11005, a proof-of-concept study.

In two different studies (SMT C11002 and SMT C11003), each of which enrolled 12 patients, patients with DMD were exposed to SMT C1100 for between 11–14 days. Including SMT C11004 there is a total SMT C1100 exposure, in all previous studies, of 615 dosing days in 22 individual boys with DMD. In contrast, should all patients complete the SMT C11005 study per protocol the total SMT C1100 exposure in days will be considerably greater (15,120 dosing days) increasing even further if all elect to continue in the Extension Phase. By measuring pharmacokinetic endpoints of SMT C1100, and its DHD metabolites, at different time points throughout the study Summit will examine the correlation between systemic exposure and longer term safety.

For this study leg MRI will be used in Cohorts 1 and 2 for monitoring disease progression after intervention with SMT C1100, by evaluating muscle fat infiltration and inflammation. Both are considered markers of disease progression in patients with DMD.

Magnetic resonance imaging measurements of inflammation and muscle adiposity are more objective and reproducible than measurements of muscle strength and are less influenced by patient effort or examiner variability [Wren *et al*, 2008]. Indeed Arpan *et al* demonstrated that boys with DMD treated with corticosteroids demonstrated a slower

rate of fat accumulation in the soleus and vastus lateralis muscles compared to corticosteroid-naive boys as measured by MRI/magnetic resonance spectroscopy (MRS) [Arpan *et al,* 2014].

There is increasing recognition of the effect of cardiomyopathy on morbidity and mortality in DMD, and improved strategies are needed to change the natural history of declining left ventricular systolic function and to attenuate its sequelae. There is also a need to slow down the loss of respiratory function in patients with this disease. Therefore Cohort 3 will also examine whether the potentially observed utrophin modulation improves MRI cardiac parameters (such as extracellular volume fraction (ECV), left ventricular strain, left ventricular ejection fraction, end-diastolic and end-systolic volumes (EDV), and late gadolinium enhancement of left ventricular mass) and respiratory function parameters (such as forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow (PEF)). Results from this cohort will also facilitate the design of a pivotal study.

To date, there are several ongoing large natural history studies in the DMD population. Summit will endeavour to access these data in order to compare age and genotype matched controls with functional status with boys in Cohort 3 of this open-label study.

1.3. Potential Risks and Benefits to Human Subjects

[redacted]

[redacted]

[redacted]

[redacted]

1.3.2. Healthy Volunteer Safety Summary

Thirty-seven healthy subjects in study SMT C11001 were exposed to SMT C1100 (F2).

SMT C1100 was well tolerated, with the majority of reported AEs being mild in severity and resolving without treatment. No severe AEs or SAEs have been reported. The only drug-related AEs were pale and/or discoloured stools, reported, predominantly, at the higher dose levels of 0.4 g/kg (single dose) and 0.2 g/kg (*bid*). These AEs were not associated with any other gastrointestinal-related AEs and are probably a consequence of a greater proportion of unabsorbed study drug passing through the gastrointestinal tract at the higher dose levels. No apparent treatment- or dose-related trends in the 12-lead ECG parameters were noted. In particular, there was no evidence of prolongation of QTc interval at each dose level of SMT C1100. No individual subjects had a QT interval, heart rate corrected using Fridericia's formula (QTcF) >480 ms following dosing of SMT C1100. In addition no subjects had an increase from baseline in QTcF >60 ms; three subjects had a maximal QTcF change in baseline of >30 ms.

Sixteen healthy male subjects enrolled in Part A of the SMT C11004 study. Eight subjects received SMT C1100 oral nanosuspension (F5) at doses of up to 6 g *bid*, and eight subjects received SMT C1100 powder for oral suspension (F6) at doses of up to 4 g *bid*. One subject who received F6 4 g *bid* (fed) discontinued after 4 days of dosing due to a TEAE of abdominal discomfort considered possibly related to study drug. All 16 subjects reported TEAEs, the majority of which were mild. 'Discoloured faeces' was the most frequently-reported TEAE. Headache and Nausea were related AEs reported with the nanosuspension and Change of Bowel Habit, Abdominal Discomfort, Faeces Pale, Abdominal Pain, Diarrhoea, Dyspepsia and Nausea were related AEs reported for the powder for oral suspension formulation. Transient increases in liver-related laboratory tests were observed during the dosing period, though no subject satisfied any of Hy's criteria and values returned to baseline after dosing had stopped. As a precaution, and because these elevations may be masked in the DMD population, who already have abnormal liver function tests (LFTs), glutamate dehydrogenase (GLDH) was also monitored in Part B together with amylase and lipase to assess pancreatic function.

1.3.3. Duchenne Muscular Dystrophy Patients Safety Summary

Thirty-two boys with DMD have taken part in three studies with SMT C1100. However as several of the boys have taken part in more than one study, 22 individual boys with DMD have been exposed to SMT C1100 in total.

In Study SMT C11002 (F2) involving 12 paediatric patients with DMD, SMT C1100 was well tolerated, with the majority of reported AEs being mild in severity. No severe AEs or SAEs were reported. The most frequently related drug-related AEs were pale stools, which were predominantly reported at the higher dose intervals of 0.1 g/kg *bid* and 0.1 g/kg *tid*. In study SMT C11002 at doses of up to 0.1 g/kg *bid* there were no significant QTc changes in ECGs. Only one patient had an increase from baseline ≥30 ms in the QTcF although all his QTcF values were <400 ms.

In Study SMT C11003 (F3) all 12 patients experienced at least one TEAE while receiving each of the three treatments, including placebo. It is important to note that placebo included excipients to mimic pale stool colour in order to maintain the blind. There were no severe or serious AEs, and no patient discontinued due to an AE. All AEs were considered mild or moderate by the investigator. The most common TEAE in the study, was pale stools, reported by all twelve patients (100%) receiving SMT C1100 and 9 patients (75%) receiving placebo.

ECG data for study SMT C11003 showed that in neither the placebo nor active groups did any patient display a maximum increase in QTcF of ≥60 ms. Nine (75%) patients in the placebo group had a maximum increase in QTcF of between 30–59 ms, compared to four (33%) patients in the 1.25 g *bid* group and three (25%) patients in the 2.5 g *bid* group. The maximum QTcF (average of replicates) recorded was 453 ms seen at the 2.5 g *bid* level. Mean increases from baseline were less than 10 ms for all groups, except the placebo group, across all time points. No significant difference was seen between the active and placebo groups for median changes in heart rate.

Overall, SMT C1100 was considered safe and well tolerated in study SMT C11003 in paediatric patients with DMD.

As described above and in the Investigator's Brochure, data from hERG studies with SMT C1100 and its major metabolites (DHD I and DHD III) indicated low risk of hERG channel blockade effects, given the actual plasma levels of DHD I and DHD III seen after dosing with SMT C1100. In study SMT C11003, DHD III levels in the patients with DMD exceeded the maximum level seen in the female rat. However, no significant changes in QTcF were seen in patients with DMD dosed with 2.5 g *bid* for 14 days. Specifically the patient with DMD with the highest SMT C1100 exposure also had the highest level of DHD III following the 1.25 g *bid* dose but did not have the longest QTcF. The maximum mean QTcF of 453 ms was seen in another patient at the 2.5 g *bid* dose level.

In study SMT C11004 examining the F6 formulation, seven of the eight patients experienced at least one TEAE, with all but one event being considered mild or moderate by the Investigator. The one severe event was also the one SAE (raised LFTs). Three patients were withdrawn from the study, two of which discontinued due to TEAEs (raised LFTS (0.25 g *bid* dose) and abdominal pain (1 g *bid* dose)). The most frequently reported TEAEs were diarrhoea (three patients), abdominal pain (two patients), abdominal pain upper (two patients) and pale faeces (two patients). All were considered at least possibly related to treatment, except one patient's diarrhoea and one patient's abdominal pain upper.

Patients with DMD have elevated AST and ALT (of muscle origin) as part of their disease pathology. In non-DMD patients the potential for severe hepatotoxicity may be

signalled by a set of findings sometimes called Hy's Law that includes an increase in leakage enzymes such as ALT and AST that may signal hepatocyte necrosis along with an increase in bilirubin suggesting a functional deficit. However, in DMD patients this rule is difficult to implement given that patient's AST and ALT are already elevated as part of their disease. Total bilirubin was raised (>ULN) in three of the eight patients during the dosing periods in SMT C11004. GLDH, another leakage enzyme, is thought to be a more reliable indicator of liver cell necrosis particularly in DMD patients and was raised (>ULN) in five of eight patients during the dosing periods. However, the increased GLDH was not dose dependent and the elevation was minimal with only one patient having a value >2x ULN.

In Study SMT C11004, there were no clinically significant increases in QTcF. No patient had a QTcF of >450 ms and no patient had a QTcF value increase by more than 60 ms.

Overall, SMT C1100 was considered safe and well tolerated in study SMT C11004 in paediatric patients with DMD although based on the liver function findings additional monitoring of these parameters and coagulations function (changes in which can also indicate liver damage) will be undertaken in Cohorts 2 and 3.

1.3.4. Risk Mitigation in Study SMT C11005

Three potential drug-related risks have been identified. One related to inhibition of the hERG channel by DHD I and DHD III, one related to potential interactions with concomitant medications, and one related to liver function test changes seen with F6.

The major metabolites of SMT C1100, DHD I and DHD III, caused between 25–45% inhibition of the hERG and human voltage-dependent calcium channel $hCa_v1.2$ at 30 μM. The highest individual plasma concentrations seen in patients dosed with F3 or F6 was at least 54-fold or 22-fold, respectively, below 30 μm for free DHD I and DHD III, and thus unlikely to cause QTc prolongation. However as a precaution and as this patient population is known to have significant ECG abnormalities and conduction defects, in this current and in previous clinical studies with patients with DMD, ECGs are being assessed frequently.

The preclinical pharmacokinetic studies indicated that SMT C1100 was primarily metabolized by CYP1A1 and CYP1A2. It was also shown that SMT C1100 could inhibit CYP1A1 and CYP1A2 in vitro; however, this inhibition was determined not to be clinically significant based on PBPK/Simcyp modelling (Study No. N-135). The metabolites of SMT C1100, DHD I and DHD III, were shown to induce CYP2B6. Based on the above, medication that induce CYP1A1 and/or CYP1A2 are restricted as are substrates of CYP2B6.

