Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 201283: An Exploratory Study to Investigate the Use of Biotelemetry to Identify Markers of Disease Progression in Subjects with Amyotrophic Lateral Sclerosis
Compound Number	:	Non-compound
Effective Date	:	03-AUG-2017

Description:

The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol [GlaxoSmithKline Document Number 2014N211002_00] and Protocol amendment [GlaxoSmithKline Document Number 2014N211002_02].

This RAP is intended to describe the exploratory and safety analyses required for the study.

This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Associate Statistician (QSI)	03-AUG-2017
PPD Principal Statistician	03-AUG-2017

Approved by:

PPD Associate Director, Statistics	03-AUG-2017

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe all planned analyses and output requirements during the study.
Protocol	This RAP is based on the original protocol / protocol amendment 2[(Dated: 21/09/2015) of study MID201283(GSK Document No.: 2014N211002_02] and eCRF Version 3.
Primary Objective	There is no primary objective/endpoints in this protocol. See Section 2.2 for exploratory objectives/endpoints.
Primary Endpoint	There is no primary objective/endpoints in this protocol. See Section 2.2 for exploratory objectives/endpoints.
Study Design	An exploratory, non-controlled, non-drug study in ALS patients. The study consists of two phases: 1. A variable length Pilot Phase to test and confirm the algorithms are capturing movement/physical activity, ensure the data transfer device is working correctly, and understand the reliability and ease of use/acceptance of the accelerometer and electrode. 2. A 48-week Core Study Phase to evaluate how measures of movement/physical activity, speech and HRV relate to ALS disease progression.
Planned Analyses	A hierarchical approach will be used to focus the analysis on the endpoints where a correlation with either the ALSFRS-R or FVC (as applicable) is present. To begin with, the correlation between the following endpoints will be explored using the analysis method detailed below: • The absolute and change from baseline in the movement/physical activity endpoints as measured by the accelerometer device and the change from baseline in the ALSFRS-R • The absolute and change from baseline in the heart rate variability endpoints as measured by the electrode device and the absolute and change from baseline in the ALSFRS-R • The absolute and change from baseline in the speech endpoints and the absolute and change from baseline in the ALSFRS-R • The absolute and change from baseline in the speech endpoints and the absolute and change from baseline in the FVC If there's correlation between these endpoints, then further analyses as described in Section 9.7 will be carried out as part of adhoc.
Analysis Populations	• Enrolled population: This will consist of all subjects who have signed consent and are not a screen failure. • Full Analysis Set (FAS): This will consist of all subjects with at least one post baseline measure for the ALSFRS-R and at least one physical

Overview	Key Elements of the RAP
	activity/movement measure, night time rest, Heart Rate Variability or Speech assessment endpoint. • Safety: Comprise of all subjects who carried out at least one protocol specified procedure. • Screen Failure: Comprise of all subjects who were a screen failure
Hypothesis	• The study is designed to explore if there is a relationship between change from baseline in the physical activity/movement, night time rest, heart rate variability and speech endpoints and change from baseline in the gold standard measures of function (ALSFRS-R and FVC).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

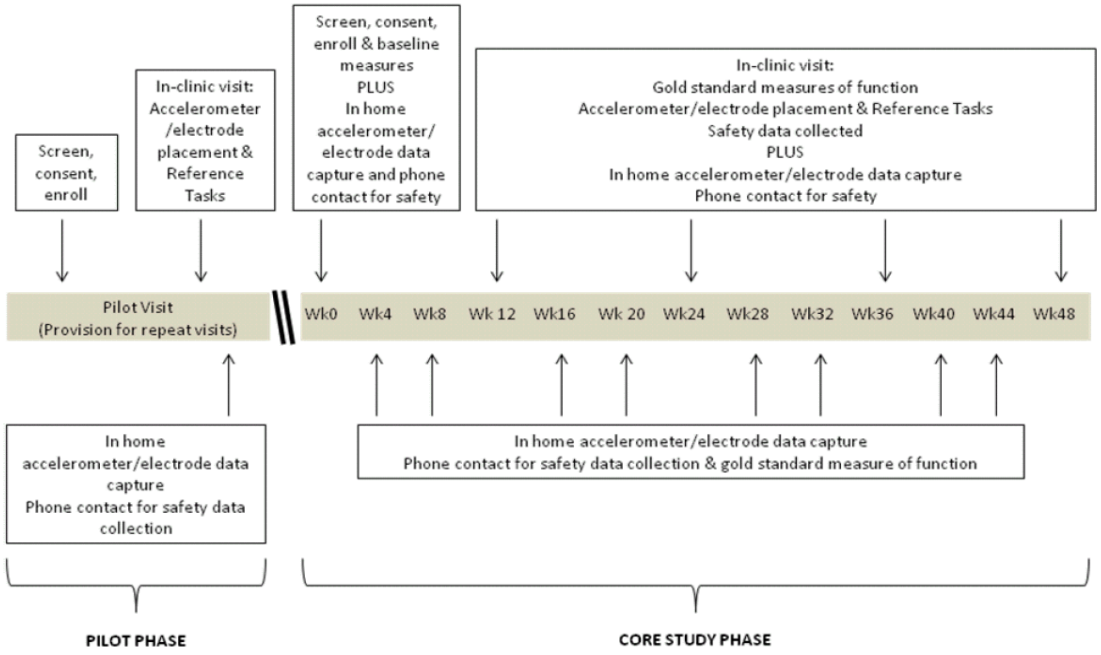
There were no changes or deviations to the originally planned statistical analysis specified in the protocol.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
Explore the application of actigraphy: • For measuring movement/physical activity in ALS subjects • As a marker of ALS disease progression	• Change over time in measurements of movement/physical activity by accelerometer-reported by day and night time. Measurements include Duration of wear time, (combining day & night values to give Wear time), Overall time spent active, Overall time spent sedentary not lying, Overall time spent lying, Overall time spent sedentary, Time spent with Sensor off, Total Activity Score, the maximum score from a 1 min window in a 24-hour period and 5 x Active Periods (5 categories: >1 to <=2min active up to >30mins active) • Change over time in measurements of night time rest by accelerometer reported endpoints: Percent Time Lying Down (at night), Number Night Time Movement Episodes, Number Night Time Movement Episodes/Hr, Percent Time Night-time Rest Efficiency, Rest Fragmentation Index =Move Time/Num Movement Episode, Average Duration Movement Episodes • Relationship between the ALSFRS and accelerometer measures of movement/activity and night time rest endpoints.
Explore the application of continuous remote monitoring of heart rate measures: • For measuring autonomic nervous system function in ALS subjects • As a marker of ALS disease progression	• Change over time in heart rate variability (HRV) as measured by a heartbeat sensing electrode. Measurements include: o Mean and variance for LF/HF (lying, sedentary not lying, active). o Mean and variance for HRV effect of being upright = LF/HF sedentary not lying minus LF/HF lying o Mean and variance for HRV effect of activity = LF/HF active minus LF/HF lying o Mean and variance for RMSSD (24 hours)

Objectives	Endpoints
	• Relationship between the ALSFRS and biotelemetry measures of HRV.
Explore the application of digital, quantitative speech testing: • For measuring speech quality in ALS subjects • As a marker of ALS disease progression.	• Change over time in digital speech measures of vowel, running speech and word measurements as captured by a high fidelity, acoustic sound capture interface. Measurements include: central tendency of fundamental frequency, jitter, shimmer, maximum gap between words, speaking rate, average phoneme rate, maximum phonation time and % pause time • Relationship between the ALSFRS and digital measures of speech. • Relationship between Forced Vital Capacity (FVC) and digital measures of speech.
Explore the impact of the accelerometer and electrode devices on everyday life in subjects with ALS	Subject/caregiver feedback. Feedback may include but not be limited to: comfort of the devices, ease of applying the devices, and ease of data transmission process.
Explore the feasibility of biotelemetry transmission of movement/physical activity and HRV data.	Assessed by successful data transmission from the telecommunications hub (Life Insight) to the central secure server at McLaren Applied Technologies (MAT).
Safety Objectives	**Safety Endpoints**
Monitor safety and tolerability.	• Type and incidence of adverse events (AEs) secondary to the devices used in this study. • Type and incidence of AEs due to study procedures.

