Congenital Muscular Dystrophy Ascending Multiple Dose Cohort Study analysing Pharmacokinetics at three dose Levels in Children and Adolescents with Assessment of Safety and Tolerability of Omigapil (CALLISTO)

Study code: SNT-I-015

Phase I study

STATISTICAL ANALYSIS PLAN

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1 Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
CMD	Congenital Muscular Dystrophy
COL6-RD	Collagen 6-related dystrophies and myopathies
CRM	Continual Reassessment Method
CV	Coefficient of Variation
EK2	Egen Klassification 2
FEV1	Forced Expiratory Volume during first second of the forced breath
FVC	Forced Vital Capacity
HHM	Hand held myometry
IFR	Inspiratory Flow Reserve
ITT	Intention to Treat
JHFT	Jebsen Hand Function Test
LAMA2-RD	Laminin Alpha 2-related dystrophy
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximum Expiratory Pressure
MFM	Motor Function Measure
MIP	Maximum Inspiratory Pressure
PCF	Peak Cough Flow
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
PUL	Performance Upper Limb
QTcF	QT corrected for HR using Fridericia's method
QTcB	QT corrected for HR using Bazett's method
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class

SVC	Slow Vital Capacity
TEAE	Treatment Emergent Adverse Event

2 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses to be conducted for study SNT-I-015, an exploratory phase I study of omigapil. The statistical methods were prospectively planned in the study protocol. This SAP was written during the study conduct and the authors and reviewers of the SAP had access to the study data. This SAP serves as documentation of statistical methods used to derive the endpoints and summarize the study data.

3 Study objectives

The study objectives were defined in the study protocol. The primary objective of the study is to establish the pharmacokinetic (PK) profile of omigapil in a range of doses in paediatric and adolescent patients with Congenital Muscular Dystrophy (CMD). The secondary objective is to evaluate the safety and tolerability of omigapil at a range of doses in paediatric and adolescent patients. The tertiary objective is to establish the feasibility of conducting disease-relevant clinical assessments in paediatric and adolescent patients with CMD to aid in the design of future studies.

4 Design and type of the study

Study SNT-I-015 is a phase I, open-label, sequential group, ascending oral dose, continual reassessment method (CRM) based model, PK, cohort study with patients randomly assigned to one of the three dose cohorts.

Dose levels were to be defined based on the following rules. Four subjects were to be treated at 0.02 mg/kg (level 1) daily for 12 weeks. In case of no toxicity, dose escalation would occur after every 4 subjects until one or more patients exceed the target $AUC_{0\text{-}24h}$ range. When exceeding the target range, subsequent dose levels were to be determined from the observed PK. Subsequent patients were to be enrolled in groups of 4 using a CRM- type dose escalation/reduction design with the possibility to interpolate between pre-specified doses (Cheung, 2011). As a result, 4 dose levels of omigapil were used for the randomized groups in the following order, along the study, (0.02 mg/kg, 0.08 mg/kg, 0.04 mg/kg, 0.06 mg/kg).

Patients were stratified by disease type (Laminin Alpha 2-related dystrophy [LAMA2-RD] or Collagen 6-related dystrophies and myopathies [COL6-RD]) and weight and will be similarly represented. One patient was to be assigned from each stratum to each dose-escalating group (cohort), so that the cohorts will have similar representation of disease type and weight, to ensure comparable PK, safety, tolerability and efficacy feasibility assessment data.

5 Sample size considerations

A total of 16-20 evaluable patients were planned to be accrued using a CRM-type dose escalation/reduction design with the possibility to interpolate between pre-specified doses. The proposed dosing schedule adapts from a CRM-like algorithm called SAVOR (Cheung, Elkind, 2010) that aims to identify a dose exceeding $AUC_{0\text{-}24h}$ of 33 ng h/ml with a probability of 10% or less. The upper end of the $AUC_{0\text{-}24h}$ of 3-33 ng h/ml was targeted because animal modelling in

CMD-relevant models showed higher efficacy at 1 mg/kg compared to 0.1 mg/kg. By enrolling up to 20 patients, 8-12 subjects were to be assigned to the dose predicted to result in the target AUC_{0-24h} range (which may be less than the highest dose).