SMT C1100, DHD I, and DHD III inhibited BCRP in vitro so given the role of this transporter in drug disposition and distribution, BCRP substrates are being excluded. DHD I and DHD III also inhibited OATP1B1 and OATP1B3 hepatic uptake transporters which could alter efficacy and increase the risk of exposure-dependent side effects of OATP1B1 and OATP1B3 substrates. Therefore, patients taking medications that are OATP1B1/1B3 substrates should be monitored for exaggerated pharmacological effects and exposure-dependent side effects as dose reduction may be needed. OATP1B1/1B3 substrates fluvastatin and rosuvastatin are also BCRP substrates and therefore excluded. Further details are provided in Section 9.2.

Abnormal liver function tests were seen in patients with DMD dosed with the F6 formulation in the SMT C11004 study. AST and ALT are enzymes already raised in patients with DMD (although the likely source is muscle) and, as such, further elevations in these enzymes due to liver toxicity may be difficult to see. GLDH is being evaluated and is considered a more specific liver enzyme marker [Schomaker *et al,* 2013]. In addition, liver disease is characterised by reduced synthesis of the procoagulant proteins II, VII, IX, X, as well as factor V and factor XI. These factor deficiencies directly affect the standard coagulation measures available in clinical laboratories, mainly the prothrombin time (PT) and its standardisation, the international normalised ratio (INR), and to a lesser extent, the activated partial thromboplastin time (aPTT) [Northup and Caldwell, 2013]. Therefore, as a precaution and as a means to monitor liver dysfunction both GLDH and coagulation times will be measured.

Finally, during the SMT C11004 study stopping criteria based on liver function were developed. These are outlined below and will be followed during this study, as applicable.

If a patient's results meet either of the criteria below, dosing should be stopped and the tests should be repeated as soon as possible. If the repeated results still meet this criterion, the study drug will be permanently stopped and may not be restarted although the patient will continue to be followed for functional and MRI assessments for the duration of the study. If the patient is withdrawn from the study, a follow up visit should be arranged:

GLDH ≥ 3x upper limit of normal (ULN)

OR

Bilirubin ≥ 2x ULN together with an INR ≥ 1.5x ULN (Cohort 2 and 3 only)

Patients in this study will receive either SMT C1100 2.5 g *bid* F3 formulation (Cohort 1 and Cohort 3) or SMT C1100 1 g *bid* F6 formulation (Cohort 2) for 48 weeks. Previous exposure at the F3 formulation 2.5 g *bid* dose level in the paediatric DMD population has

been limited to 14 days whilst that for F6 formulation 1 g *bid* dose level has been limited to 7 days. Neither has been associated with any safety signals except the observation of pale stools with both formulations and transient elevations in LFTs for the F6 formulation. The pharmacokinetics of SMT C1100 parent and metabolites, and the safety data, will be reviewed on an ongoing basis by the Sponsor and the data monitoring committee (DMC). As this is an open-label study, the Investigator should determine if an SAE is related to IMP and consider modifying the dose given. Serious AEs considered at least possibly related to IMP may require a dose reduction, a temporary hold or permanent discontinuation, with prior consultation and agreement with the Sponsor.

A risk relating to the study design is the requirement for the paediatric patients enrolled in this study to undergo up to two muscle biopsies, which will include the use of anaesthesia. This procedure may cause some discomfort but will be done with the assent of the patient, consent of their parents (or other adult legally responsible for them) and in a sensitive way that takes into account their age. The procedure will be explained to the patients in advance in an age appropriate manner and they and their parents will be given an opportunity to ask any questions they have relating to the procedure. Appropriate pain-relief will be made available following each biopsy.

1.3.5. Risk Benefit Statement

Currently there is no cure for DMD although two treatments (one in the USA and one in the EU) for a subset of boys with specific dystrophin gene mutations are available. The average life-span of patients with DMD is 25–30 years [Merlini *et al*, 2015].

This is the first Phase 2 study being performed with this compound and so is the first study to examine activity of SMT C1100 in patients with DMD. As such, it is not possible to say whether there will be any benefit to those taking part in the study. It is thought that exposure over this length of time will maintain the expression of utrophin in muscle, and potentially this will be beneficial. Investigations and assessments will be undertaken to see if these changes have a positive effect on MRI and for monitoring disease progression by evaluating muscle fat infiltration and inflammation - both considered markers of disease progression in patients with DMD.

The aim of SMT C1100 is to modulate the levels of utrophin in muscle fibres in order to reduce continued muscle deterioration in boys with DMD and it is theoretically likely to benefit those boys with adequate muscle mass and who are ambulatory. It is appropriate therefore in this situation to enrol a younger (≥5 to <10 years) population as patients with DMD usually become wheelchair bound between the ages of 8–12 [Uzark *et al*, 2012]). However, data also show that cardiac contractile dysfunction of mdx mice is generally worsened in mice also lacking utrophin [Janssen *et al,* 2005] Indeed one of the leading causes of death in patients with DMD is cardiomyopathy. It is therefore appropriate to

investigate a utrophin modulator in patients with DMD who may be older or have a reduced functional and cardiac status such as those expected to be enrolled in Cohort 3.

To date, no major safety signal has been observed in either the animal toxicology studies or in the human clinical studies. Preclinical data suggests an interaction with the hERG channel, interactions with substrates of CYP2B6 and BCRP, and inhibition of the MAO-B enzyme. These risks are mitigated by the assessment of multiple ECGs taken at frequent time points throughout the study, the exclusion of substrates of CYP2B6 and BCRP and the exclusion of drugs that have serotonergic, norepinephrinergic or dopaminergic activity. One SAE was reported following dosing with the F6 formulation in Study SMT C11004 but no SAES reported in the ongoing PhaseOut DMD study (SMT C11005) with the majority of AEs reported being mild (data up to 07 Feb 2017). Although abnormal LFTs have previously been seen in patients with DMD treated with the F6 formulation, these abnormal values quickly returned to baseline levels after dosing with the IMP was stopped. Additional safety tests including GLDH and measurement of coagulation parameters have been added to the protocol and robust stopping criteria defined. Subjects in the SMT C11005 study may continue to receive SMT C1100 following their Week 48 visit, and will provide long term safety data, useful long term efficacy data, and also provide an opportunity to compare any beneficial effects to natural history data.

The Sponsor therefore believes the current risk benefit ratio for the SMT C11005 study is favourable.

However, the Sponsor will immediately notify the Principal Investigators and Regulatory Agencies if any additional safety or toxicology information becomes available during the study. In addition, an independent DMC will, on a regular basis, review all pertinent pharmacokinetic and safety data and make recommendations on dosage adjustments, if needed during the main part of the study.

2. OBJECTIVES

All objectives apply to all cohorts unless otherwise specified.

2.1. Primary Objectives

- To investigate changes in leg MRI in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate the relationships between changes in leg MRI with plasma concentrations of SMT C1100 and its metabolites in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)

- To assess the safety and tolerability of SMT C1100 and its metabolites in paediatric patients with DMD

2.2. Secondary Objectives

- To investigate changes in utrophin expression and muscle fibre regeneration in muscle, in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate the relationships between changes in utrophin expression and fibre regeneration in muscle and safety parameters with plasma concentrations of SMT C1100 and its metabolites in paediatric patients with DMD, following treatment with SMT C1100 (Cohorts 1 and 2)
- To investigate changes in pulmonary function tests in paediatric subjects with DMD, following treatment with SMT C1100
- To investigate the relationships between changes in pulmonary function tests with plasma concentrations of SMT C1100 and its metabolites in paediatric subjects with DMD, following treatment with SMT C1100

2.3. Exploratory Objectives

- To investigate changes in functional measures, in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between functional measures and exposure
- To investigate changes in paediatric outcomes data collection instrument (PODCI) scores in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between PODCI scores and exposure
- To investigate changes in blood biomarkers in paediatric patients with DMD, following treatment with SMT C1100, including the relationship between blood biomarkers and exposure
- To investigate changes in cardiac MRI tests in paediatric subjects with DMD, following treatment with SMT C1100 (Cohort 3)
- To investigate the relationships between changes in cardiac MRI with plasma concentrations of SMT C1100 and its metabolites in paediatric subjects with DMD, following treatment with SMT C1100 (Cohort 3)

3. ENDPOINTS

All endpoints apply to all cohorts unless otherwise specified.

3.1. Primary Endpoints

- Change from baseline to Weeks 12, 24, 36 and 48 in MRI leg muscle parameters (Cohorts 1 and 2)
- SMT C1100 and metabolite plasma concentrations at Weeks 1 (Days 1 and 7, as applicable (Cohorts 2 and 3 only)), 4, 8 (Cohorts 1 and 2 only), 12, 24, 36 and 48
- Safety data including:
    - Treatment emergent AEs

3.2. Secondary Endpoints

- Change from baseline to Week 24 or 48 in utrophin expression via muscle biopsy analysis (Cohorts 1 and 2)
- Change from baseline to Week 24 or 48 in muscle regeneration biomarkers via muscle biopsy analysis (Cohorts 1 and 2)
- Change from baseline to Weeks 12, 24, 36 and 48 (Cohorts 1 and 2) and from baseline to Weeks 1, 24 and 48 (Cohort 3) in pulmonary function tests
- Safety data including:
    - Vital signs (systolic and diastolic blood pressure and heart rate)
    - Physical examination
    - Twelve-lead electrocardiogram (ECG)
    - Echocardiogram (ECHO)
    - Pulmonary function tests:
        - Forced expiratory volume in 1 second (FEV_1)
        - Forced vital capacity (FVC)
        - Maximum inspiratory pressure (MIP)
        - Maximum expiratory pressure (MEP)
        - Peak expiratory flow (PEF)
        - Peak cough flow (PCF) (Cohort 3)
        - Sniff nasal inspiratory pressure (SNIP) (Cohort 3)
    - Safety laboratory evaluations (clinical chemistry, haematology, (all 3 Cohorts) coagulation (Cohort 2 and Cohort 3) parameters and urinalysis (all 3 Cohorts))

3.3. Exploratory Endpoints

- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in 6MWD
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in North Star Ambulatory Assessment (NSAA) global score
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in timed function tests (10 meter run/walk, time to stand)
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in paediatric outcomes data collection instrument (PODCI) scores
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) measured at 6-monthly intervals for the duration of the Extension Phase in Performance of Upper Limbs (PUL)
- Change from baseline to Week 12, 24, 36 and 48 (in the main phase of the study) and measured at 6-monthly intervals for the duration of the Extension Phase of blood biomarkers, e.g., creatine kinase, matrix metallopeptidase 9 and other biomarkers
- Change from baseline to Week 48 (in the main phase of the study) and measured at 12-monthly intervals for the duration of the Extension Phase in cardiac MRI parameters (Cohort 3)
- Change from baseline in MRI leg muscle parameters measured at 6-monthly intervals for the duration of the Extension Phase (Cohorts 1 and 2)
- SMT C1100 and metabolite plasma concentrations measured at 6-monthly intervals for the duration of the Extension Phase
- Change from baseline in pulmonary function tests measured at 6-monthly intervals for the duration of the Extension Phase

It should be noted that patients in Cohort 3 may not be able to perform all of the functional tests at baseline. Therefore the patients included in the analyses for these tests will be test specific and based upon their baseline ability to perform the test.