2.3. Study Design

Overview of Study Design and Key Features	
Figure 1 Study Schematic  	
Design Features	• Study 201283 is an exploratory, non-controlled, non-drug study in ALS patients. The study consists of two phases: 1. A variable length Pilot Phase to test and confirm i) test the reliability, ease of use and acceptance of a wearable sensor capable of measuring simultaneously acceleration and inter-beat interval (R-R) ii) confirm that the wireless data transfer methodology (sensor-data hub-cloud) was working correctly and iii) optimise algorithms to identify physical activities and measure HRV. Subjects will attend at least 1 clinic visit to perform a series of set reference tasks while wearing the accelerometer and electrode. Subjects will also continuously wear the accelerometer and electrode in their routine home-life setting for approximately 3 days after the clinic visit (i.e., home monitoring). Repeat clinic visits and home monitoring might be necessary if data indicate the algorithms or equipment are not performing as expected. It is estimated that 5 subjects will participate in this Pilot Phase; however, the number may be less or more depending on the data generated. Subjects in the Pilot Phase will continue in the study and participate in the Core Study Phase. 2. A 48-week Core Study Phase to evaluate how measures of movement/physical activity, speech and HRV relate to ALS disease progression. During this phase, subjects will attend 5 clinic visits to perform gold standard measures of function and perform a series of set

Overview of Study Design and Key Features	
	reference tasks while wearing the accelerometer and electrode. Subjects will also continuously wear the accelerometer and electrode in their routine home-life setting for approximately 3 days after the clinic visits (i.e., home monitoring). In between clinic visits, subjects will attach the accelerometer and electrode and wear it for approximately 3 days in their home. A telephone contact with the subject will be made by the site at the end of each 3-day home monitoring period.
Dosing	• NA
Treatment Assignment	• This study doesn't include any treatment • Treatment of enrolled subjects will be consistent with local standard of clinical care for ALS patients
Interim Analysis	• No formal interim analyses will be performed

2.4. Statistical Hypotheses

The study is designed to explore if there is a relationship between change from baseline in the physical activity/movement, heart rate and speech endpoints and change from baseline in the gold standard measures of function (ALSFRS-R and FVC).

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses will be performed. Review of in stream data will be carried out to understand the utility of the measures and algorithms, the functionality of the data transmission process, and the durability and ease of use/acceptance of the selected accelerometer and electrode. Generated data may result in modifications to the study, such as: changes to the devices/equipment; repositioning of the accelerometer/electrode; modification to the algorithms, the supportive data collection plan or the data transmission process; dropping measures/tests which are not achievable.

McLaren Applied Technologies will not have access to the ALSFRS-R or FVC data and so modifications to the algorithms will be based solely on data collected from the accelerometer/ speech device. All modifications to the algorithms will be documented and version controlled.

3.2. Final Analyses

The final planned exploratory analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Enrolled	• Comprise of all subjects who have signed consent and are not a screen failure	• Study population
Full Analysis Set (FAS)	• This will consist of all subjects with at least one post baseline measure for the ALSFRS-R and at least one physical activity/movement measure.	• Study Population • Exploratory
Safety	• Comprise of all subjects who carried out at least one protocol specified procedure.	• Safety
Screen Failure	• Comprise of all subjects who were a screen failure	• Study Population

NOTES:

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, subject management or subject assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
9.1	Appendix 1: Time & Events
9.2	Appendix 2: Treatment States and Phases
9.3	Appendix 3: Data Display Standards & Handling Conventions
9.4	Appendix 4: Derived and Transformed Data
9.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
9.6	Appendix 6: Multicenter Studies
9.7	Appendix 7: Examination of Covariates, Subgroups & Other Strata
9.8	Appendix 8: Multiple Comparisons & Multiplicity
9.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the "Enrolled" OR "FAS" population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y		
Reasons for Screen Failure	Y		Y
Reasons for Subject Withdrawal			Y
Subjects by Country and Centre	Y		
Protocol Deviations			
Important Protocol Deviations	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y [1]
Populations Analysed			
Study Populations and Exclusions	Y		
Subjects Excluded from Any Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Race and Racial Combinations	Y		Y [2]
Medical Conditions and Concomitant Medications			
Medical Conditions			Y
Concomitant Medications	Y		Y

NOTES:

- Y = Yes display generated.

[1] Listing also includes analysis population exclusions.
[2] Listing of race.

7. STATISTICAL ANALYSES

7.1. Exploratory Analyses

7.1.1. Overview of Planned Exploratory Analyses

The efficacy analyses will be based on the "Full Analysis Set" population, unless otherwise specified.

Data Quality Deviators (for data points at each protocol time point):

Activity & Night time Rest endpoints

For all the actigraphy endpoints if the difference between visits of ALSFRS and Actigraphy is more than 21 days then the data will be excluded and will not be used for the summaries. If the first time point within a visit falls within the 21 days window, then all the time points will be considered.

Using the default sleep times for this study (22:00-07:00) which are derived from the day and night anchor times (set by the day/night algorithms used in this study), the amount of data present for a 24-hour recording period was calculated by adding up the durations for activity classifiers: active + sedentary [where sedentary = sedentary not lying + lying]. If the amount of data present is too low (conversely the amount of "off" time is too high) then the data will not be representative of a full day or night, because a subject's pattern of activity throughout a day or night is not expected to be homogenous or uniform.

A review of the literature showed that a variety of rules can be used, ex. for daytime recordings: 70-75% of data present, 10 of 16 hours (63%) data present. There are not set rules or standards. As this study utilises 22 hours recording (2 hours permitted for charging), the study team decided on the following limits: 70% for the day and 60% for the night. The % is set lower for the night as it was recognised that subjects may have more problems with night (either due to their disease, or with the technology) and so the amount of valid usable data for a night might be expected to be less. [Tudor-Locke, 2012]

Daytime Endpoints

Any data point associated with a 24-hour recording period (1440 minutes), or for a partial recording period, for DAY TIME with <9.1 hours of data for the day time is considered as a data quality data point deviator.

Day = 15 hours, permit 2 hours charging = 13 hours. 70% of 13 hours = 9.1 hours. Exclude data point if active day+sedentary day = <9.1 hours

Night time Endpoints

Any data point for a 24-hour recording period (1440 minutes), or for a partial recording period, for NIGHT TIME with <4.2 hours of data for the night time is considered as a data quality data point deviator.

Sleep = 9 hours, permit 2 hours charging = 7hours. 60% of 7 hours = 252 mins, 4.2 hours. Exclude data point if active night +sedentary night = <4.2 hours

Night time rest endpoints

Sleep = 9 hours, permit 2 hours charging = 7hours. 60% of 7 hours = 252 mins, 4.2 hours. Exclude data point if active night +sedentary night = <4.2 hours

Heart Rate Variability (24 hour endpoints only)

The amount of data present over a 24-hour recording period is also important for the 24 hour endpoints for HRV: mean and variance for HRV recorded using RMSSD methods (24 hours). 24-hour RMSSD HRV data with 40% or more data present will be accepted for analysis. The number of time windows that the HRV data is determined from is recorded in the dataset from McLaren. The following data quality rule will be applied:

Number of 5-minute windows (number of data points) in 24 hrs = 288. Allow for 2 hours charging = 24. Leaves 264 data points. Ruling = require 40% or more of data present for the 24-hour time period, otherwise it is not considered as representative of 24 hours. 40% of 264 = 105.6. Therefore, exclude data point if number of 5-minute window (number of data point) < 105.

Speech Endpoints

There is no data quality rule for Speech data as there are no data quality deviators, and all available data will be included in the summary and statistical analysis.

The data quality deviator flags will be populated in the data and the summary tables and figures will be produced for data with the deviator and without the data quality deviator.