6 Analysis sets

6.1 Intention-to-treat (ITT) dataset

The ITT dataset will include all enrolled patients who received at least one dose of the study medication and completed at least one post-baseline assessment. The ITT dataset will be used for all analyses related to disease relevant clinical assessments.

6.2 Pharmacokinetic (PK) dataset

The PK dataset will include all enrolled patients who received at least one dose of the study medication and completed at least one PK assessment. However, a review of dosing information will be performed by the investigator to consider excluding data in any period or on any day where a subject was judged to have received <80 % or >120% of the scheduled dose of the investigational product. Plasma concentration data will be excluded if concentrations are extremely low relative to other subjects' data; in these cases plasma concentrations will be excluded from all or part of the profile, as appropriate. The PK dataset will be used for all PK analyses.

6.3 Safety dataset

The Safety dataset will include all enrolled patients who received at least one dose of study medication. Safety dataset will be used for all the safety analyses.

7 Disposition of patients

The number of patients enrolled into the study at screening, the number of patients who failed the screening and the reasons for screening failures will be summarized. The number of patients entering and completing the study will be summarized by dose level and overall. Also, the number of patients who discontinued prematurely, the reasons for premature discontinuations and replacement information will be summarized by dose level and overall. The disposition data will also be presented in a listing format.

8 Demographic and other baseline characteristics

All demographic and other baseline characteristics (age, height, weight, body mass index [BMI], gender, ethnicity, race, child-bearing potential, ambulatory status, disease type (LAMA2-RD or COL6-RD), time since CMD diagnosis and use of respiratory aid [Bi-Pap]) will be listed by dose level and summarized with descriptive statistics by dose level. The physical examination findings, medical history and pregnancy test results will be listed by dose level.

Age will be calculated using month of birth and month of baseline (screening) visit as difference in months between baseline and time of birth divided by 12. Height will be estimated from ulna length by using the following formulas (Gauld, 2003, 2004):

$$\text{Height (male, age <20)} = ((4.605 * \text{ulna length [cm]}) + (1.308 * \text{age [years]}) + 28.003$$

Height (female, age < 20) = ((4.459* ulna length [cm]) + (1.315 * age [years]) + 31.485.

Height and weight will also be presented as percentages of normal growth at the age of the patient (Clinical Growth Charts, U.S. National Center for Health Statistics).

9 Concomitant medication/treatment

Concomitant medication and treatments are coded to WHO drug dictionary version September 2017, and will be listed by dose level, including the Preferred term and ATC classification levels 1 and 4.

10 Extent of exposure and compliance

The extent of exposure will be summarized based on the duration of study treatment (days). The duration of study treatment will be listed and summarized with descriptive statistics by dose level.

Compliance will be evaluated as percentage of the daily doses taken (calculated from the estimated volume withdrawn from the bottle and daily dosing volumes) since previous visit. Patients with compliance of 80-120% are considered as compliant. The compliance (as %) will be listed by dose level. In addition, the proportion of compliant patients will be tabulated by dose level.

11 Pharmacokinetics

The analysis of the PK parameters is described in a separate PK Analysis Plan (Appendix 18.3).

12 Analysis of safety and tolerability

12.1 Adverse events

All recorded adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 20.1). All treatment emergent AEs (TEAEs), i.e. events starting or worsening during study treatment or follow-up will be listed by dose level and tabulated by dose level, system organ class (SOC) and preferred term (PT). Both patient and event counts will be included in the tabulations. In addition, tabulations by severity and causality will be provided. Serious TEAEs (SAEs) and TEAEs leading to discontinuation of study treatment will be summarized as data listings. The AEs occurring during the run-in period will be listed separately.

