Statistical Analysis Plan

Title: A Phase 1/2 trial on the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of DYN101 in patients ≥ 16 years of age with centronuclear myopathies caused by mutations in *DNM2* or *MTM1*

Protocol Number: DYN101-C101

Version: 3.0

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Author:

[redacted]

Previous Versions

Version 1.0 / 16-DEC-2019, Version 2.0 / 29-SEP-2020

SAP Amendments before database lock

Version	Issue Date	Section	Revision/Addition	Rationale
0.1	12-SEP-2019			First draft for internal review
0.2	26-SEP-2019			Draft version for sponsor review
0.3	04-OCT-2019			Draft version for IDMC organizational meeting
0.4	14-NOV-2019			Version including updates based on comments.
1.0	16-DEC-2019			Version 1.0
2.0	29-SEP-2020	1 1, 6.4 6.13.5 6.14.2 - 6.14.6	Updated to the latest protocol amendment. Added COVID-19 summaries. Shift table to be presented from BL to the worst recorded result in each trial period (not by each visit).	To use the latest protocol amendment. Requirement to report impact of COVID-19. Shift table for each visit separately would get too big.
3.0	17-AUG-2022	1 4 5	Added note that only abbreviated CSR will be done due to study termination. Updated to the latest protocol and IDMC charter version. Sample size updated. Dosing information updated.	To get updated with latest document versions. Updated per the latest protocol. Updated per the latest protocol.

		6.2.6	Added details for partial date imputations.	Clarification for data derivation.
		6.2.13	Added information about the data collection.	General clarifications.
		6.4	Small clarifications in disposition section.	To update readability.
		6.10	Added summary of doses received.	New summary due to many interruptions.
		6.13.2, 6.13.3	Summary of categorical data using frequency tables not descriptive statistics.	To use better method summarizing data.
		6.13.4	Added collected data categories.	To help understand underlying data.
		6.13.5, 6.13.6	Clarified what will be reported for abbreviated CSR.	General clarification.
		6.14.2	Added data normalization for lab data.	To make lab parameters comparable across different labs.
		8	Updated primary analysis and final analysis section.	Updated to match the study termination.
		9	Updated IDMC analysis.	Per the latest IDMC charter.
		10	Added note for the changes from planned protocol analyses.	Updated to match the study termination.

		12	Removed tables that are not done for the abbreviated CSR.	Updated to match the study termination.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibodies
ADCNM	autosomal dominant centronuclear myopathy
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARCNM	autosomal recessive centronuclear myopathy
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	area under curve
BIN1	amphiphysin II
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CGI-I	Clinical Global Impression of Improvement
CI	confidence interval
CL	Clearance
CNM	centronuclear myopathy
COVID-19	coronavirus disease 2019
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
%CV	coefficient of variation
DNM2	dynamin 2
EAT-10	Eating Assessment Tool
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FEV	forced expiratory volume
FVC	forced vital capacity
GAS	Goal Attainment Scaling

GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization (previously International Conference on Harmonization)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous(ly)
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEP	maximum expiratory pressure
MFM	Motor Function Measure
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MIP	maximum inspiratory pressure
mRNA	Messenger ribonucleic acid
MRSD	minimal recommended starting dose
MTM1	myotubularin 1
NCS	not clinically significant
NHP	non-human primate(s)
NHS	natural history study
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic(s)
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	quality-of-life
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
WBC	white blood cell
WHO	World Health Organization
XLCNM	X-linked centronuclear myopathy

1 INTRODUCTION

This document details the planned statistical analyses for the Dynacure, protocol "DYN101-C101" study titled "A Phase 1/2 trial on the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of DYN101 in patients ≥ 16 years of age with centronuclear myopathies caused by mutations in *DNM2* or *MTM1*".

The proposed analyses are based on the contents of the amended version 8.0 (incorporating Amendment 5) of the Protocol (dated 15-SEP-2021) and IDMC Charter version 3.0 (dated 19-JAN-2022).

The trial will consist of a pre-screening consent, a screening period, a run-in period (if applicable), a SAD part with 4 weeks of follow-up after IMP administration and a washout period of at least 12 weeks (followed by follow-up phone calls until the MAD part starts), a MAD part of 12 weeks, and a MAD extension part of 12 weeks. All subjects will participate in the SAD, MAD and MAD extension parts, unless they withdraw.

This SAP describes analyses for both the IDMC deliverables and final CSR deliverables.

Impact of COVID-19 will be evaluated in the subject disposition section.

NOTE: The study was terminated early but this SAP includes all protocol planned analyses. However, only abbreviated CSR will be produced and not all planned analyses will be performed. Detailed list of the analyses included is given in Section 12 of this document.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the safety and tolerability of 3 single ascending dose (SAD) levels and 3 MAD levels of DYN101.

2.2 Secondary Objectives

- To assess the PK of SAD and MAD of DYN101.
- To explore target engagement in muscle of DYN101.

2.3 Exploratory Objectives

- To investigate the effect of DYN101 treatment on the clinical assessments in various affected domains (respiratory, muscle strength and function, dysphagia).

- To explore the impact of CNM and its treatment on symptoms, functioning, and health-related QoL.
- To assess the presence of anti-drug antibodies (ADA) against DYN101 by collecting blood samples.
- To assess the metabolic profile of DYN101 by collecting blood and urine samples.
- To contribute to the global understanding of CNM and its treatment by collecting blood and muscle samples for further exploratory biomarker/genetic research.

3 ENDPOINTS

3.1 Primary Endpoint

- Comparison of adverse event (AE, SAE, AESI) frequency and severity by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) and overall using the Safety Analysis Set following 12 weeks of MAD treatment and after 24 weeks of MAD treatment (12 weeks in the MAD part + 12 weeks in the MAD extension part; Week 25 visit) or discontinued earlier.

3.2 Secondary Endpoints

- Comparison of means for PK parameters of DYN101 in plasma (AUC_{τ}, AUC_{last}, AUC_{∞}, $R_{ac(AUC)}$, $R_{ac(Cmax)}$, C_{max}, $C_{av\ SS}$, CL, λ_z, $t_{1/2}$, t_{max}, V_z) by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) and overall using the Pharmacokinetic Set.
- Comparison of geometric means for PK parameters of DYN101 in plasma (C_{max} and AUCs) by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) and overall using the Pharmacokinetic Set.
- Comparison of means on DNM2 mRNA levels and DYN101 concentrations using muscle biopsy data by dose (cohort), after multiple administration, and by mutated gene (subcohort) and overall using the Pharmacokinetic Set.
- Comparison of mean change from baseline in vital signs, laboratory data and ECG by dose (cohort), for single andr multiple administration, and by mutated gene (subcohort) and overall using the Safety Analysis Set.