4. STUDY DESIGN

4.1. Summary of Study Design

4.1.1. Study Design

This is a Phase 2, open-label, study to assess the activity and safety of utrophin modulation with SMT C1100 administered *bid* to ambulatory paediatric male patients with DMD. In Cohort 1, approximately 30 patients with DMD will receive SMT C1100 2.5 g *bid* as the F3 formulation. In Cohort 2, approximately 10 patients with DMD will receive SMT C1100 1 g *bid* as the F6 formulation. In Cohort 3, approximately 15 patients, who have previously received SMT C1100, but who are not eligible for Cohorts 1 or 2, will be administered 2.5 g *bid* of F3. Cohort 1 will be conducted in the UK and USA. Cohort 2 will only be conducted at specific centres in the USA. Cohort 3, will only be conducted in the UK.

This study will be conducted in a multi-centre setting and comprises of a Screening and Baseline period of up to 28 days and initially a 48-week open label Treatment Phase.

Following completion of the 48-week open label Treatment Phase, patients will be eligible for rolling on to an Extension Phase which will continue until SMT C1100 is approved or discontinued. All patients will receive the same formulation as they had previously been receiving, twice-daily, in the Extension Phase.

Study patients not rolling on to the Extension Phase will complete a 30-day Safety Follow up following completion of the initial Treatment Phase. Similarly, when the study finishes, all patients still ongoing treatment in the study will cease their study medication and complete a 30-day Safety Follow up.

During the Treatment Phase patients will be dosed at home by their parents/responsible-adult twice-daily with approximately 8–12 hours between the breakfast dose and evening meal dose.

For boys in Cohorts 1 and 3, SMT C1100 will be administered, in the fed state, as the F3 formulation and with a glass of whole/full-fat milk. A suitable number of syringes will be provided with the IMP and the volume prescribed will relate to the gradations on the measuring device.

For boys in Cohort 2, SMT C1100 will be administered in a fed state with the F6 formulation constituted in milk prior to immediate administration. A suitable number of graduated dosing cups will be provided with the IMP. Patients in Cohort 2 will be required to attend an additional visit for blood sampling on Day 7.

A maximum of two muscle biopsies (Cohorts 1 and 2 only) will be taken one of which will be at baseline. Where the procedure is performed at screening this will be after the patient has been confirmed eligible for the study.

The patients in Cohorts 1 and 2 will be assigned as to when they will receive the second muscle biopsy procedure. The first eight patients enrolled in Cohort 1 will have a biopsy at 24 weeks and the remaining 22 patients will be assigned alternately between the 24-week and the 48-week time point. The first 6 patients enrolled in Cohort 2 will have the biopsy at the 24-week time point and the remaining 4 patients will have theirs at the 48 week time point.

If preferred by the site and patient's family then the visits at Day 7 (Cohort 2 and 3 only) and Weeks 4 (all Cohorts) and 8 (Cohorts 1 and 2 only) may be performed at the patient's house by a sponsor-provided home-nursing team.

Patients who withdraw early from the study will be asked to return for an Early Termination Visit at which, if the patient agrees, the second biopsy will be performed (if it has not already been completed) as well as other safety and functional assessments. If patients are not willing to return then this will be documented in the source documents and case report form (CRF) and will not be classed as a protocol deviation.

Details on the timing of treatment and assessments are given in the Time and Events Table.

4.1.2. Duration of Patient Participation

Patients will initially be involved (from screening to follow-up) in the study for approximately 52–56 weeks. This period includes a screening and baseline period that will last up to 28 days, a 48-week Treatment Phase and a potentially a 30-day safety follow up.

Patients who complete the 48-week open label Treatment Phase may choose to consent to roll into an Extension Phase which will last until either SMT C1100 is approved in the relevant countries or development of SMT C1100 is discontinued. Patients who are enrolled in the Extension Phase may have home visits if only vital signs and blood samples are being collected at a scheduled visit (Weeks 12 and 36 of each year of the Extension Phase); if this occurs then AE and concomitant medication checks will be performed in a documented telephone call. The patient's IMP supply should be considered when determining whether a home and telephone visit are appropriate. Patients in the Extension Phase will have a 30-day safety follow up if/when the study is stopped.

Additionally, the DMC and/or the Sponsor may recommend amending the duration of the study based on safety or efficacy findings.

4.2. Stopping Rules

4.2.1. Study Stopping Rules

Routine independent DMC meetings will be held during the course of the study in accordance with ICH-GCP and the DMC charter. Additional meetings can be requested at the DMC's discretion at any point in the study.

The responsibilities of the DMC include: (1) ongoing assessment of safety data during the trial for the purposes of safeguarding the interests of trial participants, (2) assessment of pharmacokinetic data and its relationship to the AE profile, (3) oversight of clinical trial conduct including general safety and International Council on Harmonization (ICH) GCP procedures. To enhance the integrity of the trial, the DMC may formulate recommendations relating to the selection/recruitment/retention of patients, improving adherence to protocol-specified treatment and retention of patients and procedures for data management and quality control. Based on its review of the data during periodic meetings, the DMC may provide recommendations about stopping, modifying, or continuing the trial. Summit will retain ultimate responsibility on decision making.

Summit reserves the right, at any time, to prematurely terminate the trial or trial sites. Premature termination of the trial could be for scientific or administrative reasons or for any other valid and/or ethical reason or if any safety issues arises and the overall risk/benefit evaluation changes and is no longer in favour of continuation.

4.2.2. Individual Stopping Rules

The pharmacokinetics of SMT C1100 parent and metabolites, and their relationship with all safety parameters, will be reviewed on an ongoing basis by the Sponsor and the DMC. As this is an open-label study, the decision to stop individual patients may be made on a case-by-case basis. The DMC can also recommend, in individual patients, a lowering of the SMT C1100 dose.

If a patient's results meet either of the criteria below, dosing should be stopped and the tests should be repeated as soon as possible. If the repeated results still meet this criterion, the study drug will be permanently stopped and may not be restarted although the patient will continue to be followed for functional and MRI assessments for the duration of the study. If the patient is withdrawn from the study, a follow up visit should be arranged:

- GLDH $\geq$ 3x ULN

OR

- Bilirubin ≥ 2x ULN together with an INR ≥ 1.5x ULN (Cohort 2 and 3 only)

Any intolerable AE or SAE that is at least possibly related to study drug should lead to a temporary discontinuation of the patient's study treatment. After resolution of the intolerable AE or SAE, the Investigator, in discussion with the Sponsor, may decide to either permanently discontinue the patient's study treatment, or, if recommended by the DMC and Sponsor reinstate treatment but reduce their *bid* dose to 1.25 g for Cohort 1 and 3 or reduce the frequency to once-daily dosing (2.5 g or 1.25 g for Cohorts 1 and 3; 1 g for Cohort 2; see Section 8.1.1). If a lowered dose is tolerated for at least 2 weeks the Investigator can, based on the recommendation of the DMC and Sponsor escalate the dose up to the original strength. Once-daily dosing should occur in the morning.

5. STUDY POPULATION

5.1. Number of Patients

A suitable number of potential patients will be screened in order that approximately 55 patients successfully meet the inclusion and exclusion criteria and continue into the Treatment Phase. Approximately thirty patients are expected to be enrolled in Cohort 1, approximately 10 in Cohort 2 and approximately 15 in Cohort 3. The sample size is not based upon statistical powering, but the number is considered as sufficient to initially explore the endpoints and their relationship with SMT C1100 plasma exposure.

Patients who withdraw or who are withdrawn during the Treatment Phase may be replaced if the study has not yet reached full enrolment at the time of withdrawal. Patients who withdraw or who are withdrawn for an AE considered related to SMT C1100 will not be replaced.

Efforts will be made, in Cohorts 1 and 2, to balance the study populations and attempt to have at least 50% of the boys with a fat:water fraction greater than or equal to 0.15. Efforts will also be made such that half of the boys are greater than or equal to 8 years of age at screening. Such attempts will be made manually rather than via an automatic system; achieving these recruitment goals will be attempted but complete balance will not be enforced.

All patients in Cohorts 1–3, will be eligible to be rolled into the Extension Phase.