Adverse events of special interest (AESI) will be summarized by dose level, SOC and PT. Also a listing with PFT information from all visits during the study will be presented together with the AE information for subjects experiencing AESI. The following preferred term will be considered as AESI: Pulmonary function test decreased.

12.2 Laboratory safety variables

All laboratory data will be listed by dose level. In addition, descriptive statistics of routinely measured laboratory safety variables at each visit will be computed. Both the absolute values and changes from baseline will be summarized by dose level. Frequencies of out-of-range values (low, normal or high) and clinically significant values defined by the investigator will be summarized by dose level and visit as shift tables.

12.3 Other safety variables

ECG results (Heart rate, PR, QRS, RR, QT, QTcF and QTcB times) will be listed by dose level and summarized with descriptive statistics by dose level using absolute values and changes from baseline to post-baseline pre-dose values. Moreover, the changes within each visit from pre to post-dose will be summarized. The ECG interpretation (Normal, Abnormal but not clinically significant or Abnormal and clinically significant) and abnormal QTcF and QTcB results (values >500 ms or changes of >30 ms and of > 60 ms) will be listed by dose level and summarized by visit, time point and dose level as shift tables. The QTcF and QTcB times will be calculated based on the following formulas:

$$QTcF = QT / RR^{1/3}$$

$$QTcB = QT / RR^{1/2},$$

where RR = 60 / HR.

Vital signs results (ulna length, height based on ulna length, weight, saturation of peripheral oxygen, blood pressure, heart rate, respiratory rate, body temperature, ability to stand, ambulatory status) will be listed by dose level and summarized descriptively by visit, time point and dose level. Absolute values, changes from baseline to post-baseline pre-dose values and within visit changes from pre- to post-dose values will be presented in the summaries.

Liver abdominal ultrasound results (liver span, echogenicity, presence of cysts and tumours, bile duct dilatation, gallbladder filled, presence of stones and portal vein dilatation) will be listed by dose level and summarized descriptively by dose level and visit. For the last visit, information on changes in the ultrasound from baseline will be listed.

13 Disease relevant clinical assessments

All disease relevant clinical assessment variables will be summarized as data listings by dose level. In addition, descriptive statistics/ frequency tables will be included when appropriate. Both absolute values and changes from baseline (if feasible) will be presented. The descriptive statistics/ frequency tables will be broken down by visit. Relevant background status (age of the patient, ambulatory status and type of disease) and $AUC_{0\text{-}24h}$ information from PK analysis of plasma concentrations vs time profiles of omigapil will be included in the listings.

13.1 Respiratory function testing (hospital spirometry)

Respiratory function tests will be presented as non-normalized values and as percentages of predicted values for Peak Expiratory Flow (PEF), Forced Vital Capacity (FVC), Forced Expiratory Volume during first second of the forced breath (FEV1), Maximum Expiratory Pressure (MEP) and Maximum Inspiratory Pressure (MIP). The equations presented in table 13.1.1 will be used for calculation of the percent predicted values. For the equations presented by race, the Caucasian equation will be used also for the Asian subjects. Due to loss of ambulation/ loss of ability to stand, the height will be estimated from the ulna length for all subjects. Age and height used in the equations will always be the age at the time of the measurement and calculated using month of birth and month of assessment date as time difference in months divided by 12.