3.3 Exploratory Endpoints

- Difference in mean change from baseline for clinical assessments in various affected clinical domains (respiratory, muscle strength and function, dysphagia) using the Pharmacokinetic Set by dose (cohort), for single or multiple administration, and by mutated gene (subcohort) at each post-baseline visit. The parameters to be analyzed for respiratory function are FVC (L), %FVC Predicted, FEV1 (L), %FEV1 Predicted, FEV1/FVC, MEP (cm H2O), %MEP Predicted, MIP (cm H2O), %MIP Predicted, Oxygen Saturation (%). The MyoGrip Test score will be used for analyzing muscle strength. The following parameters will be analyzed for muscle function; D1 Standing and transfers (%), D2 Axial and proximal motor function (%), D3 Distal motor function (%), Total MFM32 Score (%). Dysphagia will be assessed using the EAT-10 total score.
- Difference in mean change from baseline for PROMIS Questionnaire T-scores for the following domains (Anxiety, Depression, Fatigue, Pain Interference, Ability to Participate and Physical Function) using the Pharmacokinetic Set by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) at each post-baseline visit.
- Comparison of proportion of CGI-I responders (responders defined as responding 1 or 2) using the Pharmacokinetic Set by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) at each post-baseline visit.
- Comparison of proportion of PGI-C responders (responders defined as responding 1 or 2) using the Pharmacokinetic Set by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) at each post-baseline visit.
- Comparison of proportion of Goal Attainment Scaling (GAS) Questionnaire responders (responders defined as responding ‘YES – MUCH BETTER’, ‘YES – A LITTLE BETTER’) using the Pharmacokinetic Set by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) at each post-baseline visit.
- Comparison of means of ADA against DYN101 using the Pharmacokinetic Set by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) at each post-baseline visit.
- Comparisons of the metabolic profile of DYN101 in blood and urine using the Pharmacokinetic Set by dose (cohort), for single and multiple administration, and by mutated gene (subcohort) at each post-baseline visit.

4 SAMPLE SIZE

Sufficient subjects will be screened to ascertain approximately 18 subjects who will be dosed and finish the trial. The target is approximately 6 subjects per dose level. In each dose level, the target will be up to 6 subjects with a DNM2 mutation and up to 3 subjects with an MTM1 mutation. This sample size is deemed to be appropriate for safety and tolerability purposes and are not based on any power analysis.

5 RANDOMIZATION

This study is not randomized.

Subjects will receive DYN101 in a low (1.5 mg/kg), middle (4.5 mg/kg) or high (9 mg/kg) dose level in Cohorts 1, 2 and 3, respectively. In the MAD part, subjects may receive a different dose than what they received in the SAD part. In each cohort, there will be up to 6 subjects with a mutation in DNM2 (sub-cohort a) and up to 3 subjects with a mutation in MTM1 (sub-cohort b).

Cohorts will be enrolled in a sequential, staggered approach, with an interval of at least 7 days between dose administration of the first and second subject in a cohort, irrespective of their subcohort. The 48-hour safety data from the first subject in a cohort will be reviewed by the medical monitor before the next subject can be dosed. In addition, any SAE data from the first subject received up until the moment of treatment of the second subject will be taken into account.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Sets

Pre-Screened Set – Subjects who have signed pre-screening consent.

Screened Set – Subjects who have signed main informed consent.

Safety Analysis Set – Screened subjects who have received at least one Investigational Medicinal Product (IMP) administration.

Pharmacokinetic Set – Subjects in the Safety Analysis Set, for whom the primary PK parameters can be calculated.

Subjects excluded from the analysis sets and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

6.2 Derived Data

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

6.2.1 Age

Year of birth and age at the time of informed consent is collected in the CRF.

6.2.2 Race

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

6.2.3 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug. The same baseline will be used for all SAD, MAD and MAD extension parts using the last available records before first dose of study drug in SAD part.

6.2.4 Early Terminations Assessments

For the analysis early withdrawal visits will be assigned to the next scheduled visit where the relevant variable would have been assessed. For example subjects withdrawing after MAD week 5 will have their withdrawal visit assigned as follows: vital sign data assigned to MAD week 6 but laboratory data assigned to MAD week 9.

6.2.5 Duration/Study Day/Time

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

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose.

6.2.6 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an AE start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken and it will be assumed that the AE occurred after first dosing (earliest date of all doses during the whole study).

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved, or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's end of study visit

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the subject's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing) will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing) will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

All dates presented in the individual subject listings will be as recorded on the eCRF.

6.2.7 Exposure to Study Drug

Exposure to study drug will be calculated separately for SAD and MAD + MAD Extension parts.

SAD part: exposure will be set to 1 if subject was dosed.

MAD + MAD Extension part: date of last MAD dosing - date of first MAD dosing + 1.

The exposure calculation will not take into account breaks in therapy.

6.2.8 Treatment Compliance

Treatment compliance is calculated by visit and overall for SAD part and MAD + MAD Extension parts.

Treatment compliance at each visit will be calculated as

$$100 \times \frac{Actual\ volume\ administered\ (mL)}{Planned\ Total\ Volume\ (mL)}.$$

Overall treatment compliance for MAD + MAD Extension parts will be calculated as

$$100 \times \frac{Sum\ of\ actual\ volume\ administered\ (mL)}{Sum\ of\ planned\ Total\ Volume\ (mL)}.$$

6.2.9 Inexact Values

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

6.2.10 Electrocardiogram Data

For ECG data recorded on continuous scales, if more than one value is recorded at a time point, the mean value rounded to the integer will be presented. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

6.2.11 Unscheduled Visits

Only scheduled post-baseline laboratory and vital signs values will be tabulated. Post-baseline repeat/unscheduled assessments will be disregarded, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

6.2.12 PK Parameters

The following PK parameters will be calculated for DYN101:

AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity
C_{max}	Maximum plasma concentration
CL	Clearance after IV administration
λ_z	Terminal disposition phase rate constant
$t_{1/2}$	Terminal disposition phase half-life
t_{max}	Time of first occurrence of C_{max}
V_z	Apparent volume of distribution during the terminal disposition phase

6.2.13 Pharmacodynamic data

Patient-Reported Outcomes Measurement Information System (PROMIS) Questionnaire

Summary T-score for each domain (Anxiety, Depression, Fatigue, Pain Interference, Ability to Participate and Physical Function) will be calculated. Scoring is done by calculating total raw scores for each domain by summing subject's answers. Missing values are not allowed and if any data missing for a domain then total raw score will not be calculated. After raw scores are calculated a scoring table will be used to translate the total raw score into a T-score for each subject. Scoring tables are shown in the Appendix of this document.

For Physical Function, NHS part of the study utilized different PROMIS scale. First question was 'Can you walk 25 feet on a level surface (with or without support)?'. If subject answered 'Yes' then he/she filled all the following 12 questions. If subject answered 'No' then only 6 further questions were filled.

Respiratory Function Tests

For each parameter, the attempt should be repeated at least 3 times making sure that the subject has recovered between attempts. If, at each attempt, there is an improvement in the results, further tests can be conducted until the subject has achieved his/her best result. For summary tables the best result will be selected.

For respiratory function tests ratio of FEV1/FVC will be calculated for each subject and visit and rounded to 1 decimal place.

6.2.14 Cumulative information for IDMC meetings

The IDMC will review cumulative safety and PK and efficacy study data for all previously dosed subjects.

6.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS (Version 9.4 or higher)[2].

Summary tables will be presented by treatment group. Treatment group includes information about dose (cohort) and mutated gene (subcohort).