Table 3 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Exploratory Analyses

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F[1]	F	L	T	F	L	T	F[1]	F	L
Actigraphy - feasibility & Wear time Measures														
Wear Time (active + sedentary time)				Y			Y							
Duration of day time wear time				Y			Y							
Duration of night time wear time				Y			Y							
Actigraphy Diary Data – feasibility measures														
Actigraphy Diary data) **(Items 2, 3, 5, 6, 8)** And Feasibility				Y			Y							
Device impact Data – feasibility measures														
Device Impact				Y			Y							
Actigraphy - Day/Night measures of physical activity - exploratory efficacy measures 2 measures for 24-hour recording period: Total Activity Score and Maximum Score														
Time Spent Active							Y							
Non-normalised (Average day time active and average night time active) & normalised (% daytime active; % night time active)				Y	Y		Y				Y	Y		
Over All Time Spent sedentary not lying							Y							
Non-normalised (Average day/night time spent sedentary not lying) & normalised (% daytime sedentary not lying; % night time sedentary not lying)				Y	Y		Y				Y	Y		
Over All Time Spent Lying							Y							
Non-normalised (Average day/night over all time spent lying) & normalised (% daytime lying; % night time lying)				Y	Y		Y				Y	Y		
Over All Time Spent Sedentary							Y							

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F[1]	F	L	T	F	L	T	F[1]	F	L
Non-normalised (Average day/night over all time spent sedentary) & normalised (% daytime sedentary; % night time sedentary)				Y	Y		Y				Y	Y		
Total Activity Score Day/Night (Total Day time Activity score/hour; Total Night Time Activity score/hour)				Y	Y		Y				Y	Y		
Total Activity Score – 24 hour (derived by adding up the day & night scores)				Y	Y		Y				Y	Y		
Maximum Score –24 Hour (Maximum score of day OR night for each 24-hour recording) And Average of 3 values				Y	Y		Y				Y	Y		
Active Periods (Numbers) normalised / hr				Y	Y		Y							
Active Periods (Duration)				Y	Y		Y				Y	Y		
Relationship between the ALSFRS and actigraphy measures	Y	Y						Y	Y					
Actigraphy - Night Time Rest Endpoints - exploratory efficacy measures														
Number Night Time Movement Episodes/Hr (use average)				Y	Y		Y				Y	Y		
Percent Time Night-time Rest Efficiency (use average)				Y	Y		Y				Y	Y		
Rest Fragmentation Index (use average)				Y	Y		Y				Y	Y		
Average Duration Movement Episodes				Y	Y		Y				Y	Y		

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F[1]	F	L	T	F	L	T	F[1]	F	L
Data Quality Deviators														
Data Quality Deviators for Actigraphy				Y										
Data Quality Deviators for Heart Rate Variability				Y										
Reconciliation for Actigraphy and Diary Data														
Reconciliation of Actigraphy and Diary Data				Y										
Heart Rate Variability Measures (mean & variance) - exploratory efficacy measures														
LF/HF Lying				Y	Y		Y				Y	Y		
LF/HF Active				Y	Y		Y				Y	Y		
LF/HF Sedentary not lying				Y	Y		Y				Y	Y		
LF/HF Active Minus Lying				Y	Y		Y				Y	Y		
LF/HF Sedentary not lying minus Lying				Y	Y		Y				Y	Y		
RMSSD (24 hr average)				Y	Y		Y				Y	Y		
Relationship between the ALSFRS and biotelemetry measures of HRV.	Y	Y						Y	Y					
Quantitative Speech Testing- exploratory efficacy measures														
Change over time in digital speech measures (Group by test) (Test details are in Section 9.4.3)				Y	Y		Y				Y	Y		
Relationship between the ALSFRS and digital measures of speech.	Y	Y						Y	Y					
Relationship between Forced Vital Capacity (FVC) and digital measures of speech.	Y	Y						Y	Y					
ALSFRS-R														
ALSFRS-R Total Score				Y	Y		Y				Y	Y		
FVC														
FVC				Y	Y		Y				Y	Y		

NOTES:
[1] The figures are plotted using the absolute values over time and relative rate of decline of related endpoints. See

Section 7.1.2 for details.

- T = Table, F = Figure, L =Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.1.2. Planned Statistical Exploratory Analyses

Statistical Analyses

Endpoint(s)

- Movement/physical activity (Actigraphy) endpoints as measured by the accelerometer device. See Section 2.2 for details.
- Heart rate variability endpoints as measured by the electrode device. See Section 2.2 for details.
- Speech endpoints. See Section 2.2 for details.
- ALSFRS-R total score and ALSFRS-R scores for 4 domains: gross motor activity, fine motor activity, bulbar and respiratory function
- FVC

Model Specification

- **Descriptive Statistics**
  - Actigraphy
    - The absolute, change from baseline, and the relative rate of decline for Actigraphy related endpoints will be summarized for each protocol time point using the FAS population
    - The monthly rate of decline for the whole study period for Actigraphy related endpoints will be summarized using the FAS population
    - The absolute values over time and relative rate of decline of Actigraphy related endpoints along with the total score over time and relative rate of decline of ALSFRS-R will be plotted against time (X), respectively.
  - Heart Rate Variability
    - The absolute values, change from baseline, and the relative rate of decline for HRV related endpoints (Mean & Variance for the LF/HF and 24 hours RMSSD analyses) will be summarized for each protocol time point using the FAS population
    - The monthly rate of decline for the whole study period for HRV related endpoints (Mean & Variance for the LF/HF and 24 hours RMSSD analyses) will be summarized using the FAS population
    - The absolute values and relative rate of decline of HRV related endpoints (Mean & Variance for the LF/HF and 24 hours RMSSD analyses) along with the absolute and relative rate of decline of ALSFRS-R will be plotted against time (X) respectively.
    - The Average Value and the raw data of the endpoints from McLaren will be listed
  - Speech assessment

Statistical Analyses

- The absolute values, change from baseline, and the relative rate of decline for Speech related endpoints will be summarized for each protocol time point using the FAS population
- The monthly rate of decline for the whole study period for Speech related endpoints will be summarized using the FAS population
- The absolute values and relative rate of decline of Speech related endpoints along with the absolute values and relative rate of decline of ALSFRS-R total score and FVC values will be plotted against time (X), respectively.

- **Correlation Analysis**

  An estimate of the between-subject correlation and the within-subject correlation will be obtained using the method described in Roy, 2006. The between-subject correlation will characterize whether subjects with greater decrease in the endpoint also tend to have the greater change in ALSFRS-R. The within-subject correlation will describe whether a decrease in one endpoint within an individual is associated with a decrease in the other endpoint.

  A mixed effect model with the change from baseline in the endpoints and the change from baseline in the ALSFRS-R score as dependent variables will be fitted. An indicator variable to distinguish the two endpoints will be fitted as a fixed effect and a random effect. Other explanatory covariates will be fitted as fixed effects, as appropriate.

  The RANDOM and REPEATED statements will be used to specify the structure of the covariance matrix for the two responses. The RANDOM statement will be used to specify an unstructured variance-covariance structure for the two responses. The REPEATED statement will be used to specify the variance covariance matrix for the error terms in the model. The structure of the variance covariance matrix is constructed by taking the Kronecker product of an unstructured matrix, which models the covariance for the two endpoints, with an unstructured or autoregressive (AR (1)) covariance matrix which models the covariance for the 2 repeated measures across visits.

  If the data is not sufficient to allow for convergence of the model, then alternative variance covariance matrices may be considered. If convergence of the model parameters still cannot be achieved, the approach by Bland, 1995 will be used to estimate the within subject correlation.