5.2. Eligibility Criteria

5.2.1. Main Study

5.2.1.1. Inclusion Criteria

To be enrolled patients must meet all selected criteria for their cohort:

Criterion Number	Criterion	Cohort 1	Cohort 2	Cohort 3
1	Be able to provide written informed consent/assent as per local requirements.	✓	✓	✓
2	Be male	✓	✓	✓
3	Be aged ≥5 years to <10 years of age (from 5th birthday to 10th birthday)	✓	✓	NA
4	Have phenotypic evidence of dystrophinopathy based on the onset of characteristic clinical symptoms or signs (e.g., proximal muscle weakness, waddling gait, and Gowers' manoeuvre), an elevated serum creatinine kinase level, and ongoing difficulty with walking	✓	✓	✓
5	Have prior confirmation of the DMD diagnosis through: Documentation of the presence of a mutation in the dystrophin gene as determined by gene sequencing from a laboratory certified by the College of American Pathologists, the Clinical Laboratory Improvement Act/Amendment or an equivalent organisation. Or Documentation of the absence of dystrophin in the muscle (via biopsy)	✓	✓	✓
6	Be willing and able to comply with two muscle biopsy procedures	✓	✓	NA
7	Be able to undergo MRI examination	✓	✓	✓
8	Patients must have used stable systemic corticosteroids (prednisone, prednisolone or deflazacort) for a minimum of 6 months immediately prior to the start of the Treatment Phase, with no significant change in dosage or dosing regimen (not related to body weight change) and a reasonable expectation that dosage and dosing regimen will not change significantly for the duration of the study	✓	✓	✓
9	Have the ability to walk at least 300 meters unassisted during the screening 6MWD and be below the protocol-specified threshold for 80%-predicted 6MWD	✓	✓	NA
10	Have results of two 6MWD by Baseline determined as valid. The results of the second 6MWD (baseline) must be within 20% of the first 6MWD (screening)	✓	✓	NA
11	Have cardiac ECHO measurements showing an ejection fraction of ≥55% and fractional shortening of ≥28%	✓	✓	NA
12	Confirmed screening laboratory values within the central laboratory ranges (haematology, renal and serum electrolyte parameters and	✓	✓	✓

Criterion Number	Criterion	Cohort 1	Cohort 2	Cohort 3
	serum chemistry parameters) or considered not clinically significant in the opinion of the Investigator. Variations in specific parameters expected in a DMD population (e.g., AST, ALT, alkaline phosphatase, lactate dehydrogenase and CPK) classed by the Investigator as not clinically significant will not exclude the patient			
13	Be willing and able to comply with scheduled visits, drug administration plan, study procedures, laboratory tests and study restrictions	✓	✓	✓
14	Have taken part in a prior SMT C1100 study	NA	NA	✓

5.2.1.2. Exclusion Criteria

To be enrolled patients must not meet any of the selected criteria for their cohort:

Criterion Number	Criterion	Cohort 1	Cohort 2	Cohort 3
1	Have physical exam findings that in the investigator's opinion should be exclusionary e.g., lower limb injury that may affect 6MWD performance	✓	✓	✓
2	Have any change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation or reinitiation) in prophylaxis/treatment for congestive heart failure (CHF) within 3 months prior to the start of study treatment	✓	✓	✓
3	Have uncontrolled clinical symptoms and signs of CHF (American College of Cardiology/American Heart Association Stage C or Stage D)	✓	✓	✓
4	Have abnormal GLDH at baseline (>1.5 x ULN)	✓	✓	✓
5	Have abnormal coagulation times at baseline (>1.5 x ULN)		✓	✓
6	Have an abnormal ECG e.g., a QTcF >500 ms, left bundle-branch block or any other major conduction defect	✓	✓	✓
7	Use beta blockers (however, if during the course of the study they are clinically indicated they can be initiated)	✓	✓	NA
8	Use herbal supplements and be unwilling to stop these for the duration of the study	✓	✓	✓
8	Have a known hypersensitivity to any of the ingredients or excipients of the IMP. microfluidised oral suspension (F3): Poloxamer 188, Methylparaben, Propylparaben, Hydroxypropylmethyl cellulose, Glycerol, Non crystallising sorbitol [70%], Xanthan gum, Strawberry cream flavour [PHS-132963]	✓	NA	✓
10	Have a known hypersensitivity to any of the ingredients or excipients of the IMP. Powder for oral suspension (F6): hypromellose acetate succinate	NA	✓	NA
11	Have been exposed to another investigational drug or DMD interventional agent within 3 months prior to start of the Treatment Phase. Prior exposure to SMT C1100 or participation in an approved deflazacort access program (e.g., FOR-DMD or ACCESS DMD clinical trials) within this period would not exclude the patient (provided they have been on stable treatment for 6 months)	✓	✓	✓

Criterion Number	Criterion	Cohort 1	Cohort 2	Cohort 3
12	Have a history of major surgical procedure within 12 weeks prior to the start of the Treatment Phase (Week 1)	✓	✓	✓
13	Be undertaking ongoing immunosuppressive therapy (other than corticosteroids)	✓	✓	✓
14	Have an expectation of a major surgical procedure (e.g., scoliosis surgery) during the 12-month Treatment Phase of the study	✓	✓	✓
15	Require daytime ventilator assistance	✓	✓	✓
16	Have a prior or ongoing medical condition (e.g., concomitant illness, psychiatric condition, behavioural disorder, alcoholism, drug abuse), medical history, ECG findings, or laboratory abnormality that, in the Investigator's opinion, could adversely affect the safety of the patient, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results	✓	✓	✓
17	Be dairy or lactose intolerant or have any other dietary restrictions that might interfere with the conduct of the study	✓	✓	✓
18	Be a smoker, use other tobacco or nicotine products or be exposed to daily passive smoking (including parent/legal guardian, siblings) so as to minimise environmental factors causing CYP1A induction	✓	✓	✓
19	Be using an approved DMD medication or anticipates using one during the duration of the study e.g., ataluren, idebenone, drisapersen, Exondys51. Patients who are taking part in the FOR-DMD and ACCESS DMD studies will be allowed to take part	✓	✓	✓
20	Be using an inducer of CYP1A1 or CYP1A2	✓	✓	✓
21	Be using a substrate of CYP2B6	✓	✓	✓
22	All prescription, OTC, and herbal products that are known CYP2B6 sensitive substrates (e.g., buproprion, efavirenz) will be excluded 14 days prior to study conduct (beginning at screening) through 14 days after study conduct completion. Please note, this is not an exhaustive list of CYP2B6 substrates and a discussion with the Medical Monitor may be warranted	✓	✓	✓
23	Be using drugs that have serotonergic, norepinephrinergic or dopaminergic activity (e.g., selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, tryptophan, dextromethorphan, meperidine, bupropion, nortriptyline, desipramine, doxepin, amoxapine, rasagiline, selegiline), or treatments used in attention deficit hyperactivity disorder such as Methylphenidate, and phenethylamine (PEA)	✓	✓	✓
24	Use of substrates of BRCP (e.g., omeprazole, rabeprazole, fluvastatin, methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan)	✓	✓	✓

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6. STUDY ASSESSMENTS AND PROCEDURES

Each study patient in Cohorts 1 and 2 will require overnight hospitalisation at four time points during the study: Baseline, Week 24, Week 48 and End of study (Week 52). The purpose of these residential stays is to minimise patient activity immediately prior to certain biomarker assessments (i.e., CK) and physiological assessments (i.e., 6MWD, NSAA) as well as to facilitate pharmacokinetic sampling when conducted post-PM dose. Patients enrolled in Cohort 3 will not be required to attend residential stays.

Additional overnight hospitalisation may be requested to fit institutional requirements regarding biopsy or MRI procedures, however, this is not required.

6.1. Screening Procedures

6.1.1. Medical History

The patient's medical history will be collected by the Investigator, or suitably qualified designee. The information will be collected via an interview with the patient's parents or responsible adult and should include all diseases or conditions identified as relevant by the Investigator. The patient should be excluded from the trial if any disease or condition listed in the exclusion criteria is detected.

6.1.2. Demographics

The following demographic information should be recorded:

- Date of birth
- Sex
- Race
- Ethnicity (Hispanic/Latino or non-Hispanic/Latino)

Information that could identify the patient such as name, initials, social security number, (national) insurance number, etc. shall not be recorded in the CRF and should not be transmitted from the site to the Sponsor.

6.1.3. Nutritionist Appointment

The patient and their parents/responsible adult will meet with a nutritionist at the end of the screening process to discuss the nutritional requirements of the patient while they are enrolled in the study.

6.2. Pharmacodynamic Procedures

6.2.1. Muscle Biopsy

Each patient in Cohorts 1 and 2 will undergo two muscle biopsies during the study at the times outlined in the Time and Events Table. Cohort 3 will not undergo muscle biopsies. The first eight patients in Cohort 1 will have a biopsy at 24 weeks and the remaining 22 patients will be alternately assigned between the 24 week and the 48 week time points. Six patients in Cohort 2 will undergo their second biopsy at 24 weeks and the remaining four patients at Week 48. The patient may have to travel and have the biopsy procedure undertaken at a different location to the patient's usual site of care. Ultrasound guidance is recommended though not required.

Patients who do not complete the 48-week dosing period may have their second biopsy at or around the Early Termination visit if it has not already been performed and they are willing to do so.

A detailed description of the methods relating to the collection of the biopsy sample and the processing of the sample can be found in the reference manuals. In order to detect whether daily dosing with SMT C1100 modulates the effect of utrophin with corresponding reduction in fibre regeneration within a muscle biopsy, the levels of utrophin protein at the myofibre membrane will be calculated for all fibres found in a biopsy section. In parallel, the quantity of regenerating fibres will also be calculated using markers of regeneration namely myosin protein intensity and myofibre cross sectional area.

Biopsy sampling may be performed using local or general anaesthetic according to the Investigator's clinical judgment as to which route is better for the patient. The biopsy should be taken from the biceps muscle.

6.2.2. Blood Biomarkers

Blood samples for analysis of biomarkers should be collected at the times outlined in the Time and Events Table.

Blood samples should be collected and details on collection and processing can be found in the laboratory manual. If patients have consented blood samples will be retained for future biomarker analysis.

6.2.3. Magnetic Resonance Imaging

6.2.3.1. Leg Scan

Patients in Cohorts 1 and 2 will undergo MRI/MRS scans of the leg at the times outlined in the Time and Events Table.

The MRI scans will be performed using a 3 Tesla whole body instrument. The same machine should be used for all scans for an individual patient.

Further details on the MRI procedures can be found in the study reference manual. Patients should refrain from exercise for 24 h prior to each MRI procedure. Scans may be performed at a different location to the patient's usual site.

6.2.3.2. Cardiac Scan

Patients in Cohort 3 will undergo cardiac MRI scans at the times outlined in the Time and Events Table.

The MRI scans will be performed using a 3 Tesla whole body instrument. The same machine should be used for all scans for an individual patient.

Further details on the MRI procedures can be found in the study reference manual. Scans may be performed at a different location to the patient's usual site.