Table 13.1.1 Percent predicted equations for respiratory function tests

Value (Reference)	Formula
PEF%p (Hankinson, 1999)	<u>*Caucasian*</u> Male (age < 20 years): PEF/((-0.5962–(0.12357*age)) + (0.013135* (age^2))+((0.00024962*(height^2))*1))/60*100 Female (age < 18 years): PEF/((-3.6181+(0.60644*age))-(0.016846* (age^2))+((0.00018623*(height^2))*1))/60*100 <u>*Black or African-American*</u> Male (age < 20 years): PEF/((-0.2684–(0.28016*age))+(0.018202*(age^2)) +((0.00027333*(height^2))*1))/60*100 Female (age < 18 years): PEF/((-1.2398+(0.16375*age))+ ((0.00019746*(height^2))*1))/60*100
FVC%p (Hankinson 1999)	<u>*Caucasian*</u> Male (age < 20 years): FVC*100/((-0.2584-(0.20415*age))+(0.010133* (age^2))+((0.00018642*(height^2))*1)) Female (age < 18 years): FVC*100/((-1.2082+(0.05916*age)) +((0.00014815*(height^2))*1)) <u>*Black or African American*</u> Male (age < 20 years): FVC*100/((-0.4971-(0.15497*age))+ (0.007701*(age^2))+((0.00016643*(height^2))*1)) Female (age < 18 years): FVC*100/((-0.6166-(0.04687*age))+ (0.003602*(age^2))+ (0.00013606*(height^2))*1))
MEP%p (age < 18) (Domenech-Clar, 2003)	Male: MEP*100/(7.619+(7.806*age)+(0.004*height*weight)) Female: MEP*100/(17.066+(7.220*age))
MIP%p (Domenech-Clar, 2003)	Male: -MIP*100/(–27.020–(4.132*age)–(0.003*height*weight)) Female: -MIP*100/(–33.854–(1.814*age)–(0.004*height*weight))
FEV1%p (Hankinson 1999)	<u>*Caucasian*</u> Male (age < 20 years): FEV1*100/((-0.7453-(0.04106*age))+ (0.004477*(age^2))+((0.00014098*(height^2))*1))

Value (Reference)	Formula
	Female (age < 18 years): FEV1*100/((-0.8710+(0.06537*age))+ ((0.00011496*(height^2))*1)) *Black or African American* Male (age < 20 years): FEV1*100/((-0.7048-(0.05711*age))+ (0.004316*(age^2))+((0.00013194*(height^2))*1)) Female (age < 18 years): FEV1*100/((-0.9630+(0.05799*age))+ ((0.00010846*(height^2))*1))

The highest respiratory function test value at each visit will be used in the calculations.

Percent predicted values for PCF will be counted by using the 50th percentiles by age presented in table 12.1.2 (Bianchi, 2008) with the following formula: PCF%p = PCF*100/ 50th percentile for the age. Age used in defining the percentiles will be the age at the time of the measurement and calculated with precision using month of birth and month of assessment date.

Table 13.1.2 Percentile values of peak cough flows (liters/min) by gender and age (Bianchi 2008)

	Females						
Age, yrs	5th	10th	25th	50th	75th	90th	95th
4	110	112	124	147	179	202	209
5	125	132	171	185	219	245	273
6	161	161	191	230	242	284	317
7	179	200	228	247	265	302	330
8	200	219	270	299	321	340	351
9	270	270	290	311	347	369	369
10	270	284	299	330	361	380	399
11	296	299	347	380	399	441	478
12	305	340	361	399	412	450	459
13	311	330	361	395	441	508	545
14	361	372	399	428	478	518	561
15	344	384	424	469	508	550	596
16	358	412	428	469	508	550	626
17	369	416	433	469	513	550	633
18	399	420	441	488	513	556	639
	Males						
Age, yrs	5th	10th	25th	50th	75th	90th	95th
4	130	132	143	162	194	226	230
5	138	153	179	194	226	262	270
6	166	171	204	226	250	279	293
7	200	211	235	270	299	340	351
8	215	247	279	299	321	340	347
9	217	237	293	311	340	372	424
10	250	260	296	321	351	380	428
11	290	299	340	369	399	420	441
12	311	317	334	369	399	450	498
13	321	337	392	450	518	567	578
14	380	395	498	608	672	713	750
15	380	428	534	633	706	788	829
16	493	518	539	652	713	728	871
17	498	545	561	645	846	898	944
18	518	545	602	728	880	898	944

Additionally, Slow Vital Capacity (SVC) will be evaluated as non-normalized values and Inspiratory Flow Reserve (IFR) both as a fraction and as absolute based on the following formulas:

IFR, fraction (%) = (1 – (V'I, max (t)/ V'I, max (FVC)) *100

IFR, absolute = V'I, max (FVC) – V'I, max (t).