  - Actigraphy
    - The absolute values and change from baseline for the actigraphy endpoints will be analyzed for correlation with absolute values and change from baseline of Total score of ALSFRS-R, respectively.
    - The absolute values and change from baseline in the time spent active (day only), Time Spent sedentary not lying (day only), Time Spent Lying (day only), Time Spent Sedentary (day only), Total Activity Score (By 24 Hour and by Day), Maximum Score(By 24 Hour and by Day), Active Periods (Numbers) (day only), Active Periods (Duration) (day only) will be analysed for correlation with the absolute values and change from

Statistical Analyses
baseline to the gross motor domain and fine motor domain of ALSFRS-R, respectively. ▪ For the above endpoints analyzed for correlation, scatter plots will be done The correlation analysis will be performed on both non normalized and normalized data. Only the quality data (i.e. the data without the data quality deviators as defined in Section 7.1.1) will be used for the statistical analysis. o Heart Rate Variability ▪ The absolute values and change from baseline in the heart rate variability endpoints will be analyzed for correlation with the absolute values and change from baseline in the Total score of ALSFRS-R, respectively. ▪ For the above endpoints analyzed for correlation, scatter plots will be done Only the quality data will be used for the statistical analysis. o Speech assessment ▪ The absolute values and change from baseline in the speech endpoints will be analyzed for correlation with the absolute values and change from baseline in the Total ALSFRS-R, respectively. ▪ The absolute values and change from baseline in the speech endpoints will be analyzed for correlation with the absolute values and change from baseline of bulbar domain and respiratory domain of ALSFRS-R, respectively. ▪ The absolute values and change from baseline in the speech endpoints will be analyzed for correlation with the absolute values and change from baseline in the FVC, respectively. Only the quality data will be used for the statistical analysis.
Model Results Presentation
• **Descriptive Statistics** o Data listings o Summary tables o Visualization graphs • **Correlation Analysis** o Result tables o Visualization graphs

7.2. Safety Analyses

7.2.1. Overview of Planned Analyses

The safety analyses will be based on the "Safety" population, unless otherwise specified.

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Safety Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC	Y		Y
Serious AEs by SOC	Y		Y
AEs Leading to Withdrawal from Study by SOC and PT	Y		Y
AEs based on Intensity	Y		Y
Relationship Between AE SOCs, PT & Verbatim Text			Y
Death			
Number of deaths	Y		Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8. REFERENCES

Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 1—Correlation within subjects. BMJ, 1995;310:446.

Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III), J Neurol Sci. 1999 Oct31;169(1-2):13-21.

Clavelou P, Blanquet M, Peyrol F, Ouchchane L, Gerbaud L. Rates of progression of weight and forced vital capacity as relevant measurement to adapt Amyotrophic Lateral Sclerosi management for patient – Result of a French multicentre cohort survey. Journal of the Neurological Sciences. 2013; 331:126-131.

Cudkowicz M, Qureshi M, Shefner J. Measures and Markers in Amyotrophic Lateral Sclerosis. The Journal of the American Society for Experimental NeuroTherapeutics. 2004;1:273-283.

Czaplinski A, Yen AA, Appel SH. Forced vital capacity as an indicator of survival and disease progression in an ALS clinic population. J Neurol Neurosurg Psychiatry. 2006;77:390-392.

GlaxoSmithKline Document Number 2014N211002_02 Study ID MID201283. An Exploratory Study to Investigate the Use of Biotelemetry to Identify Markers of Disease Progression in Subjects with Amyotrophic Lateral Sclerosis. Effective date 21-SEP-2015 (Study Protocol)

Roy A. Estimating Correlation Coefficient between Two Variables with Repeated Observations using Mixed Effects Model. Biometrical Journal. 2006; 48(2), 286–301

Tudor-Locke C, Camhi SM, Troiano RP. A Catalog of Rules, Variables, and Definitions Applied to Accelerometer Data in the National Health and Nutrition Examination Survey, 2003–2006. Prev Chronic Dis 2012;9:110332.

9. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 9.1	Appendix 1: Time and Events
Section 9.2	Appendix 2: Treatment States & Phases
Section 9.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 9.4	Appendix 4: Derived and Transformed Data • General, Study Population & Safety • Efficacy
Section 9.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 9.6	Appendix 6: Multicentre Studies
Section 9.7	Appendix 7: Examination of Covariates and Subgroups
Section 9.8	Appendix 8: Multiple Comparisons and Multiplicity
Section 9.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 9.10	Appendix 10: Abbreviations & Trade Marks
Section 9.11	Appendix 11: List of Data Displays

9.1. Appendix 1: Time & Events

9.1.1. Protocol Defined Time & Events

Table 1 Time and Events – Pilot Phase

Procedures	Clinic Visit Screening Day 0	Home Monitoring (~ 3 days)	Telephone Contact[a] (TC)	Repeat Clinic Visit[b]	Home Monitoring[b] (~ 3 days)	Telephone Contact[a,b]	EWD
Informed consent	X						
Eligibility criteria	X						
Demography	X						
Medical and ALS history	X						
Brief neurological exam	X			X			
AEs/SAEs	X		X	X		X	X
Sensor placement	X	X		X	X		
Reference tasks	X			X			
Subject completes diary		X			X		
Site obtains diary information			X			X	X
Device impact questionnaire			X			X	X

a. Telephone contact to follow the 3-day home monitoring period to ensure the subject has completed the home monitoring period, diary, and to assess AEs, as appropriate. The expectation is that this call would occur on the first weekday following the home monitoring period.
b. May be repeated as necessary

Table 2 Time and Events – Core Study Phase

Study Day/Week[a]	Screen/Baseline Day 1/Week 0 Clinic Visit 1[b]	Weeks 0, 4, 8 Home Monitoring (~3 days)	Week 12 Clinic Visit 2	Weeks 12, 16, 20 Home Monitoring (~3 days)	Week 24 Clinic Visit 3	Weeks 24, 28, 32 Home Monitoring (~3 days)	Week 36 Clinic Visit 4	Weeks 36, 40, 44, 48[c] Home Monitoring (~3 days)	Week 48 or EWD Clinic Visit 5
Procedures									
Informed consent	X[b]								
Eligibility criteria	X[b]								
Demography	X[b]								
Medical and ALS history	X[b]								
Neurological exam	X								
Smoking details	X		X		X		X		X
Brief neurological exam			X		X		X		X
AEs/SAEs[d]	X	X	X	X	X	X	X	X	X
Concomitant medications[e]	X	X	X	X	X	X	X	X	X
ALSFRS-R[e]	X	X	X	X	X	X	X	X	X
FVC	X		X		X		X		X
Speech assessment	X		X		X		X		X
Sensor placement	X	X	X	X	X	X	X	X	X
Reference tasks	X		X		X		X		X
Device impact questionnaire			X		X		X		X
Subject completes diary		X		X		X		X	
Site obtains diary information[f]		X	X	X	X	X	X	X	X
Follow-up Telephone Contact[g]		X		X		X		X	

a. Clinic visits and home monitoring periods should be conducted within ± 7 days of the scheduled visit/home period and should be scheduled according to the Baseline Visit.
b. Subjects transitioning from the Pilot Phase do not need to perform these procedures.
c. The Week 48 home monitoring period will occur the three days prior to the Week 48 in-clinic visit (Visit 5).
d. Assessed in clinic at Weeks 0, 12, 24, 36, and 48 and by telephone at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44.
e. Assessed in clinic at Weeks 0, 12, 24, 36, and 48 and by telephone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.
f. Diary information should be obtained by telephone at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44.
g. Telephone contact to follow each 3-day home monitoring period. The expectation is that this call would occur on the first weekday following the home monitoring period.

9.2. Appendix 2: Study States and Phases

9.2.1. Treatment States for AE Data

Treatment State	Definition
Onset Time Since 1st (Days)	If Start Date of wearing the device of date of first protocol specified procedure > AE Onset Date = AE Onset Date - Start Date of wearing the device If Start Date of wearing the device or date of first protocol specified procedure ≤ AE Onset Date = AE Onset Date - Start Date of wearing the device +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Study-related	If relationship to study participation marked 'YES' on [Inform/CRF OR value is missing].

Note: wearing the device refers to either the at home monitoring, or the use of the device to carry out the in clinic set reference tasks.