6.3. Pharmacokinetic Procedures

Blood samples for analysis of SMT C1100 parent and its metabolites (DHD I and DHD III) in plasma will be collected at the times outlined in the Time and Events Table. Day 7 (Cohort 2 only) and Week 4 and 8 assessments may be conducted by the sponsor-provided home nursing vendor

Pharmacokinetic samples for SMT C1100 and metabolites will be measured frequently. As this will be a sparse sampling pharmacokinetic assessment each patient in Cohort 1 and 2 will have three samples taken around either the AM dose or around the PM dose only. There will be six time points at which samples can be taken; pre-AM dose, 3 hours after the AM dose, 6 hours after the AM dose, or pre PM dose, 4 hours after the PM dose and 10 hours (+ up to 4 hours but before the next AM dose) after the PM dose. Sampling will be done around the AM dose during Day 1, Weeks 8, 12 and 36 (there is the option of samples being collected at the patient's house at the Week 8 time point). Sampling will be done around the PM dose during Weeks 4, 24 and 48 (there is the option of samples being collected at the patient's house at the Week 4 time point). Where the patient has been reduced to once-daily dosing only AM sampling points will be undertaken. For

subjects in Cohort 2 a single additional sample will be taken at 4 h post-AM dose on Day 7.

In the Extension Phase all subjects, all cohorts will have a 4 h post-AM dose sample taken at the times outlined in the Time and Events Table.

For the 0–8 h samples a ±15 minute window will be allowed for each time point. Further details on collection, processing and shipping can be found in the laboratory and shipping manuals, respectively.

Samples for determination of SMT C1100 and metabolites (DHD I and DHD III and overall metabolite profile, as specified in the laboratory manual) concentrations in plasma will be analysed using appropriate bioanalytical methods, which will be described in a separate bioanalytical report.

6.4. Safety Procedures

6.4.1. Twelve-Lead Electrocardiogram

Twelve-lead ECGs will be performed at the times outlined in the Time and Events Table. A single ECG (in triplicate) will be performed at Screening, Baseline, Weeks 12 and 36. At Weeks 1, 24 and 48 ECGs will be performed pre-AM dose and 0.5, 2, 4 and 6 h post-AM dose or pre-PM dose and 0.5, 2 and 4 h post-PM dose.

Triplicate ECGs separated by approximately 2 to 5 minutes should be collected at each time point. The ECGs will be transmitted on an ongoing basis to a centrally based cardiologist who will independently examine the ECGs. Further details on performing and transmitting ECGs can be found in the Study Reference Manual.

Measurements will be made using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, and QT.

All ECG traces will be reviewed and signed by the PI or a Study Physician and any abnormalities will be marked as clinically significant or not clinically significant. If the average QTc(F) is ≥500 ms then an additional ECG should be repeated after at least a 5-minute interval.

6.4.2. Echocardiogram

Echocardiograms will be performed at the times outlined in the Time and Events Table.

Patients should rest in a supine position for 10 minutes before the ECHO is performed. Further details can be found in the Study Reference Manual.

6.4.3. Vital Signs

Vital signs (pulse, respiratory rate, oral temperature and systolic and diastolic blood pressure) will be assessed at the times outlined in the Time and Events Table. Patients should rest in a supine position for 10 minutes before the vital signs are assessed.

Patients who are enrolled in the Extension Phase may have home visits if only vital signs and blood samples are being collected at a scheduled visit (Weeks 12 and 36 of each year of the Extension Phase); if this occurs then AE and concomitant medication checks will be performed in a documented telephone call.

6.4.4. Physical Examination

The physical examination will be performed by a qualified physician at the times outlined in the Time and Events Table. At a minimum the following will be assessed: ear, nose and throat, cardiovascular system, pulmonary system, skin, abdomen and neurological system.

Body weight (kg) and height (meters) will be assessed at each physical examination. Patients will be weighed without shoes in light, indoor clothing. Height will be assessed with the patients shoes removed.

6.4.5. Pulmonary Assessment

The pulmonary assessments will be performed by trained site staff at the times outlined in the Time and Events Table.

Spirometry assessments (FEV_1, FVC, PEF, MIP and MEP) should be performed in Cohorts 1 and 2 accordance with American Thoracic Society/European Respiratory Society guidelines. Predicted normal values will be calculated using local reference ranges. In Cohort 3 both these assessments and additional spirometry assessments (PCF and SNIP) should be performed.

At all time points, three technically acceptable measurements should be made and recorded. All spirometry assessments should be made using the same make/model of spirometer throughout the study.

Technically acceptable spirometry assessments should be repeatable i.e., values should vary ≤150 mL for both FEV_1 and FVC readings. A minimum of three and a maximum of eight attempts may be made to provide the three reproducible readings. If repeatability has not been achieved after eight attempts, the highest value should be recorded (a technical comment should be made on the printout in such instances). The highest values for FEV_1 and FVC may derive from different exhalation efforts.

The predicted values for spirometry assessments should be adjusted for age and sex. Assessments will be adjusted for race as shown in Table 1.

Table 1 Adjustment of spirometry according to race

Race	Adjustment to predicted values
Caucasian	100%
All other races (including those of mixed race)	90%

Further information on performing spirometry assessments can be found in the Study Reference Manual.

6.4.6. Laboratory Assessments

Please note Day 7 (Cohort 2 and 3 only), Week 4 (all cohorts) and Week 8 (Cohort 1 and 2 only) assessments may be conducted by the sponsor-provided home nursing vendor.

Patients who are enrolled in the Extension Phase may have home visits if only vitals and blood samples are being collected at a scheduled visit; if this occurs then AE and concomitant medication checks will be performed in a documented telephone call.

6.4.6.1. Haematology and Coagulation Times

Blood for the assessment of haematology parameters will be collected at the times outlined in the Time and Events Table. The following parameters will be assessed at each time point:

- Haemoglobin
- Haematocrit
- Mean corpuscular volume
- White blood cells
- Red blood cells
- Neutrophils (percentage and absolute)
- Lymphocytes (percentage and absolute)
- Monocytes (percentage and absolute)
- Eosinophils (percentage and absolute)
- Basophils (percentage and absolute)
- Platelets

Blood samples will be analysed centrally and samples will be maintained for confirmatory testing and then either destroyed or retained according to what the patient's parents have consented. Further details on processing and shipping can be found in the laboratory and shipping manuals, respectively.

6.4.6.2. Clinical Chemistry

Blood for the assessment of serum chemistry parameters will be collected at the times outlined in the Time and Events Table. The following parameters will be assessed at each time point:

- Total calcium
- Potassium
- Sodium
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Gamma-glutamyl transferase
- Bilirubin (total, direct and indirect)
- Amylase
- Lipase
- Urea/BUN
- Uric acid
- Lactate dehydrogenase
- Glutamate dehydrogenase
- Creatine kinase
- Creatinine
- Fasting glucose
- Fasting lipids
- Cystatin C

Additionally LFT, GLDH, amylase, lipase and coagulation parameters will be assessed on Day 7 in patients from Cohorts 2 and 3.

Blood samples will be analysed centrally and samples will be maintained for confirmatory testing and then either destroyed or retained according to what the patient's parents have consented. Further details on processing and shipping can be found in the laboratory and shipping manuals, respectively.

6.4.6.3. Additional Clinical Chemistry

Blood for the assessment of additional serum chemistry parameters (FGF-19 and C4) will be collected at the times outlined in the Time and Events Table. At screening and the end of study visit a single sample will be taken. At Week 1 two samples will be taken: pre-AM dose and 3 h post AM dose. At Weeks 24 and 48 four samples will be taken: pre-AM dose, 3 h post AM dose, pre-PM dose and 4 h post PM dose.

The following parameters will be assessed at each time point:

- Fibroblast growth factor 19
- C4 (7α-hydroxy-4-cholesten-3-one)

Blood samples will be analysed centrally and samples will be maintained for confirmatory testing and then either destroyed or retained according to what the patient's parents have consented. As at least two central laboratories will be used for analysing these parameters blood should be collected into a minimum of two tubes. Further details on processing and shipping can be found in the laboratory and shipping manuals, respectively.

6.4.6.4. Coagulation Parameters

Blood for the assessment of coagulation parameters will be collected at the times outlined in the Time and Events Table in Cohorts 2 and 3. The following parameters will be assessed at each time point:

- Activated partial thromboplastin time
- Prothrombin time
- International normalised ratio

Blood samples will be analysed centrally and samples will be maintained for confirmatory testing and then either destroyed or retained according to what the patient's parents have consented. Further details on processing and shipping can be found in the laboratory and shipping manuals, respectively.

6.4.6.5. Urinalysis

Urine for the assessment of urinalysis parameters will be collected at the times outlined in the Time and Events Table. The following parameters will be assessed at each time point using a dipstick test:

- Glucose
- Bilirubin
- Ketones
- Specific gravity
- Blood
- pH
- Protein
- Urobilinogen
- Nitrites
- Leucocytes

Urine samples will be analysed locally using a dipstick and samples will be maintained for confirmatory testing and then either destroyed or retained according to what the patient's parents have consented. If the following parameters have a result of ++ or higher, then a sample will be sent to the central laboratory for microscopic analysis:

- Glucose
- Bilirubin
- Ketones
- Blood
- Protein
- Leucocytes

6.5. Efficacy Procedures

If consent is given, the patient may be filmed during these procedures to enable study physicians to examine the patient's movements.

6.5.1. North Star Ambulatory Assessment

The NSAA should be performed without shoes at the times outlined in the Time and Events Table.

Where possible this should be carried out by the same assessor in order to reduce variability. A copy of the instructions for patients and an example score sheet can be found in the Study Reference Manual. The order of the assessments is important and needs to be followed precisely.

6.5.2. 10-Metre Run or Walk

The 10-metre run or walk should be performed at the times outlined in the Time and Events Table and as referenced in the Study Manual.

A 10-metre straight course should be plotted out. Patients should be asked to complete the course as quickly as they can. Patients should start from immediately behind the start line and the time should start from the moment they cross the line until they reach 10 meters. Patients should be asked to repeat the test after a 10 minute rest and both times will be recorded in the source documents and transcribed to the CRF.

6.5.3. Six-Minute Walk Distance

The 6MWD should be performed at the times outlined in the Time and Events Table and as referenced in the Study Manual.