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 6.4 or higher) or SAS (Version 9.4 or higher). PK concentration data will be summarized by analyte, treatment group (cohort, subcohort) at each nominal sample time. PK parameter data will be summarized by analyte and treatment group (cohort, subcohort).

Treatment group (cohort, subcohort) labels will be displayed as follows:

1.5 mg/kg DNM2

1.5 mg/kg MTM1

1.5 mg/kg Overall

4.5 mg/kg DNM2

4.5 mg/kg MTM1

4.5 mg/kg Overall

9 mg/kg DNM2

9 mg/kg MTM1

9 mg/kg Overall

Overall

Summary tables will be presented by the above groups. Overall group will not be displayed in the PK tables.

Listings will be sorted in the following order treatment group (cohort, subcohort), subject, parameter, and visit unless otherwise stated. All data will be listed.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum and maximum values. Summaries for PK concentrations and AUCs and C_{max} will be including additionally %CV, geometric mean, geometric SD and geometric %CV.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Decimal places for derived data described in section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the derived data. Percentages will be displayed with one decimal place. CV% will be reported to 1 decimal place.

P-values will be quoted to 4 decimal places. P-values < 0.001 will be presented as p<0.001. Where this value is less than 0.05, 0.01 or 0.001, attention will be drawn to this fact using the conventional "*", "**" or "***" annotation, respectively.

6.4 Subject Disposition

Subject disposition will be summarized by treatment group (cohort, subcohort) and overall. Subject disposition will be summarized as follows:

- Screening failures: The number of subjects who failed screening and the reasons for failure will be tabulated for all subjects.
- Analysis sets: The number of subjects in Pre-Screened Set, Screened Set, Safety Analysis Set, Pharmacokinetic Set.
- Enrollment by region, country and clinical investigator: The number of subjects enrolled in each region, country and clinical investigator.
- Cumulative proportion of information: The number of subjects completing each visit.
- Subject disposition: The number of subjects completing study and early withdrawals including reason for withdrawal and time to withdrawal.
- Inclusion/exclusion criteria: The number of subjects not meeting all inclusion/exclusion criteria.
- The impact of the COVID-19 will be evaluated as follows:
    - Screening failures related to COVID-19
    - Early withdrawals related to COVID-19
    - Visits/Assessments Affected by COVID-19.

If needed, the impact of COVID-19 will be further evaluated based on the above summaries. This might include more detailed summaries how COVID-19 affected visits/assessments and study endpoints.

All disposition data will be listed.

6.5 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2.

6.6 Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous (n, mean, SD, median, min, max) or categorical (frequencies and percentages) variable summaries will be presented by treatment group (cohort, subcohort) for the following variables based on the Safety Analysis Set:

- Age in years
- Gender
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Fertility status for female subjects.

All baseline data will be listed.

6.7 Medical History Related to CNM

Separate tabulations of medical history related to CNM disease at screening will be presented by treatment group (cohort, subcohort) and overall for the Safety Analysis Set. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term in descending order in overall group and then alphabetically.

All medical history data will be listed.

6.8 Medical History Unrelated to CNM

Separate tabulations of medical history not related to CNM disease at screening will be presented by treatment group (cohort, subcohort) and overall for the Safety Analysis Set. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term in descending order in overall group and then alphabetically.

All medical history data will be listed.

6.9 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by treatment group (cohort, subcohort) and overall for the Safety Analysis Set. Prior medications are defined as all medications ending before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Concomitant medications will be summarized using ATC Level 2 and preferred term in descending order in overall group and then alphabetically.

All medication data will be listed.

6.10 Exposure to Study Drug

Extent of exposure (number of days of exposure to study drug) will be presented by treatment group (cohort, subcohort) for the Safety Analysis Set and separately for SAD and MAD parts.

Additionally, number of doses will be summarized.

All dosing information will be listed.

6.11 Treatment Compliance

Treatment compliance will be presented by treatment group (cohort, subcohort) for the Safety Analysis Set and separately for SAD and MAD parts.

All dosing information will be listed.

6.12 Pharmacokinetic Analyses

Blood samples for determination of plasma concentrations of DYN101 will be collected according to pharmacokinetic sampling schedule in the study protocol.

Concentration-time data will be tabulated by nominal time, analyte, and treatment group (cohort, subcohort) using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero for pre-dose records and to BLQ for records after study drug dosing.

Individual subject and mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales. Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times.

PK parameters for DYN101 will be calculated as described in section 6.2.12.

PK parameters will be summarized by analyte and treatment group (cohort, subcohort) using descriptive statistics (n, mean, SD, median, min, max, %CV, geometric mean, geometric SD, geometric %CV).

Geometric mean will be calculated as

$$\mu_g = \sqrt[n]{x_1 x_2 x_3 \ldots x_n},$$

where n is the number of observations and x_i are the observed data.

Geometric SD will be calculated as

$$\sigma_g = \exp\left(\sqrt{\frac{\sum_{i=1}^{n}\left(\ln x_i - \ln \mu_g\right)^2}{n}}\right),$$

where the square root is the arithmetic standard deviation of logarithmic data.

Geometric CV % is calculated as

$$\%CV_g = 100 \cdot \sqrt{e^{(\ln \sigma_g)^2} - 1} 100 \times {\sigma_g}^{1/\mu_g}.$$

All concentration and PK parameter data will be listed.

6.12.1 Analysis of dose proportionality

The dose proportionality will be assessed by comparing dose-normalized Cmax and dose-normalized AUC_{last} or AUC_{∞}. single or multiple doses in all cohorts, where possible.

6.12.2 Anti-Drug Antibodies

The impact of immunogenicity (anti-drug antibodies, ADA) on the PK of DYN101 will be explored.

Blood samples for determination of ADA will be taken in the MAD part and the MAD extension part at the time points specified in the Trial Schedules.

Descriptive statistics (n, mean, SD, median, min, max) of the observed values will be presented by treatment group (cohort, subcohort) and visit for each parameter.

All data will be listed.

6.12.3 Metabolic Profiling blood/urine

Blood samples for metabolic profiling of DYN101 will be taken in MAD Week 12 at 2 and 168 hours post-dose.

Urine for metabolic profiling will be collected in MAD Week 12 by collecting urine over a 24-hour interval starting at the same time with the infusion.

Descriptive statistics (n, mean, SD, median, min, max) of the observed values will be presented by treatment group (cohort, subcohort) and visit for each parameter.

All data will be listed.

6.13 Pharmacodynamic and Exploratory Efficacy Analyses

6.13.1 PROMIS Questionnaire

Patient-Reported Outcomes Measurement Information System (PROMIS®) is a National Institutes of Health Initiative, created to assess patient–reported health status for physical, mental, and social well–being to reliably and validly measure patient-reported outcomes in chronic diseases for clinical research and practice. The PROMIS domains tested in this trial are Anxiety (8 items), Depression (8 items), Fatigue (8 items), Pain Interference (8 items), Ability to Participate (8 items) and Physical Function (10 items).

Descriptive statistics (n, mean, SD, median, min, max) for observed values and changes from baseline in T-scores will be presented by treatment group (cohort, subcohort) at each visit for each domain score.