The best values on the CRF, i.e. the lowest V'I, max (t) and the highest V'I, max (FVC) will be used in the calculations.

For all respiratory parameters, information of use of respiratory aid (Bi-Pap) will be given in the data listings.

13.2 Respiratory function testing (handheld ASMA-1 device)

PEF and FEV1 will be presented as non-normalized values and as percent predicted (see equations in 12.1.1). Information of use of respiratory aid (Bi-Pap) will be given in the data listings.

13.3 Muscle strength and motor function testing

13.3.1 Hand-Held Myometry (HHM)

Knee extension, knee flexion, elbow extension and elbow flexion, measured in Newton units will be presented separately for right and left side. Also, total lower limb score and upper limb score as the sum of extension and flexion results, will be summarized. Upper limb results will also be presented by dominant side. Normalized values (as percentage of normal HHM) will be given for both extension and flexion results. For normalization, the HHM results will be scaled by weight (i.e. knee flexion (N)/ weight (kg)). Average normal HHM values scaled by weight presented by Beenakker (2001) will be used as reference for children aged 4-16. For adults the following formulas from NIH, previously presented by Bohannon (1997), for normalization will be used:

Knee flexors	No formula for adults
Knee extensors (KE) %p, Female	Dominant side: ((KE/ weight)/(465.22-84.7-(4.803*age) +(0.325*(4.4482216*weight))))*100 Non-dominant side: ((KE/ weight)/(480.7-95-(4.868*age)+(0.31*(4.4482216*weight))))*100
Knee extensors (KE) %p, Male	Dominant side: ((KE/weight)/(465.22-(4.803*age) +(0.325*(4.4482216*weight))))*100 Non-dominant side: ((KE/weight)/(480.7-(4.868*age) +(0.31*(4.4482216*weight))))*100
Elbow flexion (EF) %p, Female	Dominant side: ((EF/weight)/(188.36-96.5-(0.61*age) +(0.14*(4.4482216*weight))))*100 Non-dominant side: ((EF/weight)/(188.25-89.2-(0.65*age)+(0.132*(4.4482216*weight))))*100
Elbow flexion (EF) %p, Male	Dominant side: ((EF/weight)/(188.36-(0.61*age) +(0.14*(4.4482216*weight))))*100 Non-dominant side: ((EF/weight)/(188.25-(0.65*age) +(0.132*(4.4482216*weight))))*100
Elbow extensors (EE) %p, Female	Dominant side: ((EE/weight)/(156.49-73-(1.032*age) +(0.116*(4.4482216*weight))))*100 Non-dominant side: ((EE/weight)/(150.37-71.5-(1.044*age)+(0.126*(4.4482216*weight))))*100
Elbow extensors	Dominant side: ((EE/weight)/(156.49-(1.032*age)

(EE) %p, Male	+(0.116*(4.4482216*weight))))*100 Non-dominant side: ((EE/weight)/(150.37-(1.044*age)+(0.126*(4.4482216*weight))))*100

13.3.2 Goniometry

Goniometry results include measurements of knee extension, elbow extension and ankle dorsiflexion, and the results are presented as grades by side (right/left).

13.3.3 Myotools

The Myotools results will be presented as grip strength (kg) and as key pinch (kg) for the dominant hand.

13.3.4 Motor function scales

Jebsen Hand Function Test (JHFT) will be presented as a total score (sec) separately for dominant and non-dominant hand. In addition, data from all subtests will be only listed (without descriptive statistics). For Performance Upper Limb (PUL) and North Star Ambulatory Assessment, total scores will be presented. Moviplate test score values will be presented separately for the dominant hand.