The 6MWD should be performed indoors in a flat, seldom used corridor at least 30 meters in length. The length of the corridor should be marked every 3 meters. A cone (or equivalent) should be placed at the far end of the corridor to mark the turnaround spot and the start/stop line marked with another cone. Enough space should be allowed at each end of the corridor for the patient to turn around easily without bumping into anything.

Patients should be instructed to walk as far as they can in 6 minutes by walking up and down the corridor remembering to go around the cone. If required they can stop to rest but should resume walking as soon as possible. They should be reminded that they need to walk not run along the course.

If patients do not produce two values where the second is within 20% of the first at screening then this procedure may be repeated once on a separate day as part of the same screening procedure.

6.5.4. Paediatric Outcomes Data Collection Instrument

The PODCI should be performed at the times outlined in the Time and Events Table. The patient's parent or responsible adult should be given a copy of the questionnaire and asked to complete it. A copy of the questionnaire and scoring system can be found in the Study Reference Manual.

6.5.5. Performance of the Upper Limb

The PUL assessment was specifically designed to assess upper limbs in patients with DMD [Mayhew, 2013]. The PUL should be performed at the times outlined in the Time and Events Table and BEFORE any biceps biopsy of patients. It consists of 21 items testing shoulder, elbow and distal upper limb performance reflecting functional tasks and a copy can be found in the Study Reference Manual.

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

Patients must not use or consume any of the following throughout their involvement in the study:

- Cigarette smoke in the form of passive smoking where possible. They should not smoke cigarettes/e-cigarettes or any other source of nicotine (e.g., cigars, snuff, etc).
- Herbal supplements
- Daily intake of chargrilled meat above 250 grams/day
- Cruciferous vegetables above 150 grams/day

8. INVESTIGATIONAL MEDICINAL PRODUCT

8.1. Dosage and Administration

Throughout the Treatment Phase all patients will receive SMT C1100 *bid.* Doses will be administered on an outpatient basis by their parent or responsible adult. There should be 8–12 hours between the breakfast dose and evening meal dose.

For boys in Cohorts 1 and 3, SMT C1100 will be administered, in the fed state, as the F3 formulation and with a glass of whole/full-fat milk. A suitable number of syringes will be provided with the IMP and the volume prescribed will relate to the gradations on the measuring device.

For boys in Cohort 2 SMT C1100 will be administered in a fed state with the F6 formulation constituted in milk prior to immediate administration and followed by a

measure of milk to rinse the container. A suitable number of graduated dosing cups will be provided with the IMP. The Treatment Phase for all Cohorts in the main study will last 48 weeks. The Extension Phase will extend until drug approval/discontinuation.

8.1.1. Dose Modification Guidelines

The Investigator should determine if each SAE is related to study drug. Serious AEs considered at least possibly related to study drug may require a dose reduction after discussion with the Sponsor, a temporary hold, or permanent discontinuation.

8.2. Dose Rationale

Lower than expected SMT C1100 exposure levels were observed in the first clinical study (SMT C11002) using an aqueous microfluidised suspension F2. Further analysis of the data from the study identified the importance of diet and fat intake. Clinical study SMT C11003 using the microfluidised formulation (F3) with an appropriate diet plus the immediate consumption of full fat milk after the dose increased SMT C1100 plasma exposure to levels believed to be able to modulate the utrophin mechanism (based on EC_{50} data in primary human myotubes). In parallel, additional formulation development work was undertaken with the aim of increasing further the systemic exposure to SMT C1100 in DMD patients. Results in a 7-day rat study (N-109) showed that two new formulations (F6, a powder for oral suspension and F5, a nanosuspension) gave higher exposure levels to SMT C1100 with no significant change in the ratio of parent to DHD I and DHD III when compared to the F3 microfluidised suspension. There was a relative increase in exposure of three-fold and two-fold seen with the F6 and F5 formulations, respectively, in the rat.

In study SMT C11002, maximum exposure was seen at the 100 mg/kg *bid* dose which supported a fixed dose of 2.5 g *bid* in a Duchenne patient with a projected lean body mass (LBM) of 25 kg (Griffiths *et al* 1988). Thus a fixed escalating dose of 1.25 g *bid* and then 2.5 g *bid* was used in the SMT C11003 study with the F3 formulation. Based on the higher rat exposure for the newer formulations relative to F3, the starting dose of the F6 powder for oral suspension and F5 nanosuspension formulations in SMT C11004 study Part A (healthy adult subjects with a projected LBM of 60 kg) were lowered accordingly (three-fold for the F6 formulation [~32 mg/kg] and two-fold for the F5 formulation [~50 mg/kg]) to achieve an approximate exposure equivalence to the 2.5 g dose for the F3 formulation in SMT C11003. Consequently the doses selected for investigation in SMT C11004 Part A were 2 g *bid* and 4 g *bid* for the F6 formulation and 3 g *bid* and 6 g *bid* for the F5 formulation. As shown in the top half of Table 1, the F6 formulation in healthy volunteers gave approximately two- to three-fold higher exposure than F5 when comparing the dose normalized C_{max} and AUC values, respectively. As the F6 formulation showed a more than 10-fold increase in exposure (AUC) compared to the F3

formulation in the normal healthy subjects, a starting dose of 0.25 g *bid* for the F6 formulation was chosen for the first 7-day dosing period with the goal of achieving a similar SMT C1100 exposure to the current 2.5 g *bid* F3 formulation. Subsequent dose escalations were to 0.5 g *bid* for 7 days and 1 g *bid* for 7 days. Using the Geometric mean Cmax for F6 formulation of 389 ng/mL, the Cmax concentration in DMD patients was >6 fold higher than observed with the F3 formulation at these doses, as shown in the bottom half of Table 1.

Table 1 – SMT C1100 exposure (Geometric means) comparison across three formulations

Study	Subject [a]	Formulation[b]	Dose Level (*bid*)	Day[c]	C_{max} (ng/mL)	Dose Normalised C_{max}[d]	AUC (ng*h/mL)	Dose Normalised AUC[d]
SMTC11004	HV	F5	3 g	3	389	130	2681	984
SMTC11004	HV	F6	2 g	3	746	373	3870	1935
SMTC11003	DMD	F3	2.5 g	14	61	25	350	140
SMTC11004	DMD	F6	1 g	7	416	416	3855[e]	1928

[a] HV – Healthy volunteer; DMD – Patient
[b] F3 – Microfluidised aqueous oral suspension; F5 – Aqueous oral nanosuspension; F6 – powder for oral suspension
[c] Day C_{max} and AUC was obtained which was the last day of dosing at the respective dose level
[d] C_{max} and AUC value normalised to 1 g
[e] All AUC's are 0–12 h except for DMD patients with F6 which is AUC 0–24 h. Based on *bid* dosing, the corresponding dose level was used for dose normalisation (g/*bid* dose for 0–12 h and g/day for 0–24 h)

SMT C1100 given as the F6 formulation was found to be generally safe and well tolerated at doses up to 1 g *bid* given for 7 days in the DMD subjects (Study SMT C11004). Adverse events were seen across all doses but no increase with dose could be discerned. The majority of the AEs were gastrointestinal in nature with diarrhoea being the most frequently reported event. All but one of the AEs were mild or moderate in nature. There was one serious (severe) AE of elevated liver function test abnormalities with the 0.25 g *bid* dose, the cause of which is unknown (CIOMS SMT2016GB000034). The patient himself was clinically well but nevertheless discontinued from the study after a positive rechallenge with 0.25 g *bid* in Part B, Period 2. The patient's laboratory values were within the normal range at the 2-week follow-up visit. One additional subject discontinued on Day 7 after his AM dose in the 1 g *bid* dose period for an AE of abdominal pain.

The potential of SMT C1100 to induce utrophin modulation in primary human skeletal muscle cells (myotubes) was assessed in the utrophin induction assay (Study No. N-058). SMT C1100 was shown to trigger utrophin protein modulation in a dose-dependent manner with a maximal 1.45-fold increase and the EC_{50} was determined to be 205 nM (67 ng/mL). In SMT C11004 Part B, at the two highest dose levels, mean (geometric) SMT C1100 C_{max} was > 70 ng/mL, with the highest geometric mean C_{max} over 24 hours being 390 ng/mL at the 1 g *bid* dose level at steady state (Day 7). In study N-115, DHD III has also shown potential to modulate utrophin transcription in the H2K cell reporter assay with 6-fold lower potency (EC_{50} ~4.5µM) compared to SMT C1100. Thus the relatively high levels of DHD III metabolite (mean C_{max} of 14 µM at steady state) may provide a meaningful contribution to pharmacology. DHD I was much less potent in the reporter assay- 30-fold lower than SMT C1100 - and plasma exposure is also lower than DHD III so the DHD I metabolite is less likely to play a key role in pharmacology.

In Study SMT C11004, overall there was an increase in steady state SMT C1100 C_{max} and $AUC_{0–24}$ with increasing dose which was greater than dose proportional at doses of 0.5 g *bid* and 1 g *bid* for 7 days. There was little to no accumulation of SMT C1100 with repeated dosing. There was dose proportionality between the 0.25 g *bid* and 0.5 g *bid* dose levels. The F6 powder for oral suspension at a dose of 1 g *bid* achieved a greater than six-fold increase in maximum SMT C1100 plasma levels (14-fold if comparing dose normalised data) in DMD patients compared to those achieved with the current clinical formulation, F3, and consequently this formulation and dose will be investigated in a small number of patients in Study SMT C11005.