All data, including responses to questionnaire items and T-scores, will be listed.

6.13.2 CGI-I Questionnaire

Clinical Global Impression of Improvement (CGI-I) is a 7-point scale ranging from (1) very much improved to (7) very much worse and is used to assess global changes in the subject's condition compared to the condition before treatment.

Frequency tables for observed values will be presented by treatment group (cohort, subcohort) at each visit. As the questionnaire collects information in relation to the condition before treatment, there is no need to summarize change from baseline.

Additionally, CGI-I responders will be summarized where responder is defined as subject responding 'Very Much Improved' or 'Much Improved'.

All CGI-I data will be listed.

6.13.3 PGI-C Questionnaire

Patient Global Impression of Change (PGI-C) is a scale similar to the CGI-I. It is a 7-point scale ranging from (1) very much improved to (7) very much worse and needs to be completed independent of the investigator who completes the CGI-I.

Frequency tables for observed values will be presented by treatment group (cohort, subcohort) at each visit. As the questionnaire collects information in relation to the condition before treatment, there is no need to summarize change from baseline.

Additionally, PGI-C responders will be summarized where responder is defined as subject responding 'Very Much Improved' or 'Much Improved'.

All PGI-C data will be listed.

6.13.4 GAS Questionnaire

Goal Attainment Scaling is an instrument that is intended for individual evaluation of an intervention. It allows subjects to set individual goals, together with their physician. The number of goals and the content of these goals may differ per subject, but the attainment of the goals is measured in a standardized way. This makes a standardized evaluation of an intervention possible, even when the subjects are all in a different stage of their disease.

Frequency tables for observed values ('YES - MUCH BETTER', 'YES - A LITTLE BETTER', 'YES - AS EXPECTED', 'NO - PARTIALLY ACHIEVED', 'NO - SAME AS BASELINE', 'NO - WORSE') will be presented by treatment group (cohort, subcohort) at each visit.

Additionally, GAS responders will be summarized where responder is defined as subject responding ‘YES – MUCH BETTER’, ‘YES – A LITTLE BETTER’).

All GAS data will be listed.

6.13.5 Respiratory Function Tests

Assessment of the respiratory function will be performed with a handheld device.

Descriptive statistics (n, mean, SD, median, min, max) of the observed values and change from baseline (continuous data) will be presented by treatment group (cohort, subcohort) and visit for each parameter. For summary tables the best result will be selected. All collected data will be included in the listings.

Continuous parameters:

- FVC (L)
- %FVC Predicted
- FEV1 (L)
- %FEV1 Predicted
- FEV1/FVC
- MEP (cm H_2O)
- %MEP Predicted
- MIP (cm H_2O)
- %MIP Predicted
- Oxygen Saturation (%).

For the abbreviated CSR reporting only FVC and MIP will be included.

Respiratory function (Normal; Abnormal NCS, Abnormal CS) will be summarized by treatment group (cohort, subcohort) and period in a shift table from baseline to the worst recorded result in each trial period.

All data, including details of clinically significant findings will be listed.

6.13.6 Muscle Strength and Function Tests

MyoGrip

MyoGrip is an extremely sensitive tool to measure muscle strength in severely disabled subjects where current tools are unable to measure changes or benefit. For disorders such as CNM, the ability to use the joystick of their electric wheelchair or other fine motor functions is important to the subject. These sensitive measures can also assist in detecting early signals of efficacy of administered drug.

For MyoGrip reporting only the best strength test result will be summarized. Descriptive statistics (n, mean, SD, median, min, max) of the observed values and percent change from baseline will be presented by treatment group (cohort, subcohort) and visit for each parameter.

All data, including all strength test repeats, will be listed.

Motor Function Measure (MFM)

Motor Function Measure (MFM) is classically used as a measure of functional capacities in subjects with neuromuscular disorders. The MFM 32-item list (MFM32) is a scale to enable an objective assessment of the motor abilities of subjects with neuromuscular diseases whatever the motor function deficiency. Three dimensions are taken into account: D1: standing position and transfers, D2: axial and proximal motor function, and D3: distal motor function.

Descriptive statistics (n, mean, SD, median, min, max) of the observed values and change from baseline will be presented by treatment group (cohort, subcohort) and visit for the following parameters:

- D1 Standing and transfers (%)
- D2 Axial and proximal motor function (%)
- D3 Distal motor function (%)
- Total MFM32 Score (%).

For the abbreviated CSR reporting only Total MFM32 Score will be included.

All data, including responses to questionnaire items and total scores, will be listed.

6.13.7 Dysphagia Questionnaire

Descriptive statistics (n, mean, SD, median, min, max) of the observed values and change from baseline will be presented by treatment group (cohort, subcohort) and visit for the EAT-10 score.

All data, including responses to questionnaire items and total scores, will be listed.

6.13.8 Muscle Biopsy

Descriptive statistics (n, mean, SD, median, min, max) of the observed values and change from baseline will be presented by treatment group (cohort, subcohort) and visit.

All data will be listed.

6.13.9 Biomarker and DNA samples

Samples for genetic (DNA) research and biomarkers may be taken from subjects who provide separate informed consent for these samples to be collected and for their samples to be stored for other research studies. This data will not be reported in this study.

6.13.10 Exploratory Bayesian Analyses

The MFM 32, continuous respiratory measures and continuous strength measures (in absolute values) will also be analyzed in an exploratory manner using Bayesian statistical modeling. Bayesian methods are used as they allow for an easy construction of the predictive distributions. These distributions will be used to assess whether deviations from the natural course of the disease as observed from the run-in and the natural history data are observed after administration of the IMP.

A hierarchical model will be fitted to each of the responses using Bayesian methods. Only non-informative priors will be considered. The data used for the modeling consist of the NHS data or the run-in for patients who did not participate in the NHS. This hierarchical model will contain a random slope and intercept for each subject. The other covariates of the model will be time in months and treatment group. The baseline is at time 0. These models will be performed for each mutation separately.

Using the posterior distributions of the different parameters of the model fitted using NHS or run-in data only, the predictive distributions at future time points of interest in the current study will be generated. Then the predictive probability that an observation would have occurred given the natural course of each patient's disease will be computed. This predictive probability under the assumption of the natural evolution of the disease will also be considered as an additional endpoint or transformation of the clinical endpoint to evaluate the potential effect of the IMP.

The appropriate distribution or transformation to be applied on the observed endpoints will be justified to reflect the nature of the data. For example, the Beta distribution may be used for bounded scales or a logistic transformation for percentages.

These assessments will only be realized at the end of the study and will not be conducted for IDMC purposes.

Theses Analyses will be conducted by PharmaLex Belgium using SAS v9.4. Bayesian estimations will be realized with the proc MCMC procedure.

6.14 Safety Analyses

The safety analyses (AE, clinical laboratory tests, physical examination, vital signs and ECG) will be presented by the treatment received for the Safety Analysis Set.

6.14.1 Adverse Events

Adverse events will be reported separately for SAD and MAD + MAD Extension parts.

A pre-therapy AE is defined as any AE that starts before the first dose of study drug.

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug and before last dose of study drug + 28 days.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug and before the last dose of study drug + 28 days.