9.3. Appendix 3: Data Display Standards & Handling Conventions

9.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions	
	Data Displays for Reporting
Code	**Description**
A	Mega Faros Device + Fast fix

9.3.2. Baseline Definition & Derivations

9.3.2.1. Baseline Definitions

For all endpoints the baseline value will be the latest assessment prior to or at the baseline visit (Visitnum=10 or 90), with the following exceptions which may use the TC at week 0 (Visitnum=100) if available:

- Actigraphy endpoints
- HRV endpoints
- Speech endpoints
- ALSFRS-R
- FVC

For all endpoints this will be referred to as Baseline, Week 0.

9.3.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Baseline Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Baseline Visit Value – Baseline) / Baseline]

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 9.3.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

9.3.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	:UK1salx00175
HARP Area	:175\gsk1223249\mid201283
QC Spreadsheet	: Mc Laren-QC Sheet

Reporting Process
Analysis Datasets
• Analysis datasets will be created according to IDSL standards.
Generation of RTF Files
• RTF files will be generated for all the summary tables.

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • If unscheduled visits are included, provide details of how summaries will be displayed (i.e. unscheduled visits will be slotted to closest planned visit). • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

9.4. Appendix 4: Derived and Transformed Data

9.4.1. General

Multiple Measurements at One Time Point
• For the ALSFRS-R, if the closest assessment is not evaluable, the other assessment would be used.
Study Day

• Calculated as the number of days from baseline visit (visitnum=10 or 90)
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Baseline Visit Date → Study Day = Ref Date – Baseline Visit Date
  • Ref Data ≥ Baseline Visit Date → Study Day = Ref Date – Baseline Visit Date + 1

9.4.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Adverse Event
For this non-drug study, an AE is any untoward medical occurrence in a clinical investigation subject which, in the opinion of the investigator, is related to a protocol-mandated procedure or one of the devices used by the subject during the study.

9.4.3. Exploratory

ALSFRS-R Total Score
The ALS functional rating scale – revised (ALSFRS-R) assesses the functioning of ALS subjects across 4 domains: gross motor activity, fine motor activity, bulbar and respiratory function. The ALSFRS-R [Cedarbaum, 1999] consists of 12 questions each of which are scored on a 5-point scale from 0-4, where 4 is the best possible outcome and 0 is the worst. The total score will be calculated by summing responses to each of the 12 individual questions. The maximum total score is therefore 48, lower scores indicate worse functioning. If there are any missing questions, then the total score will be set to missing. ALSFRS will be grouped to four different domains: Fine motor, Gross motor, Respiratory and Bulbar Domain [Cedarbaum, 1999]

FVC

FVC is a measure of respiratory function and is the volume of air that can forcibly be blown out after a single, full breath. FVC is a sensitive measure of ALS disease progression, is used as a standard test for ALS management, and is recommended as a secondary outcome measure in ALS clinical trials [Cudkowicz, 2004; Czaplinski, 2006; Clavelou, 2013].

FVC will be performed by experienced site personnel according to local protocol using a calibrated spirometer. Every effort should be made to have the same individual perform the FVC for a given subject throughout the study. For each time point, the best FVC result (in litres) will be recorded in the eCRF.

Relative Rate of Decline and Monthly Rate of Decline (Slope)

$$\text{Relative Rate of Decline} = \frac{\text{Value at a time point} - \text{Value at the Baseline}}{\text{Value at the Baseline}}$$

$$\text{Monthly rate of decline at each visit} = \frac{\text{Change from baseline of the endpoint at each post-baseline visit}}{\text{Study day}/30.4}$$

Monthly Rate of Decline= Average of Monthly Rate of Decline at each visit and is populated only for the last visit.

For Monthly Rate of Decline, if an assessment took place over a number of consecutive days then the average of that will be taken and the recent visit (last time point) will be considered to calculate study day.

Actigraphy

Activity classifiers = Active / lying / “sedentary not lying”.

NMTMSG – expected to be 24 hr (1440 mins) but could be less if partial recording day
NMTMSG = Active, lying, “sedentary not lying”, off

Each activity classifier & activity endpoint is recorded by McLaren TWICE, once for day time once for night time.

1440 = day time Active, day time lying, day time “sedentary not lying”, day time off + night time Active, night time lying, night time “sedentary not lying”, night time off

Therefore, wear time = 1440 minus [day off time + night off time]

Off time here represents the time that the sensor was either switched off or the patient was not wearing it (or both).

For all the parameters, derivation will be done twice – one with all data and one with the quality data (i.e., excluding data quality deviators).

For each endpoint for the CSR (& interpretation of the study) 3 splits of data will be reported:

- Day time activity endpoints – from McLaren
- Night tine activity endpoints – from McLaren
- 24 hour endpoints – derived by GSK – add day time + night time values

DERIVED	Wear time (mins)	Time Active + Time sedentary [where time sedentary = time lying + time sedentary not lying]
DERIVED	Duration of day time wear time (mins)	Day time wear time = day time Active + day time lying + day time "sedentary not lying"
DERIVED	Duration of night time wear time (mins)	Night time wear time = night time Active + night time lying + night time "sedentary not lying"
ACTIVETM	Overall time spent active Average day time active % daytime ACTIVE % night time ACTIVE	Number mins per day/night for 24-hour recording period Add up the total amount of time active across all the recording periods and divide by the number of recording periods. 1 value per subject per time point DAYTIME ACTIVETM (Day 1+2+3) divided by total amount of day time duration across the 3 recording days – expressed as a % Where total amount of daytime duration = [Day 1-day time ACTIVETM + day time LIETM + day time "sedentary not lying" – SEDTMNL] + Day 2 (ditto) + Day 3 [ditto] NIGHTTIME ACTIVETM (Day

		1+2+3) divide by total amount of night time duration across the 3 recording days – expressed as a % Where total amount of night time duration = [Day 1-night time ACTIVETM + night time LIETM + night time "sedentary not lying" – SEDTMNL] + Day 2 (ditto) + Day 3 [ditto]
SEDTMNL	Overall time spent sedentary not lying % daytime SEDENTARY NOT LYING % night time SEDENTARY NOT LYING	Needs the same approach as above
LIETM	Overall time spent lying % daytime LYING % night time LYING	Needs the same approach as above
SEDENTM	Over all time spent sedentary % daytime SEDENTARY % night time SEDENTARY	Same Approach as above
OFFTM	Time spent with sensor	
ACTIVISC	Total activity score 24- Hour Daytime total activity score Night time total activity score	Total Activity Score (add day + night) Day time total activity score (Day 1+2+3) divide by the total day time for that protocol time point. Night time total activity score Day (Day 1+2+3) divide by the total day time for that protocol time point.
MAXACTSC	The maximum score from a 1 min window in a 24-hour	3 values per protocol time point or more if more days are

	period Daytime maximum activity score Daytime mean maximum activity score (mean of all recording periods) Night time maximum activity score Night time mean maximum activity score (mean of all recording	recorded for home monitoring. • Take the maximum over the 3 days • Average over 3 days
WKPER01, WKPER02, WKPER05, WKPER15, WKPER30	Active Periods (Numbers)	To normalise 'Active Periods (Number)' to a per hour unit (Algorithm is given below)
WKPERDUR	Average duration of active periods greater than 1 minute.	