Chronic nonclinical toxicology studies provide up to 14-fold exposure multiple to SMT C1100 compared to 1 g *bid* in DMD patients using the F6 formulation. This includes 26 weeks of dosing in rodent (rat and mouse) and 39 weeks of dosing in non-rodent (minipig). No adverse findings were observed in these nonclinical studies up to the limit dose. Exposure to DHD I was also two- to three-fold higher (based on total or free DHD I levels, respectively) in rats on the 26 week toxicology study versus F6 in DMD patients. Patient exposure to DHD III using the F6 formulation is approximately four-fold higher than observed in nonclinical toxicology studies, or less than two-fold higher based on calculated free DHD III levels, although rat DHD III levels were underestimated approximately 40% by the calculation method that was used. However, despite the lack of nonclinical toxicology coverage of DHD III, this metabolite is not considered to have any unique safety risks based on *in vitro* and *in silico* assessments relative to SMT C1100 or DHD I (see below). Additionally, DHD III may be pharmacologically active given the ability to modulate utrophin transcription in the H2K cell reporter assays. A number of potential off-target effects have been identified for SMT C1100, DHD I, and DHD III based on a battery of *in vitro* assays. However, the majority of these off-target effects had in vitro IC_{50}values that are above the total or calculated free levels at the highest patient exposure level (1 g *bid* with the F6 formulation). Additionally, there were no associated

in vivo findings from chronic toxicology studies and 7 days dosing in patients at three dose levels up to 2 g/day. A possible exception could be inhibition of the OATP1B1 transporter by DHD I and III which may have contributed to elevated conjugated bilirubin observed in one patient. Other potential safety risks such as inhibition of BCRP, and MAO-B as well as induction/inhibition of CYP2B6 have been addressed by excluding the respective substrates as co-medications during SMT C1100 administration. Potential inhibition of hERG and $Ca_v1.2$ by DHD I and III have not corresponded to any arrhythmias from nonclinical safety pharmacology studies nor were there ECG findings in patients. If the dihydrodiols are potent inhibitors *in vivo*, it's possible that inhibition of both cardiac ion channels has an off-setting effect counteracting any torsadogenic effect [Kramer *et al*, 2013] as may occur with verapamil. Overall, the risk:benefit of using the F6 formulation to increase exposure to SMT C1100 and thus increase the probability of achieving sufficient utrophin levels to have a beneficial effect in DMD patients is considered favourable.

8.3. Blinding

This is an open-label study so no blinding is required.

8.4. Packaging and Labelling

Investigational medicinal product will be supplied to the sites in multi-dose bottles for the F3 formulation (Cohorts 1 and 3) and as unit doses for the F6 formulation (Cohort 2). The sites will dispense appropriate numbers of bottles to the parent/responsible adult who will be undertaking the outpatient dosing activities. Written instructions will be provided for the parent including the exact dose that should be given and instructions for preparation and storage. Where required, appropriate measuring devices (e.g., syringes) will be provided to the parent/responsible adult to ensure that they can give an accurate dose. New medication bottles should be issued at each study visit, and used bottles should be returned and collected for reconciliation.

In an effort to manage the adversity of site visits for patients, IMP and ancillary supplies may be shipped directly to the subject's residence at regular intervals, as required and based on available inventory, for the duration of the Treatment and Extension Periods. This will only be undertaken following approval from the IEC/IRB, Investigator and patient parent/guardian. All used and unused IMP will be returned to the site or central drug depot, as applicable, for the purposes of drug accountability.

Investigational product labels will contain all information required to meet the local applicable regulatory requirements.

8.5. Preparation

No additional preparation of the microfluidised aqueous suspension (F3) is required after dispensing. The powder for oral suspension (F6) requires constitution in vehicle ahead of dosing. Written instructions will be provided for the parent/responsible adult to prepare and administer the dose.

8.6. Handling and Storage

The F3 formulation (Cohorts 1 and 3) will be stored at site at room temperature (<25ºC) and protected from light. The parent/responsible adult looking after the IMP for outpatient dosing will be asked to keep it at room temperature (<25ºC) and protected from light. The IMP should be kept out of the reach of children.

The F6 formulation (Cohort 2) will be stored at site at refrigerated temperature (2-8ºC). The parent/responsible adult looking after the IMP for outpatient dosing will be asked to keep it at refrigerated temperature (2–8ºC). The IMP should be kept out of reach of children.

No special procedures for the safe handling of SMT C1100 are required. The Sponsor will be permitted, upon request, to audit the supplies, storage, dispensing procedures and records at each site.

8.7. Product Accountability and Assessment of Compliance

In accordance with GCP, each study centre will account for all supplies of SMT C1100 provided to them. Details of receipt, storage, assembly and return will be recorded. The unit of accountability will be one bottle of SMT C1100.

All unused supplies of SMT C1100 will either be destroyed or returned to the study Sponsor at the end of the study in accordance with instruction by the Sponsor.

Patients will be counted as compliant with the protocol if they take ≥95% of their medication as scheduled.

8.8. Treatment of Investigational Product Overdose

If the patient receives an overdose of the IMP (classed as having >2.5 g of SMT C1100 F3 in Cohorts 1 and 3 or >1 g of SMT C1100 F6 in Cohort 2 in a 4 hour period) then the Investigator should be notified as soon as possible.

The Investigator will treat the overdose according to their clinical judgment depending on the extent of the overdose and the clinical signs and symptoms exhibited by the patient. It

should be noted that drug-related AEs of pale and/or discoloured stools have been reported in clinical trials to date. These AEs have been reported at doses of 1.25 g *bid* and 2.5 g *bid* with SMT C1100 F3 in a 14-day DMD patient study and at doses of 0.5 g *bid* with SMT C1100 F6 in a 7-day DMD patient study. The AEs were possibly a consequence of a greater proportion of unabsorbed study drug passing through the gastrointestinal tract at higher dose levels. Changes in liver function tests were also noted at doses of 0.25–1 g *bid* with F6 in the 7-day DMD patient study.

The Sponsor and Quintiles pharmacovigilance should be informed in writing of all overdoses within 24 hours of the Investigator becoming aware of them.

8.9. Occupational Safety

No specific risks have been identified for staff handling SMT C1100. The Material Safety Data Sheet will be made available where required by local regulations.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. Permitted Medications

Permitted medications include the following:

- Systemic corticosteroids (required for 6 months prior to study entry with stable dose [intermittent dosing is allowed] for at least 6 months prior to start of trial), including but not limited to, prednisolone, prednisone and deflazacort
- Angiotensin converting enzyme inhibitors (e.g., perindopril and lisinopril)
- Angiotensin-receptor blockers (e.g., losartan, irbestartan, valsatan and candesartan)
- Bisphosphonates (oral and intravenous), Vitamin D and calcium supplements

Investigators should use caution when concomitantly administering SMT C1100 and drugs that are substrates of OATP1B1 and/or OATP1B3 e.g., angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists. They should monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1/1B3 and consider reduction of the dose of these drugs.

9.2. Prohibited Medications

Use of the following therapies is prohibited during the study and for at least five half-lives prior to the start of dose administration, unless otherwise stated below:

- Substrates of CYP2B6 e.g., Ketamine, Pentobarbitol, Lidocaine (see Appendix 1 for further details), except as used for anaesthesia during the study-required biopsy in a hospital setting.
- Inducers of CYP1A1 and/or CYP1A2 e.g., Omeprazole, Carbamazepine, Rifampin (see Appendix 1 for further details)
- Nicotine, including exposure to daily passive smoking (including parent/legal guardian, siblings) to minimise CYP1A induction
- Herbal supplements and homeopathic preparations should be stopped 7 days prior to the start of the Treatment Phase
- Substrates of BRCP (e.g., omeprazole, rabeprazole, fluvastatin, methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan)
- Beta-blockers (these may be started during the study if required but patients must not be enrolled whilst taking them)
- All prescription, OTC, and herbal products that are known CYP2B6 sensitive substrates (e.g., buproprion, efavirenz) will be excluded from 14 days prior to study conduct through to 14 days after study conduct completion. Please note, this is not an exhaustive list of CYP2B6 substrates and a discussion with the medical monitor may be warranted. Further details of CYP2B6 substrates are found in Appendix 1.
- Be using drugs that have serotonergic, norepinephrinergic or dopaminergic activity (e.g., selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, tryptophan, dextromethorphan, meperidine, bupropion, nortriptyline, desipramine, doxepin, amoxapine, rasagiline, selegiline), or treatments used in attention deficit hyperactivity disorder such as Methylphenidate, and phenethylamine (PEA).

In the interests of patient safety and acceptable standards of medical care the Investigator will be permitted to prescribe treatment(s) at his/her discretion. All treatments must be recorded in the patient's source documents and transcribed to the CRF (medication, dose, treatment duration and indication).

10. PATIENT COMPLETION AND WITHDRAWAL

10.1. Patient Completion

A patient will be classed as having completed the study at the end of the 30-day Safety Follow-Up unless they are rolled into the Extension Phase.

10.2. Patient Withdrawal

10.2.1. Patient Withdrawal from Investigational Medicinal Product

A patient will be withdrawn from treatment for any of the following reasons:

- Withdrawal of consent/assent to continue taking treatment
- The study Investigator or Sponsor, for any reason, decides the patient should be withdrawn from the treatment
- Adverse events, classed as possibly or probably related by the Investigator, which cannot be tolerated by the patient

If a patient is withdrawn from treatment where possible they should continue to attend all remaining study visits so that data can be collected. If patients will not assent or their parents/guardian will not consent to this then they should be withdrawn from the study.

10.2.2. Patient Withdrawal from Study

A patient will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent/assent
- Patient is not in compliance with requirements of the study
- Death
- The study Investigator or Sponsor, for any reason, decides the patient should be withdrawn from the study
- The study Investigator or Sponsor, for any reason, stops the study

If a patient is lost to follow-up, every possible effort must be made by the study centre personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow-up must be documented.

When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the source documents and transcribed to the CRF. Study drug assigned to the withdrawn patient may not be assigned to another patient.

Where possible any patient that withdraws from the study will complete the Early Termination Visit as outlined in the Time and Events Table.

10.3. Treatment after the End of the Study

No IMP will be provided after the end of the Treatment Phase unless the subject continues into the Extension Phase.

10.4. Screen and Baseline Failures

Data collected from screening failures will be limited to reason for screen failure and related data.

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse events will be recorded from the signing of the consent form until the end of the safety follow-up period or completion of the Extension Phase.

11.1.1. Causal Relationship

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

- Probable relationship: event occurs in a plausible time relationship to the medication administration and cannot be explained by concurrent disease or other drugs or chemicals; the response to the withdrawal of the drug should be clinically plausible
- Possible relationship: event occurs with a reasonable time sequence to the medication administration, but could also be explained by concurrent disease or other drugs or chemicals; information on the drug withdrawal may be lacking or unclear
- Unlikely relationship: event occurs with little temporal relationship to the medication administration and other factors such as drugs, chemicals or underlying disease provide plausible explanations

- Not related: event has no temporal relationship to the medication administration or there is a definite alternative aetiology

11.1.2. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

- **Mild**: awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities
- **Moderate**: sufficient discomfort is present to cause interference with normal activity
- **Severe**: extreme distress causing significant impairment of functioning or incapacitation. Prevents normal, everyday activities

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the patient (e.g., laboratory abnormalities).