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

Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented for AEs:

- Summary of All Adverse Events, incidence and the number of events.
- Pre-therapy AEs by system organ class and preferred term, incidence and number of events
- TEAEs by system organ class and preferred term, incidence and number of events
- Treatment-related TEAEs by system organ class and preferred term, incidence and number of events

- Serious TEAEs by system organ class and preferred term, incidence and number of events
- TEAEs leading to treatment withdrawal by system organ class and preferred term, incidence and number of events
- All AEs of special interest by system organ class and preferred term, incidence and number of events
- TEAEs by system organ class, preferred term and maximum severity, incidence
- Treatment related TEAEs by system organ class, preferred term and maximum severity, incidence
- TEAEs by system organ class, preferred term and study drug relationship, incidence
- Listing of Deaths (presented in the Table section of the appendices)
- Listing of Serious TEAEs (presented in the Table section of the appendices)

All AEs will be listed.

6.14.2 Laboratory Data

Descriptive statistics (n, mean, SD, median, min, max) of the observed values and change from baseline (continuous data) will be presented by treatment group (cohort, subcohort) and visit for each hematology, chemistry and urinalysis parameter.

Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to the worst recorded result in each trial period will be presented.

In addition to central laboratory, platelet counts will be analyzed in local laboratory. This local laboratory data will be reported as part of the laboratory tables describe above.

All laboratory data will be listed.

Some laboratory samples are analyzed in local laboratory instead of central laboratory. If data from same sample is available from both central and local laboratory then the records from central laboratory will be used. Local laboratory might use different units and/or normal ranges to central laboratory and this need to be taken into account as described below.

For shift tables (low/normal/high) local lab data will use the original units and normal ranges.

For descriptive statistics, local laboratory results are normalized using location-scale normalization or scale normalization to be comparable to central lab results. These methods are described by Karvanen (2003).

Result Normalization

Location-scale normalization is used when both central lab and local lab have both lower and upper limits for normal specified in the data:

$$s_{\text{location-scale}} = L_S + (x - L_X)\frac{(U_S - L_S)}{(U_X - L_X)}$$

If location-scale normalization reaches negative value for a parameter then for that parameter scale normalized value will be used instead (giving priority for value using upper normal limit).

Scale normalization is used when either central lab or local lab have and only lower or upper limits for normal specified in the data (or location-scale normalization reaches negative value):

$$s_{\text{scale(upper)}} = x\frac{U_S}{U_x} \quad \text{or} \quad s_{\text{scale(lower)}} = x\frac{L_S}{L_x}$$

The notation in the above formulas are as follows:

s	normalized result
x	local laboratory result
L_X	lower normal limit in local lab
U_X	upper normal limit in local lab
L_S	lower normal limit in central lab
U_S	upper normal limit in central lab.

As a result of normalization the normalized values will be comparable to central lab results and are using the same units and normal ranges.

6.14.3 Coagulation Data

Descriptive statistics (n, mean, SD, median, min, max) of the observed values and change from baseline (continuous data) will be presented by treatment group (cohort, subcohort) and visit for each parameter.

Shift tables in relation to the normality (Normal, Abnormal NCS, and Abnormal CS) from baseline to the worst recorded result in each trial period will be presented.

All data, including details of any abnormalities, will be listed.

6.14.4 Complement Data

Descriptive statistics (n, mean, SD, median, min, max) of the observed values and change from baseline (continuous data) will be presented by treatment group (cohort, subcohort) and visit for each parameter.

Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to the worst recorded result in each trial period will be presented.

6.14.5 Vital Signs

Descriptive statistics (n, mean, SD, median, min, max) for observed values and changes from baseline in the following vital signs will be presented by treatment group (cohort, subcohort) at each visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)
- Pulse Oximetry (SpO2)
- Body weight (kg)
- BMI (kg/m^2)

All vital sign data will be listed.

6.14.6 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated by treatment group (cohort, subcohort) at each visit:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTc interval (ms)

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to the worst recorded result in each trial period will be presented.

All ECG data, including details of any abnormalities, will be listed.

6.14.7 Physical Examination

All data, including details of clinically significant findings will be listed.

At baseline and after 24 weeks of MAD treatment (Week 25 visit), the symptom-directed physical examination will include a neurological assessment. Neurological examination will be presented similarly to physical examination.

6.14.8 Liver Ultrasound and Hepatic Elastography

The observed data for liver ultrasound and hepatic elastography assessments will be listed only.

7 INTERIM ANALYSIS

Not applicable. Study was terminated before the interim analysis.

8 PRIMARY AND FINAL ANALYSIS

The study was terminated early and therefore planned primary and final analyses will not be performed. Reporting will include only same set of outputs as was delivered for the IDMC meetings (full safety analyses) and selected key efficacy endpoints. Section 12 of this SAP is updated to highlight which outputs are excluded from the planned.

9 INDEPENDENT DATA MONITORING COMMITTEE ANALYSIS

The purpose of the IDMC is to review study data of the cohorts, before proceeding to the next dose level. Further details about Independent Data Monitoring Committee (IDMC) meetings and deliverables are described in IDMC Charter. IDMC will be reviewing data at least 4 time during the study:

1. Organizational Meeting.
2. First Data Review Meeting
    - When last subject from SAD1 has completed study visit SAD1 W3 (Day 15).
3. Second Data Review Meeting
    - When last subject from SAD2 has completed study visit SAD2 W3 (Day 15)
4. Third Data Review Meeting
    - When at least two subjects in each sub cohort have passed study visit MAD1 W6 and all available SAD3 data available at the time of the meeting (SAD3 dosing is optional for this IDMC meeting)

5. Fourth Data Review Meeting
    - When last subject from MAD1 has completed study visit MAD1 W13 and last subject from MAD2 has completed study visit MAD2 W13

9.1 IDMC Open Session / Closed Session

Separate outputs will be delivered for IDMC open and closed sessions.

Open session tables will be including only overall treatment group. Closed session reports will be including treatment groups (cohort, subcohort) and overall as defined in section 6.3 of this document.

10 CHANGES TO PLANNED PROTOCOL ANALYSIS

Additional exploratory Bayesian analyses for MFM 32, continuous respiratory measures and continuous strength measures were added in section 6.13.10.

The study was stopped and the final reporting will be including only the IDMC outputs and selected efficacy parameters (FVC, MIP, Total MFM32 Score and PGI-C).

11 REFERENCES

1. Phoenix™ WinNonlin® (Version 6.4, Pharsight Corporation)
2. SAS Institute Inc., Cary, NC, 27513, USA
3. Karvanen J. The Statistical Basis of Laboratory Data Normalization. Drug Information Journal, Vol. 37, pp. 101–107, 2003, 0092-8615/2003

12 LIST OF TABLES, FIGURES AND LISTINGS FOR THE IDMC, PRIMARY ANALYSIS AND FINAL ANALYSIS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Note: Strikethrough tables are ones that were originally planned for primary and final analysis but will be excluded from the abbreviated CSR because of the termination of the study.