To normalise 'Active Periods (Number)' :

1. Add up the total number of 'active periods' for the recording periods (value 1).
    - Please note this is done by adding the 'number of active periods (all the categories)1min<x<2min' + 'number of active periods 2min<x<5min' + 'number of active periods 5min<x<15min' + 'number of active periods 15min<x<30min' + 'number of active periods >30min'

2. Calculate the 'wear time' for the recording period <u>in days</u>(i.e. minutes/ 1440). (value 2).
    - Please remember that 'wear time = active + sedentary time' for the recording period (either day time or night time)

3. Value 1 / Value 2 is the normalised measure required

<u>Rules for reconciliation of Actigraphy and Diary data</u>

Actigraphy and Diary data will be reconciled and a frequency table on the rules below will be summarized;

Rule1: Subjects present both in Actigraphy and Diary data

Rule2: Subjects present only in Actigraphy data

Rule3: Subjects present only in Diary data

Night Time Endpoints

These endpoints need to be reported as the "average" or "mean" for each protocol time point (due to the amount of day or night time not matching a protocol day or night)

CODE	DESCRIPTION
NNTMTEPHR	Number Night Time Movement Episodes/Hr
NTRESTEF	Percent Time Night-time Rest Efficiency
RFRGI	Rest Frag Index=Move Time/Num Movement Episode
AVGDURMTE	Average Duration Movement Episodes
Number Night Time Movement Episodes/Hr. NNTMTEPHR	Limitations of each 24-hour recording period = the 24-hour recording periods do NOT match protocol days, due to the mixed start times that are governed by the sensor "activation." (first data recorded by the sensor) – as such reporting the data out by recording day does NOT make sense, the data must be reported over the 3 days for each protocol timepoint (ie data need to be averaged out). A note pertaining to this must be added to any data that lists out the raw data for each recording period. Average number night time movements/hour (Day 1+2+3) divide by 3, ie Day 1 + Day 2 etc. / actual number of recording periods at each time point (sometimes there are more or less values at each protocol time point)
Percent Time Night-time Rest Efficiency NTRESTEF	Core study phase only. Limitations as above Average % time night time rest efficiency (Day 1+2+3 values) divide by 3, ie Day 1 value + Day 2 value etc. / actual number of recording periods at each time point (sometimes there are more or less values at each protocol time point)
Rest Frag Ind=Move Time/Num RFRGI Movement Episode	Core study phase only. Limitations as above Average night time rest fragmentation index (Day 1+2+3 values) divide by 3, ie Day 1 value + Day 2 value etc. / actual number of recording periods at each time point (sometimes there are more or less values at each protocol time point)

Avg Duration Movement Episodes AVGDURMTE	Done for each 24 hours' period But again, need 1 value for protocol time point. An average of the average over 3 days. – Use the number of active periods in the categories above – add up to derive a total, use that total to create a more accurate average. Average duration of movement disorders = values [Day 1 + day 2 + day 3]/total number of night time movements [Days 1+2+3]

Speech Assessments

The 4 tests for speech assessments are:

- Short ah
    - Central tendency of fundamental F0, relative jitter, relative shimmer
- Long ah
    - Central tendency of fundamental F0, relative jitter, relative shimmer
- Single word – doily
    - Average phoneme rate, average phonation time
- Running speech (bamboo passage)
    - Speaking rate % pause time

CODE	DESCRIPTION
AA001 HZ	Central tendency of fundamental F0 (code 001: short ah) (code 002: long ah) ?? middle five seconds of the phonation interval??
AA002 %	Relative Jitter (code 001: short ah) (code 002: long ah)
AA003	Relative Shimmer (code 001: short ah)

	%	(code 002: long ah)
	AA004 (Hz/s)	Average phoneme rate (Phoneme – subpart of word) code 003: “single word” doily
	AA005 (s)	Average phonation time code 003: “single word” doily
	AA007 %	% pause time (Code 004: running speech)
	AA008 (WPM)	Speaking rate (Code 004: running speech)

Heart Rate Variability (all LF/HF HRV metrics are over 5 minutes’ windows)

HRV data are captured for each of the activity classifiers: Active + Lying + “sedentary not lying”. “Lying minus active” and “Lying minus sedentary not lying” is derived based on the following:

MLFHFN	Mean LF/HF (Avg over 5 min windows of lying down)	Use the sum of the means over each recording day (Day 1 + Day 2 + Day 3) divided by the total number of recording points over the 3 days (number Day 1+2+3) (number of lying periods of good enough quality to obtain HRV from)
VLFHFN	Var of LF/HF (Avg over 5 min windows of lying down)	Use the sum of the variances over each recording day (Day 1 + Day 2 + Day 3) divided by the total number of recording points over the 3 days (number Day 1+2+3) (number of lying periods of good

		enough quality to obtain HRV from)
MLFHFSD	Mean LF/HF (avg-stationary-day) Stationary = sedentary not lying	Derive 1 average value for each protocol time point, Use the sum of the means over each recording day (Day 1 + Day 2 + Day 3) divided by the total number of recording points over the 3 days (number Day 1+2+3) (number of 'sedentary not lying' periods of good enough quality to obtain HRV from)
VLFHFSD	Var of LF/HF (avg-stationary-day) Stationary = sedentary not lying	Derive 1 average value for each protocol time point, Use the sum of the variances over each recording day divided by the total number of recording points (number of 'sedentary not lying' periods of good enough quality to obtain HRV from)
MLFHFAD	Mean LF/HF (avg-daytime activity)	Derive 1 average value for each protocol time point, Use the sum of the means over each recording day divided by the total number of recording points (number of active periods of good enough quality to obtain HRV from)
VLFHFAD	Var of LF/HF (avg-daytime activity)	Derive 1 average value for each protocol time point, Use the sum of the variances over each recording day divided by the total number of recording points (number of active periods of good enough quality to obtain HRV from)
MRMSSD	Mean RMSSD (24 hr avg)	
VRMSSD	Var of RMSSD (24 hrs avg)	

- HRV effect of being upright = LF/HF stationary minus LF/HF lying
- HRV effect of activity = LF/HF active (MLFHFAD) minus LF/HF lying (MLFHFN)

9.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

9.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as a subject is one who has completed the study through the Week 48 visit. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

9.5.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Statistical analyses	• For all other endpoints no imputation will be made for missing data.

9.5.2.1. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• The recorded partial date will be displayed in listings.
Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. o However, if these results in a date prior to Day 1 and the event could possibly have occurred during the On-Device phase from the partial information, then the Day 1 date will be assumed to be the start date. o The AE will then be considered to start on-device (worst case). o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

9.6. Appendix 6: Multicentre Studies

This study aims to enrol subjects using two sites based in the UK.

In this multicentre study, listings will be presented by investigative site.

9.7. Appendix 7: Examination of Covariates, Subgroups & Other Strata

9.7.1. Handling of Covariates, Subgroups & Other Strata

There was no randomisation and therefore no strata used in this study.

Due to the small number of subjects in the study, no subgroups will be specified here although subgroup analyses may take place ad hoc.

The following is a list of covariates that may be used in descriptive summaries and/ or statistical analyses (See Section 7.1.1and Section 7.1.2 for further details).

Additional covariates of clinical interest may also be considered.

These analyses will be carried out as part of ADHOC if necessary.

Category	Covariates and / or Subgroups
Correlation of ALSFRS-R and movement actigraphy data/ HRV data	In additional to the model described in Section 7.1.2, the following explanatory variables may be considered: • Baseline value for each of the dependent variables being correlated • Phenotype at onset: Bulbar/Limb/Other • Age at baseline • Sex – Male/ Female • Time since onset of muscle weakness
Correlation of FVC/ ALSFRS-R and speech data	In additional to the model described in Section 7.1.2, the following explanatory variables may be considered: • Baseline value for each of the dependent variables being correlated • Phenotype at onset: Bulbar/Limb/Other • Smoking status at baseline • Age at baseline • Sex – Male/ Female • Time since onset of muscle weakness
Mixed model repeated measures analyses	For the MMRM Baseline, Visit, Baseline by Visit covariates will be included in model. The following explanatory variables may also be considered: • Phenotype at onset: Bulbar or Other/ Limb • Smoking status at baseline • Age at baseline • Sex – Male/ Female • Time since onset of muscle weakness

9.8. Appendix 8: Multiple Comparisons & Multiplicity

As this is an exploratory study, no adjustment will be made for multiple comparisons. Assessments about the correlation between endpoints will be made on the strength of the correlation coefficients.