Motor Function Measures (MFM32 or MFM20) will be presented both separately for each dimension (D1 Standing and Transfer, D2 Axial and Proximal Motor Function, D3 Distal Motor function) and as a total score, as % of highest possible scores. In MFM32 the highest possible scores by dimension and in total are D1: 39, D2: 36, D3: 21 and Total: 96. In MFM20 the highest possible scores by dimension and in total are D1: 24, D2: 24, D3: 12 and Total: 60.

13.3.5 Timed tests

The walking distance at 1 and 2 minutes will be presented as meters. In case the subject did not complete the test, the distance at the time the test was stopped will be used for the first missing distance value for the calculation of the descriptive statistics. In this case, the time elapsed when the test was stopped will be shown in the listings.

The time to complete the 10-meter run test and the time to stand from supine will be presented as seconds. In case the subject did not complete the test, the time will be set as missing for the calculation of the descriptive statistics.

Both timed tests will be performed only for ambulatory subjects. Other reasons for not performing the test will be summarized in the listings.

13.3.6 Function scales

The total scores of ACTIVLIM and the Egen Klassification 2 (EK2) will be presented. In addition, the distribution of individual scores by question will be tabulated and the individual scores listed.

14 Deviations from the analyses planned in the study protocol

Per protocol analysis will not be conducted because the disease relevant clinical assessments are a tertiary objective of the study, there is no primary disease relevant clinical assessment and while a protocol deviation which is relevant for one organ system may not be relevant for another organ system, definition of a per protocol population is not feasible. Instead, relevant deviations potentially affecting the disease relevant clinical assessments will be discussed case by case on an individual patient and assessment level where appropriate.

15 Execution of statistical analyses

Statistical analyses will be performed by Oy 4Pharma Ltd and/or Santhera Pharmaceuticals.

16 Hardware and software

Statistical analysis, tables and patient data listings will be performed with SAS® version 9.3 or higher for Windows (SAS Institute Inc., Cary, NC, USA).

17 References

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18 Appendices

18.1 Table and figure plan (section 14 in the Study report)

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Table 14.3.5.1 Descriptive statistics of ACTIVLIM results

Table 14.3.5.2 Descriptive statistics of Egen Klassification 2 results

18.2 Data listing plan (section 16 in the Study report)

16.2.1 Demographic listings

Listing 16.2.1.1 Inclusion criteria
Listing 16.2.1.2 Exclusion criteria
Listing 16.2.1.3 Medical history
Listing 16.2.1.4 Concomitant medication
Listing 16.2.1.5 Informed consent / Demographic data / Reproductive status
Listing 16.2.1.6 Protocol deviations
Listing 16.2.1.7 Visit dates
Listing 16.2.1.8 End of study information
Listing 16.2.1.9 Populations
Listing 18.2.1.10 Physical examination

16.2.2 Compliance and/or Drug concentration data

Listing 16.2.2.1 Dispensing of study medication and dosing
Listing 16.2.2.2 Date of first dose of study medication
Listing 16.2.2.3 Collection of medicine and compliance

16.2.3 Individual efficacy response data

Listing 16.2.3.1 Office spirometry
Listing 16.2.3.2 ASMA-1
Listing 16.2.3.3 Muscle strength
Listing 16.2.3.4 Motor function
Listing 16.2.3.5 Timed tests
Listing 16.2.3.6 Functional tests
Listing 16.2.3.7 Muscle imaging

16.2.4 Safety data listings

Listing 16.2.4.1 Adverse events
Listing 18.2.4.2 Vital signs
Listing 18.2.4.3 ECG

16.2.5 Listing of individual laboratory measurements by subject

Listing 16.2.5.1 Lab data listings: Pharmacokinetics
Listing 16.2.5.2 Lab data listings: Haematology
Listing 16.2.5.3 Lab data listings: Biochemistry
Listing 16.2.5.4 Lab data listings: Urine analysis
Listing 16.2.5.5 Lab data listings: Cardiac and urinary biomarkers