Table Number	Table Title	Included in IDMC meetings	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.				
14.1	**Demographic Data**			
14.1.1.1	Subject Enrollment – Screened Set	1-4	IP	
14.1.1.2	Screen Failures – Screened Set	1-4	IP	
14.1.1.3	Inclusion/Exclusion Criteria – Screened Set	1-4	IP	
14.1.1.4	Analysis Sets – Pre-Screened Set	1-4	IP	
14.1.1.5	Cumulative proportion of information – Safety Analysis Set	1-4	IP	
14.1.1.6	Subject Disposition – Safety Analysis Set	1-4	IP	
14.1.1.7	Subject Disposition by Country – Safety Analysis Set	1-4	IP	14.1.1.6
~~14.1.1.8~~	~~Visits/Assessments Affected by COVID-19 – Safety Analysis Set~~		~~IP~~	
14.1.2.1	Demographics – Safety Analysis Set	1-4	IP	
14.1.3.1	Medical History Related to Centronuclear Myopathy (CNM) – Safety Analysis Set	1-4	IP	
14.1.3.2	Medical History Unrelated to Centronuclear Myopathy (CNM) – Safety Analysis Set	1-4	IP	14.1.3.1
14.1.4.1	Prior Medications – Safety Analysis Set	1-4	IP	
14.1.4.2	Concomitant Medications – Safety Analysis Set	1-4	IP	14.1.4.1
14.1.5.1	Treatment Exposure – Safety Analysis Set	1-4	IP	
14.1.5.2	Treatment Compliance – Safety Analysis Set	1-4	IP	
14.2	**Pharmacodynamics and Exploratory Efficacy**			

Table Number	Table Title	Included in IDMC meetings	Validation Method	Shell Number (if repeat)
~~14.2.1.1~~	~~PROMIS Questionnaire, Descriptive Statistics – Pharmacokinetic Set~~		~~IP~~	
~~14.2.2.1~~	~~CGI-I Questionnaire, Frequency Table – Pharmacokinetic Set~~		~~IP~~	
~~14.2.2.2~~	~~CGI-I Questionnaire, Responders – Pharmacokinetic Set~~		~~IP~~	~~14.2.2.1~~
14.2.3.1	PGI-C Questionnaire, Frequency Table – Pharmacokinetic Set		IP	14.2.2.1
14.2.3.2	PGI-C Questionnaire, Responders – Pharmacokinetic Set		IP	14.2.2.1
~~14.2.4.1~~	~~GAS Questionnaire, Frequency Table – Pharmacokinetic Set~~		~~IP~~	~~14.2.2.1~~
~~14.2.4.1~~	~~GAS Questionnaire, Responders – Pharmacokinetic Set~~		~~IP~~	~~14.2.2.1~~
14.2.5.1	Respiratory Function Tests, Descriptive Statistics – Pharmacokinetic Set	4	IP	14.2.1.1
14.2.5.2	Respiratory Function Tests, Shift Table – Pharmacokinetic Set	4	IP	
14.2.5.3	Explorative Bayesian Analysis for Respiratory Function Tests – Pharmacokinetic Set		Stat IP	
~~14.2.6.1~~	~~MyoGrip, Descriptive Statistics – Pharmacokinetic Set~~	~~4~~	~~IP~~	~~14.2.1.1~~
~~14.2.6.2~~	~~Explorative Bayesian Analysis for MyoGrip – Pharmacokinetic Set~~		~~Stat IP~~	~~14.2.5.3~~
14.2.7.1	MFM32, Descriptive Statistics – Pharmacokinetic Set	4	IP	14.2.1.1
14.2.7.2	Explorative Bayesian Analysis for MFM32 – Pharmacokinetic Set		Stat IP	14.2.5.3
~~14.2.8.1~~	~~Dysphagia Questionnaire, Descriptive Statistics – Pharmacokinetic Set~~	~~4~~	~~IP~~	~~14.2.1.1~~
~~14.2.9.1~~	~~Muscle Biopsy, Descriptive Statistics – Pharmacokinetic Set~~	~~4~~	~~IP~~	~~14.2.1.1~~
14.3	**Safety Data**			
14.3.1	**Displays of Adverse Events**			
14.3.1.1.1	Overall Summary of Adverse Events – Safety Analysis Set	1-4	IP	
14.3.1.2.1	Pre-Therapy AEs by System Organ Class and Preferred Term – Safety Analysis Set	1-4	IP	
14.3.1.2.2	TEAEs by System Organ Class and Preferred Term – Safety Analysis Set	1-4	IP	14.3.1.2.1
14.3.1.2.3	Treatment Related TEAEs by System Organ Class and Preferred Term – Safety Analysis Set	1-4	IP	14.3.1.2.1
14.3.1.2.4	Serious TEAEs by System Organ Class and Preferred Term – Safety Analysis Set	1-4	IP	14.3.1.2.1
14.3.1.2.5	TEAEs Leading to Treatment Withdrawal by System Organ Class and Preferred Term – Safety Analysis Set	1-4	IP	14.3.1.2.1
14.3.1.2.6	All AEs of Special Interest by System Organ Class and Preferred Term – Safety Analysis Set	1-4	IP	14.3.1.2.1

Table Number	Table Title	Included in IDMC meetings	Validation Method	Shell Number (if repeat)
14.3.1.3.1	TEAEs by System Organ Class, Preferred Term and Maximum Severity – Safety Analysis Set	1-4	IP	
14.3.1.3.2	Treatment Related TEAEs System Organ Class, Preferred Term and Maximum Severity – Safety Analysis Set	1-4	IP	14.3.1.3.1
14.3.1.4.1	TEAEs by System Organ Class, Preferred Term and Strongest Study Drug Relationship – Safety Analysis Set	1-4	IP	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**			
14.3.2.1	Listing of Deaths – Safety Analysis Set	1-4	IP	
14.3.2.2	Listing of Serious TEAEs – Safety Analysis Set	1-4	IP	14.3.2.1
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**			
	Not Applicable			
14.3.4	**Abnormal Laboratory Values**			
14.3.4.1.1	Listing of Abnormal Laboratory Values	1-4	IP	
14.3.5	**Laboratory Data**			
14.3.5.1.1	Hematology Data, Descriptive Statistics – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.1.2	Hematology Data, Shift Table – Safety Analysis Set	1-4	IP	14.2.5.2
14.3.5.2.1	Serum Chemistry Data, Descriptive Statistics – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.2.2	Serum Chemistry Data, Shift Table – Safety Analysis Set	1-4	IP	14.2.5.2
14.3.5.3.1	Urinalysis Data, Frequency Table – Safety Analysis Set	1-4	IP	
14.3.5.4.1	Coagulation Data, Descriptive Statistics – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.4.2	Coagulation Data, Shift Table – Safety Analysis Set	1-4	IP	14.2.5.2
14.3.5.5.1	Complement Data, Descriptive Statistics – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.5.2	Complement Data, Shift Table – Safety Analysis Set	1-4	IP	14.2.5.2
14.3.6	**Vital Signs**			
14.3.6.1	Vital Signs, Descriptive Statistics – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.7	**ECG**			
14.3.7.1	ECG Data, Descriptive Statistics – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.7.2	ECG Data, Shift Table – Safety Analysis Set	1-4	IP	14.2.5.2
14.3.8	**Physical Examination**			
	Not Applicable			
14.4	**Pharmacokinetics**			
14.4.1.1	Pharmacokinetic Concentrations – Pharmacokinetic Set	1-4	IP	
14.4.2.1	Pharmacokinetic Parameters – Pharmacokinetic Set	4	IP	14.4.1.1
~~14.4.2.2~~	~~Analysis of Dose Proportionality – Pharmacokinetic Set~~		~~Stat IP~~	
~~14.4.2.3~~	~~Analysis of Terminal Disposition Phase Rate Constant λ_z – Pharmacokinetic Set~~		~~Stat IP~~	