9.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

9.9.1. Statistical Analysis Assumptions

Endpoint(s)	• Actigraphy, HRV and Speech
Analysis	• MMRM

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.
  - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
  - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

9.10. Appendix 10: – Abbreviations & Trade Marks

9.10.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AIC	Akaike's Information Criteria
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
A&R	Analysis and Reporting
CI	Confidence Interval
CS	Clinical Statistics
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FAS	Full Analysis Set
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HF	High Frequency
HRV	Heart Rate Variability
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LF	Low Frequency
MMRM	Mixed Model Repeated Measures
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
QC	Quality Control
RAP	Reporting & Analysis Plan
RMSSD	Root Mean Square
SAC	Statistical Analysis Complete
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

9.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
McLaren
Mega Faros
SAS

9.11. Appendix 11: List of Data Displays

9.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.8	NA
Exploratory	2.1 to 2.155	2.1 to 2.94
Safety	3.1 to 3.5	NA
Section	**Listings**	
ICH Listings	1 to 15	
Other Listings	16 to 70	

9.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in a separate document.

Section	Figure	Table	Listing
Study Population	NA	NA	NA
Exploratory	EFF_F1	EFF_T1	EFF_L1
Safety	NA	SAFE_T1	SAFE_L1

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

9.11.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	FAS	CP_ES1	Summary of Subject Disposition		SAC
1.2.	Screen Failure	ES6	Summary of Reasons for Screen Failure		SAC
1.3.	FAS	NS1	Summary of Number of Subjects by Country and Centre		SAC
Protocol Deviations					
1.4.	FAS	DV1	Summary of Important Protocol Deviations		SAC
Population Analysed					
1.5.	Enrolled	SP1	Summary of Study Populations and Exclusions		SAC
Demographic and Baseline Characteristics					
1.6.	FAS	DM3	Summary of Demographic Characteristics	Add ALSFRS-R and FVC at baseline	SAC
1.7.	FAS	DM5	Summary of Race and Racial Combinations		SAC
Prior and Concomitant Medications					
1.8.	FAS	CM1	Summary of Concomitant Medications		SAC