11.1.3. Reporting Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the patient's last study-related procedure (which may include contact for follow-up of safety). The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common aetiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the source documents and the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

The patient’s parents or responsible adult must be provided, on Day 1, with a "study card" indicating the following:

- Patient's name
- Patient number
- Patient's data of birth
- Name of the investigational product

- Investigator's name and 24 hour contact information
- Statement that the patient is participating in a clinical trial

11.2. Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity

  or

- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not reach the above definition but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an accident and emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Serious AEs will be recorded from the signing of the consent form until the end of the safety follow-up period.

11.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to an IMP and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious.

11.2.2. Reporting Serious Adverse Events

All SAEs occurring during clinical studies must be reported to the appropriate Sponsor-designated contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to Quintiles using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational

staff, and transmitted to Quintiles pharmacovigilance within 24 hours. The initial and follow-up reports of an SAE should be sent to one of the following:

Quintiles Drug Safety Fax (EAPA): 0 800 132 079

Quintiles Drug Safety Fax (NA): 1 800 41 48 460

Quintiles Drug Safety Centre Email: QLS_SMTC1100@quintiles.com

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilises
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a patient's participation in a clinical study must be reported as an SAE, except hospitalisations for the following:

- Surgery or procedure planned before entry into the study (must be documented in the source documents and CRF)

The cause of death of a patient in a clinical study within 30 days of last dose, whether or not the event is expected or associated with the investigational agent, is considered a SAE.

The Sponsor or designee assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor (or designee) will also report to the Investigator all SAEs that are SUSARs (unexpected) and associated with the use of the drug. The Investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee (IEC)/Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Before the study database is locked a statistical analysis plan will be finalised providing detailed methods for the analyses outlined below.

12.1. Data Analysis Considerations

12.1.1. Analysis Populations

The 'Safety' and 'Intent-To-Treat (ITT)' populations will both be defined as all patients who receive at least one dose of study medication.

Separate populations will be identified for MRI and functional activity endpoints, based upon their baseline ability to be assessed for the relevant endpoint. Further information on these populations will be provided in the Statistical Analysis Plan.

12.1.2. Treatment Comparisons

Though the study includes a single treatment group, comparisons will be made with SMT C1100 plasma exposure and MRI parameters and other endpoints through concentration response analyses. Similarly, the relationship between utrophin expression and other endpoints will be explored.

12.1.3. Interim Analysis

A DMC will review the study data throughout the study (Section 13.2). As the study is open-label the data will also be explored on a regular basis by the Sponsor.

12.1.4. Key Elements of Analysis Plan

Where appropriate the data from the different cohorts will be pooled for analyses. Baseline characteristics will be summarised for each cohort separately and over all patients.

Changes from baseline in primary and secondary endpoints will be summarised and plotted by visit, as will blood biomarker data and pharmacokinetic data. In addition to descriptive statistics (n, mean, standard deviation, median, minimum and maximum) data will be summarised categorically through the count of patients with specific levels of improvement or deterioration from baseline with the different endpoints.

Data for sub-groups based on baseline characteristics, SMT C1100 concentrations and utrophin expression will also be summarised.

If possible, changes from baseline may be compared with historical control data.

12.1.4.1. Pharmacodynamic Analyses

All pharmacodynamic endpoints will be summarised.

The relationship between MRI parameters (leg MRI for Cohorts 1 and 2 and cardiac MRI for Cohort 3) over time and SMT C1100 exposure will be investigated along with relationship of other endpoints (including changes in utrophin expression) and SMT C1100 exposure over time. Similarly, the relationship between changes in utrophin expression and MRI parameters will be investigated.

12.1.4.2. Pharmacokinetic Analyses

Plasma concentrations of SMT C1100 parent and metabolites will be summarised and plotted by time point. Using a model exposure parameters will be predicted for each subject at the relevant visits. These parameters will be used as the exposure parameters when investigating the relationships with other data.

Data will be summarised for each cohort separately, combining Cohorts 1 and 3 (F3 formulation), and over all patients.

12.1.4.3. Safety Analyses

Adverse events will be summarised by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. The frequency and percentage of patients will be tabulated for each of the following:

- All causality AEs
- Treatment-related (possibly or likely related to study drug) AEs
- Intensity (mild/moderate/severe) of AEs
- Serious AEs
- Adverse events leading to study drug discontinuation

Changes from baseline in laboratory assessments, vital signs measurements, pulmonary function parameters (including FEV and FVC) and ECG parameters will be summarised.

The relationship between safety endpoints and SMT C1100 parent and metabolite exposure may also be investigated.

12.1.4.4. Efficacy Analyses

All activity endpoints will be summarised.

The relationship between changes from baseline over time and SMT C1100 exposure will be investigated.

12.1.5. Missing, Unused and Spurious Data

Missing data will be accounted for in all summaries by time, with reasons provided where possible (e.g., discontinuation). If any data are excluded from analyses the reason for their exclusion will be documented in the clinical study report.

12.1.6. Reporting Deviations from the Statistical Plan

Any deviations from the planned analyses will be described and justified in the final clinical study report.

13. STUDY ADMINISTRATION

13.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, the Sponsor will obtain approval from the appropriate regulatory agency to conduct the study in accordance with the ICH GCP and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable patient privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2013, including, but not limited to:

- Institutional review board review and approval of study protocol and any subsequent amendments
- Patient informed consent
- Investigator reporting requirements

The Sponsor will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent and assent must be obtained from each patient (and their parents/guardian) prior to participation in the study. Written informed consent will be

collected following a review of the patient's information leaflet by the potential patient and their parents/guardian and a discussion between the patient and their parents/guardian and the Investigator or suitably-qualified designee.

The Investigator will cooperate with all regulatory inspections and will notify the Sponsor as soon as they are aware of an inspection which may involve this study. With the exception of statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of the clinical site(s) by an outside authority before the Inspectors are permitted access to any of the study records or the study areas.

13.2. Data Monitoring Committee

While the study is in progress, a DMC will conduct planned reviews of the study data to evaluate the safety and tolerability of the study drug treatment.

A DMC charter defining the objectives and operational details of the DMC (including timing of meetings) has been finalised prior and further changes will be version controlled.

13.3. Study Monitoring

In accordance with applicable regulations, GCP and the Sponsor's and/or delegate procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and the Sponsor's requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of source documents.

The Sponsor and or delegated monitors will visit each trial site during the conduct of the study to ensure that:

- The data are authentic, accurate and complete
- The patient's safety and rights are being protected
- The study is conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements

13.3.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor, Sponsor-appointed auditors and regulatory inspectors direct access to all relevant documents.

13.3.2. Data Handling and Record Keeping

Following closure of the study, the Investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The Sponsor will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, the Sponsor standard operating procedures (SOPs), and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

13.4. Provision of Study Results and Information to Investigators

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete study results at a mutually agreeable location.

The Sponsor will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study patients, as appropriate.

The study will be registered automatically in the EU Clinical Trials Register and a results summary will be posted to the Register no later than 12 months after the last patient last

visit (LSLV). In addition, the study will be posted on ClinicalTrials.gov and the results will be uploaded no later than 12 months after LSLV.

13.5. Confidentiality of Study Patients

All information obtained during the conduct of the study with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Monitors, auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification but the patient's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent.

The study data shall not be disclosed to a third party without the written consent of the Sponsor. All data shall be secured against unauthorised access.

The Investigator will maintain a list of patient names and identifying information (e.g., unique patient identification number, patient's hospital number, patient randomisation number). This list will not be collected by the Sponsor.

13.6. Data Management

For this study patient data will be collected using a CRF and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with the applicable Sponsor or designee standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities and WHODrug.

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor or designee will:

a. Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

b. Maintain SOPs for using these systems.

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

d. Maintain a security system that prevents unauthorised access to the data.

e. Maintain a list of the individuals who are authorised to make data changes.

f. Maintain adequate backup of the data.

g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

Training on the use of the electronic data collection system will be provided to all relevant study site staff.

13.7. Insurance, Indemnity and Finance

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

The Sponsor will indemnify all Investigators participating in this study against future claims by study participants the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all study procedures have been carried out according to this protocol.

The financial aspects of the study are addressed in a separate agreement.

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15. APPENDIX 1: INDUCERS OF CYP1A1, CYP1A2 SUBSTRATES OF CYP2B6 AND BRCP

Please note, this is not an exhaustive list of inducers of CYP1A1/CYP1A2 or substrates of CYP2B6. Please contact your medical monitor for a discussion if in doubt about permitted or prohibited medications.

(1) Inducers of CYP1A1 and CYP1A2

• CARBAMAZEPINE • DAILY INTAKE OF CHARGRILLED MEAT ABOVE 250 GRAMS/DAY • CRUCIFEROUS VEGETABLES ABOVE 150 GRAMS/DAY	• RIFAMPIN • OMEPRAZOLE • TOBACCO

(2) CYP2B6 Substrates

• CYCLOPHOSPHAMIDE • IFOSFAMIDE • TAMOXIFEN • EFAVIRENZ • NEVIRAPINE • BUPROPION • MEPHOBARBITAL • VALPROIC ACID • MEXILETINE • PROCAINAMIDE • ARTEMISININ • TAZOFELONE • AMINOPYRINE • ANTIPYRINE	• PROPOFOL • KETAMINE • PENTOBARBITAL • ROPIVACAINE • LIDOCAINE • SEVOFLURANE • METHADONE • PETHIDINE • SELEGILINE • DIAZEPAM • TEMAZEPAM • CLOTIZAZEPAM • MIDAZOLAM • ESTRONE • TESTOSTERONE

(3) BRCP Substrates

• IMATINIB • IRINOTECAN • LAPATINIB • ROSUVASTATIN • SULFASALAZINE • TOPOTECAN	• OMEPRAZOLE • RABEPRAZOLE • FLUVASTATIN • METHOTREXATE • MITOXANTRONE