Table Number	Table Title	Included in IDMC meetings	Validation Method	Shell Number (if repeat)
~~14.4.3.1~~	~~Anti-Drug Antibodies, Descriptive Statistics – Pharmacokinetic Set~~		~~IP~~	~~14.2.1.1 and/or 14.2.2.1~~
~~14.4.4.1~~	~~Metabolic Profiling (Blood), Descriptive Statistics – Pharmacokinetic Set~~		~~IP~~	~~14.2.1.1~~
~~14.4.4.2~~	~~Metabolic Profiling (Urine), Descriptive Statistics – Pharmacokinetic Set~~		~~IP~~	~~14.2.1.1~~

Figure Number	Figure Title	Included in IDMC meetings	Validation Method	Shell Number (if repeat)
14.2.1.1	PGI-C Questionnaire, Mean Profiles – Pharmacokinetic Set		IP	
14.2.1.2	PGI-C Questionnaire, Individual Profiles – Pharmacokinetic Set		IP	
14.2.2.1	Respiratory Function Tests, Mean Profiles – Pharmacokinetic Set		IP	14.2.1.1
14.2.2.2	Respiratory Function Tests, Individual Profiles – Pharmacokinetic Set		IP	14.2.1.2
14.2.3.1	MFM32, Mean Profiles – Pharmacokinetic Set		IP	14.2.1.1
14.2.3.2	MFM32, Individual Profiles – Pharmacokinetic Set		IP	14.2.1.2
14.3.5.1.1	Hematology, Mean Profiles – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.1.2	Hematology, Individual Profiles – Safety Analysis Set	1-4	IP	14.2.1.2
14.3.5.2.1	Serum Chemistry, Mean Profiles – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.2.2	Serum Chemistry, Individual Profiles – Safety Analysis Set	1-4	IP	14.2.1.2
14.3.5.4.1	Coagulation Data, Mean Profiles – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.4.2	Coagulation Data, Individual Profiles – Safety Analysis Set	1-4	IP	14.2.1.2
14.3.5.5.1	Complement Data, Mean Profiles – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.5.5.2	Complement Data, Individual Profiles – Safety Analysis Set	1-4	IP	14.2.1.2
14.3.6.1.1	Vital Signs, Mean Profiles – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.6.1.2	Vital Signs, Individual Profiles – Safety Analysis Set	1-4	IP	14.2.1.2
14.3.7.1.1	ECG, Mean Profiles – Safety Analysis Set	1-4	IP	14.2.1.1
14.3.7.1.2	ECG, Individual Profiles – Safety Analysis Set	1-4	IP	14.2.1.2
14.4.1.1	Pharmacokinetic Concentrations, Mean Profiles on Linear and Semi-Logarithmic Scales – Pharmacokinetic Set	1-4	IP	
14.4.1.2	Pharmacokinetic Concentrations, Individual Profiles on Linear and Semi-Logarithmic Scales – Pharmacokinetic Set	1-4	IP	

Listing Number	Listing Title	Included in IDMC meetings	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**			
16.2.1	**Discontinued Subjects**			
16.2.1.1	Screen Failures – Screened Set	1-4	IP	
16.2.1.2	Inclusion/Exclusion Criteria – Screened Set	1-4	IP	
16.2.1.3	Study Completion – Safety Analysis Set	1-4	IP	
~~16.2.1.4~~	~~COVID-19 Summary – Screened Set~~		~~IP~~	
~~16.2.1.5~~	~~COVID-19 Visit Log – Screened Set~~		~~IP~~	
16.2.2	**Protocol Deviations**			
16.2.2.1	Protocol Deviations – Screened Set		IP	
16.2.3	**Subjects Excluded From The Efficacy Analyses**			
16.2.3.1	Analysis Sets – Pre-Screened Set	1-4	IP	
16.2.4	**Demographic Data**			
16.2.4.1	Informed Consent – Safety Analysis Set		IP	
16.2.4.2	Demographics – Safety Analysis Set	1-4	IP	
16.2.4.3	Medical History Related to CNM – Safety Analysis Set	1-4	IP	
16.2.4.4	Medical History Unrelated to CNM – Safety Analysis Set	1-4	IP	
16.2.4.5	Prior and Concomitant Medications – Safety Analysis Set	1-4	IP	
16.2.4.6	Prior and Concomitant Non-Drug Therapies and Procedures – Safety Analysis Set		IP	
16.2.5	**Compliance and/or Drug Concentration Data**			
16.2.5.1	Exposure and Compliance – Safety Analysis Set	1-4	IP	
16.2.5.2	Infusion Interruption / Infusion Rate Change – Safety Analysis Set	1-4	IP	
16.2.5.3	Pharmacokinetic Concentrations – Safety Analysis Set	1-4	IP	
16.2.5.4	Pharmacokinetic Parameters – Safety Analysis Set	4	IP	
16.2.6	**Individual Efficacy Response Data**			
~~16.2.6.1~~	~~PROMIS – Pharmacokinetic Set~~		~~IP~~	
~~16.2.6.2~~	~~CGI-I Questionnaire – Pharmacokinetic Set~~		~~IP~~	
16.2.6.3	PGI-C Questionnaire – Pharmacokinetic Set		IP	
~~16.2.6.4~~	~~GAS Questionnaire – Pharmacokinetic Set~~		~~IP~~	
16.2.6.5	Respiratory Function Tests – Pharmacokinetic Set	4	IP	
~~16.2.6.6~~	~~MyoGrip – Pharmacokinetic Set~~	~~4~~	~~IP~~	
16.2.6.7	MFM32 – Pharmacokinetic Set	4	IP	
~~16.2.6.8~~	~~Dysphagia Questionnaire – Pharmacokinetic Set~~	~~4~~	~~IP~~	
~~16.2.6.9~~	~~Muscle Biopsy – Pharmacokinetic Set~~	~~4~~	~~IP~~	
16.2.7	**Adverse Event Listings**			
16.2.7.1	Adverse Events – Safety Analysis Set	1-4	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**			
16.2.8.1	Hematology – Safety Analysis Set	1-4	IP	
16.2.8.2	Serum Chemistry – Safety Analysis Set	1-4	IP	
16.2.8.3	Urinalysis – Safety Analysis Set	1-4	IP	

Listing Number	Listing Title	Included in IDMC meetings	Validation Method	Shell Number (if repeat)
16.2.8.4	Coagulation Data – Safety Analysis Set	1-4	IP	
16.2.8.5	Complement Data – Safety Analysis Set	1-4	IP	
16.2.8.6	Vital Signs – Safety Analysis Set	1-4	IP	
~~16.2.8.7~~	~~Pregnancy Test – Safety Analysis Set~~		~~IP~~	
16.2.8.8	ECG – Safety Analysis Set	1-4	IP	
16.2.8.9	Physical Examination – Safety Analysis Set	1-4	IP	
16.2.8.10	Neurological Examination – Safety Analysis Set	1-4	IP	
~~16.2.8.11~~	~~Anti-Drug Antibodies – Safety Analysis Set~~		~~IP~~	
~~16.2.8.12~~	~~Metabolic Profiling (Blood) – Safety Analysis Set~~		~~IP~~	
~~16.2.8.13~~	~~Metabolic Profiling (Urine) – Safety Analysis Set~~		~~IP~~	
16.2.8.14	Liver ultrasound Including Hepatic Elastography – Safety Analysis Set		IP	
16.2.9	**Abnormal Safety Results**			
16.2.9.1	Abnormal Laboratory, ECG and Vital Sign Results – Safety Analysis Set	2-4	IP	

13 APPENDIX

13.1 PROMIS Scoring Tables

13.1.1 ABILITY TO PARTICIPATE IN SOCIAL ROLES AND ACTIVITIES

Ability to Participate Social Roles and Activities 4a Adult version	
Raw Score	**Scale Score**
4	27.5
5	31.8
6	34.0
7	35.7
8	37.3
9	38.8
10	40.5
11	42.3
12	44.2
13	46.2
14	48.1
15	50.0
16	51.9
17	53.7
18	55.8
19	58.3
20	64.2

Ability to Participate Social Roles and Activities 8a Adult version	
Raw Score	**Scale Score**
8	25.9
9	29.7
10	31.3
11	32.6
12	33.6
13	34.5
14	35.3
15	36.2
16	36.9
17	37.7
18	38.5
19	39.3
20	40.2
21	41.1
22	42.0

Ability to Participate Social Roles and Activities 8a Adult version	
Raw Score	**Scale Score**
23	43.0
24	44.0
25	45.0
26	46.0
27	47.0
28	48.0
29	48.9
30	49.9
31	50.8
32	51.7
33	52.7
34	53.6
35	54.6
36	55.7
37	56.8
38	58.2
39	60.2
40	65.4

13.1.2 ANXIETY

Anxiety 8a Adult v1.0	
Raw Score	**Scale Score**
8	37.1
9	43.2
10	45.9
11	47.8
12	49.4
13	50.8
14	52.1
15	53.2
16	54.3
17	55.4
18	56.4
19	57.4
20	58.4
21	59.4
22	60.4
23	61.4
24	62.5
25	63.5
26	64.5
27	65.6
28	66.6
29	67.7
30	68.7
31	69.8
32	70.8
33	71.9
34	73.0
35	74.1
36	75.4
37	76.7
38	78.2
39	80.0
40	83.1

13.1.3 DEPRESSION

Depression 8a Adult v1.0	
Raw Score	**Scale Score**
8	38.2
9	44.7
10	47.5
11	49.4
12	50.9
13	52.1
14	53.2
15	54.1
16	55.1
17	55.9
18	56.8
19	57.7
20	58.5
21	59.4
22	60.3
23	61.2
24	62.1
25	63.0
26	63.9
27	64.9
28	65.8
29	66.8
30	67.7
31	68.7
32	69.7
33	70.7
34	71.7
35	72.8
36	73.9
37	75.0
38	76.4
39	78.2
40	81.3

13.1.4 FATIGUE

Fatigue 8a Adult v1.0	
Raw Score	**Scale Score**
8	33.1
9	38.5
10	41.0
11	42.8
12	44.3
13	45.6
14	46.9
15	48.1
16	49.2
17	50.4
18	51.5
19	52.5
20	53.6
21	54.6
22	55.6
23	56.6
24	57.5
25	58.5
26	59.4
27	60.4
28	61.3
29	62.3
30	63.3
31	64.3
32	65.3
33	66.4
34	67.5
35	68.6
36	69.8
37	71.0
38	72.4
39	74.2
40	77.8

13.1.5 PAIN INTERFERENCE

Pain Interference 8a Adult v1.1	
Raw Score	**Scale Score**
8	40.7
9	47.9
10	49.9
11	51.2
12	52.3
13	53.2
14	54.1
15	55.0
16	55.8
17	56.6
18	58.1
19	58.1
20	58.8
21	59.5
22	60.2
23	60.8
24	61.5
25	62.1
26	62.8
27	63.5
28	64.1
29	64.8
30	65.5
31	66.2
32	66.9
33	67.7
34	68.4
35	69.2
36	70.1
37	71.0
38	72.1
39	73.5
40	77.0

13.1.6 PHYSICAL FUNCTION

Physical Function 10a Adult v2.0	
Raw Score	**Scale Score**
10	13.5
11	16.6
12	18.3
13	19.7
14	20.9
15	22.1
16	23.1
17	24.1
18	25.0
19	26.0
20	26.9
21	27.7
22	28.6
23	29.4
24	30.2
25	31.0
26	31.8
27	32.5
28	33.3
29	34.0
30	34.8
31	35.5
32	36.3
33	37.0
34	37.8
35	38.5
36	36.3
37	40.1
38	40.9
39	41.7
40	42.6
41	43.5
42	44.4
43	45.5
44	46.6
45	47.9
46	49.4
47	51.2
48	53.4
49	55.8
50	61.9

13.1.6.1 Scale used in NHS part

Physical Function 12a Adult v1.0			
Short Form Conversion Table for People Who Can Walk (answered 12 items)		**Short Form Conversion Table for People Who Cannot Walk (answered 6 items)**	
Raw Score	**Scale Score**	**Raw Score**	**Scale Score**
12	13.3	6	13.8
13	16.1	7	16.8
14	18.1	8	19.0
15	19.6	9	20.7
16	20.9	10	22.3
17	22.1	11	23.7
18	23.1	12	25.0
19	24.1	13	26.2
20	25.1	14	27.4
21	26.0	15	28.6
22	26.8	16	29.8
23	27.7	17	31.0
24	28.5	18	32.2
25	29.3	19	33.4
26	30.0	20	34.6
27	30.8	21	35.9
28	31.5	22	37.3
29	32.3	23	38.8
30	33.0	24	40.4
31	33.7	25	42.2
32	34.4	26	44.7
33	35.1	27	46.9
34	35.8	28	49.8
35	36.5	29	52.8
36	37.1	30	59.9
37	37.8		
38	38.5		
39	39.2		
40	39.9		
41	40.6		
42	41.3		
43	42.0		
44	42.8		
45	43.5		
46	44.3		
47	45.2		
48	46.1		
49	47.0		
50	47.9		
51	48.9		
52	50.0		
53	51.1		
54	52.4		

Physical Function 12a Adult v1.0			
Short Form Conversion Table for People Who Can Walk (answered 12 items)		Short Form Conversion Table for People Who Cannot Walk (answered 6 items)	
Raw Score	Scale Score	Raw Score	Scale Score
55	53.8		
56	55.8		
57	57.3		
58	59.5		
59	61.7		
60	66.1		