9.11.4. Exploratory Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Actigraphy - feasibility & Wear time Measures					
2.1.	FAS	EFF_T1	Summary of Wear Time (mins) (All data)	By visit and Overall Paginate by Pilot Phase and Core Phase	SAC
2.2.	FAS	EFF_T1	Summary of Wear Time (mins) (Quality data)	By visit and Overall Paginate by Pilot Phase and Core Phase	SAC
2.3.	FAS	EFF_T1	Summary of Duration of Day Wear Time (All data)	Same as Above	SAC
2.4.	FAS	EFF_T1	Summary of Duration of Day Wear Time (Quality data)	Same as Above	SAC
2.5.	FAS	EFF_T1	Summary of Duration of Night Time Wear Time (All data)	Same as Above	SAC
2.6.	FAS	EFF_T1	Summary of Duration of Night Time Wear Time (Quality data)	Same as Above	SAC
Actigraphy - Day/Night measures of physical activity - exploratory efficacy measures 2 measures for 24-hour recording period: Total Activity Score and Maximum Score					
2.7.	FAS	EFF_T1	Summary of Time Spent Active (All data)	Categorise into: Average Day/Night Time active %Day Time Active %Night Time Active	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	FAS	EFF_T1	Summary of Time Spent Active (Quality data)	Categorise into: Average Day/Night Time active %Day Time Active %Night Time Active	SAC
2.9.	FAS	EFF_T1	Summary of Change from Baseline of Time Spent Active (All data)	Same as Above	SAC
2.10.	FAS	EFF_T1	Summary of Change from Baseline of Time Spent Active (Quality data)	Same as Above	SAC
2.11.	FAS	EFF_T1	Summary of Relative Rate of Decline of Time Spent Active (All data)	Same as Above	SAC
2.12.	FAS	EFF_T1	Summary of Relative Rate of Decline of Time Spent Active (Quality data)	Same as Above	SAC
2.13.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Time Spent Active (Quality data)	Same as Above	SAC
2.14.	FAS	EFF_T1	Summary of Overall Time Spent Sedentary Not Lying (All data)	Same as Above	SAC
2.15.	FAS	EFF_T1	Summary of Overall Time Spent Sedentary Not Lying (Quality data)	Same as Above	SAC
2.16.	FAS	EFF_T1	Summary of Change from Baseline of Overall Time Spent Sedentary Not Lying (All data)	Same as Above	SAC
2.17.	FAS	EFF_T1	Summary of Change from Baseline of Overall Time Spent Sedentary Not Lying (Quality data)	Same as Above	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18.	FAS	EFF_T1	Summary of Relative Rate of Decline of Overall Time Spent Sedentary Not Lying (All data)	Same as Above	SAC
2.19.	FAS	EFF_T1	Summary of Relative Rate of Decline of Overall Time Spent Sedentary Not Lying (Quality data)	Same as Above	SAC
2.20.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Overall Time Spent Sedentary Not Lying (Quality data)	Same as Above	SAC
2.21.	FAS	EFF_T1	Summary of Time Spent Lying (All data)	Categorise into: Average Day/Night Overall Time Spent Lying %Day Time Lying %Night Time Lying	SAC
2.22.	FAS	EFF_T1	Summary of Time Spent Lying (Quality data)	Categorise into: Average Day/Night Overall Time Spent Lying %Day Time Lying %Night Time Lying	SAC
2.23.	FAS	EFF_T1	Summary of Change from Baseline of Time Spent Lying (All data)	Same as Above	SAC
2.24.	FAS	EFF_T1	Summary of Change from Baseline of Time Spent Lying (Quality data)	Same as Above	SAC
2.25.	FAS	EFF_T1	Summary of Relative Rate of Decline of Time Spent Lying (All data)	Same as Above	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.26.	FAS	EFF_T1	Summary of Relative Rate of Decline of Time Spent Lying (Quality data)	Same as Above	SAC
2.27.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Time Spent Lying (Quality data)	Same as Above	SAC
2.28.	FAS	EFF_T1	Summary of Time Spent Sedentary (All data)	Categorise into: Average Day/Night Time Spent Sedentary %Day Time Sedentary %Night Time Sedentary	SAC
2.29.	FAS	EFF_T1	Summary of Time Spent Sedentary (Quality data)	Same as Above	SAC
2.30.	FAS	EFF_T1	Summary of Change from Baseline of Time Spent Sedentary (All data)	Same as Above	SAC
2.31.	FAS	EFF_T1	Summary of Change from Baseline of Time Spent Sedentary (Quality data)	Same as Above	SAC
2.32.	FAS	EFF_T1	Summary of Relative Rate of Decline of Time Spent Sedentary (All data)	Same as Above	SAC
2.33.	FAS	EFF_T1	Summary of Relative Rate of Decline of Time Spent Sedentary (Quality data)	Same as Above	SAC
2.34.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Time Spent Sedentary (Quality data)	Same as Above	SAC
2.35.	FAS	EFF_T1	Summary of Total Activity Score Day/Night (All data)	Categorise into: Total Day Time Activity Score Total Night Time Activity Score	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.36.	FAS	EFF_T1	Summary of Total Activity Score Day/Night (Quality data)	Same as Above	SAC
2.37.	FAS	EFF_T1	Summary of Change from Baseline of Total Activity Score Day/Night (All data)	Same as Above	SAC
2.38.	FAS	EFF_T1	Summary of Change from Baseline of Total Activity Score Day/Night (Quality data)	Same as Above	SAC
2.39.	FAS	EFF_T1	Summary of Relative Rate of Decline of Total Activity Score Day/Night (All data)	Same as Above	SAC
2.40.	FAS	EFF_T1	Summary of Relative Rate of Decline of Total Activity Score Day/Night (Quality data)	Same as Above	SAC
2.41.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Total Activity Score Day/Night (Quality data)	Same as Above	SAC
2.42.	FAS	EFF_T1	Summary of Total Activity Score – 24 Hour (All data)		SAC
2.43.	FAS	EFF_T1	Summary of Total Activity Score – 24 Hour (Quality data)		SAC
2.44.	FAS	EFF_T1	Summary of Change from Baseline of Total Activity Score – 24 Hour (All data)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.45.	FAS	EFF_T1	Summary of Change from Baseline of Total Activity Score – 24 Hour (Quality data)		SAC
2.46.	FAS	EFF_T1	Summary of Relative Rate of Decline of Total Activity Score – 24 Hour (All data)		SAC
2.47.	FAS	EFF_T1	Summary of Relative Rate of Decline of Total Activity Score – 24 Hour (Quality data)		SAC
2.48.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Total Activity Score – 24 Hour (Quality data)		SAC
2.49.	FAS	EFF_T1	Summary of Maximum Score (1 min – 24 Hour Window) (All data)	Categorise into: • Daytime maximum activity score • Daytime mean maximum activity score (mean of all recording periods) • Night time maximum activity score • Night time mean maximum activity score (mean of all recording	SAC
2.50.	FAS	EFF_T1	Summary of Maximum Score (1 min – 24 Hour Window) (Quality data)	Same as above	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.51.	FAS	EFF_T1	Summary of Change from Baseline Maximum Score (1 min – 24 Hour Window) (All data)	Same as above	SAC
2.52.	FAS	EFF_T1	Summary of Change from Baseline Maximum Score (1 min – 24 Hour Window) (Quality data)	Same as above	SAC
2.53.	FAS	EFF_T1	Summary of Relative Rate of Decline of Maximum Score (1 min – 24 Hour Window) (All data)	Same as above	SAC
2.54.	FAS	EFF_T1	Summary of Relative Rate of Decline of Maximum Score (1 min – 24 Hour Window) (Quality data)	Same as above	SAC
2.55.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Maximum Score (1 min – 24 Hour Window) (Quality data)	Same as above	SAC
2.56.	FAS	EFF_T1	Summary of Active Periods (Numbers) (All data)	For day and night active periods separately & for each category (> 1 to <= 2 minutes, > 2 to <= 5 minutes etc. etc): Categorise into Day and Night Time Modify EFF_T1 as: Add n (%) instead of statistics Add columns for categories	SAC
2.57.	FAS	EFF_T1	Summary of Active Periods (Numbers) (Quality data)	Same as Above	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.58.	FAS	EFF_T1	Summary of Active Periods (Duration) (All data)	Categorise into Day and Night Time	SAC
2.59.	FAS	EFF_T1	Summary of Active Periods (Duration) (Quality data)	Same as Above	SAC
2.60.	FAS	EFF_T1	Summary of Change from Baseline of Active Periods (Duration) (All Data)	Same as Above	SAC
2.61.	FAS	EFF_T1	Summary of Active Change from Baseline of Periods (Duration) (Quality data)	Same as Above	SAC
2.62.	FAS	EFF_T1	Summary of Relative Rate of Decline of Active Periods (Duration) (All data)	Same as Above	SAC
2.63.	FAS	EFF_T1	Summary of Relative Rate of Decline of Active Periods (Duration) (Quality data)	Same as Above	SAC
2.64.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Active Periods (Duration) (Quality data)	Same as Above	SAC
2.65.	FAS	EFF_T3	Statistical Analysis of Relationship between Absolute Values of Actigraphy endpoints and Absolute Value of Total ALSFRS-R		SAC
2.66.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of Actigraphy endpoints and Change from Baseline of Total ALSFRS-R		SAC
2.67.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of Actigraphy endpoints and Slope of Total ALSFRS-R		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.68.	FAS	EFF_T3	Statistical Analysis of Relationship between Absolute Values of Actigraphy endpoints and Absolute Value of gross motor domain of ALSFRS-R		SAC
2.69.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of Actigraphy endpoints and Change from Baseline of gross motor domain of ALSFRS-R		SAC
2.70.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of Actigraphy endpoints and Slope of gross motor domain of ALSFRS-R		SAC
2.71.	FAS	EFF_T3	Statistical Analysis of Relationship between Absolute Values of Actigraphy endpoints and Absolute Value of fine motor domain of ALSFRS-R		SAC
2.72.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of Actigraphy endpoints and Change from Baseline of fine motor domain of ALSFRS-R		SAC
2.73.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of Actigraphy endpoints and Slope of fine motor domain of ALSFRS-R		SAC
Night Time Rest Endpoints					
2.74.	FAS	EFF_T1	Summary of Number Night Time Movement (All data)		SAC
2.75.	FAS	EFF_T1	Summary of Number Night Time Movement (Quality data)		SAC
2.76.	FAS	EFF_T1	Summary of Change from Baseline of Number Night Time Movement (All data)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.77.	FAS	EFF_T1	Summary of Change from Baseline of Number Night Time Movement (Quality data)		SAC
2.78.	FAS	EFF_T1	Summary of Relative Rate of Decline of Number Night Time Movement (All data)		SAC
2.79.	FAS	EFF_T1	Summary of Relative Rate of Decline of Number Night Time Movement (Quality Da data ta)		SAC
2.80.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Number Night Time Movement (Quality data)		SAC
2.81.	FAS	EFF_T1	Summary of Percent Time Night-time Rest Efficiency (All data)		SAC
2.82.	FAS	EFF_T1	Summary of Percent Time Night-time Rest Efficiency (Quality data)		SAC
2.83.	FAS	EFF_T1	Summary of Change from Baseline of Percent Time Night-time Rest Efficiency (All data)		SAC
2.84.	FAS	EFF_T1	Summary of Change from Baseline of Percent Time Night-time Rest Efficiency (Quality data)		SAC
2.85.	FAS	EFF_T1	Summary of Relative Rate of Decline of Percent Time Night-time Rest Efficiency (All data)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.86.	FAS	EFF_T1	Summary of Relative Rate of Decline of Percent Time Night-time Rest Efficiency (Quality data)		SAC
2.87.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Percent Time Night-time Rest Efficiency (Quality data)		SAC
2.88.	FAS	EFF_T1	Summary of Rest Fragmentation Index (All data)		SAC
2.89.	FAS	EFF_T1	Summary of Rest Fragmentation Index (Quality data)		SAC
2.90.	FAS	EFF_T1	Summary of Change from Baseline of Rest Fragmentation Index (All data)		SAC
2.91.	FAS	EFF_T1	Summary of Change from Baseline of Rest Fragmentation Index (Quality data)		SAC
2.92.	FAS	EFF_T1	Summary of Relative Rate of Decline of Rest Fragmentation Index (All data)		SAC
2.93.	FAS	EFF_T1	Summary of Relative Rate of Decline of Rest Fragmentation Index (Quality data)		SAC
2.94.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Rest Fragmentation Index (Quality data)		SAC
2.95.	FAS	EFF_T1	Summary of Average Duration Movement Episodes (All data)		SAC
2.96.	FAS	EFF_T1	Summary of Average Duration Movement Episodes (Quality data)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.97.	FAS	EFF_T1	Summary of Average Change from Baseline of Duration Movement Episodes (All data)		SAC
2.98.	FAS	EFF_T1	Summary of Average Change from Baseline of Duration Movement Episodes (Quality data)		SAC
2.99.	FAS	EFF_T1	Summary of Relative Rate of Decline of Duration Movement Episodes (All data)		SAC
2.100.	FAS	EFF_T1	Summary of Relative Rate of Decline of Duration Movement Episodes (Quality data)		SAC
2.101.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Duration Movement Episodes (Quality data)		SAC
2.102.	FAS	EFF_T3	Statistical Analysis of Relationship between Absolute Values of Night Rest Endpoints and Absolute Value of Total ALSFRS-R		SAC
2.103.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of Night Rest Endpoints and Change from Baseline of Total ALSFRS-R		SAC
2.104.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of Night Rest Endpoints and Slope of Total ALSFRS-R		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Heart Rate Variability					
2.105.	FAS	EFF_T1	Summary of Mean HRV LF/HF (All data)	Include: • Mean HRV Lying minus active • Mean HRV Lying minus 'sedentary not lying' • Mean HRV Lying (average) • Mean HRV Active(average) • Mean HRV 'sedentary not lying'(average)	SAC
2.106.	FAS	EFF_T1	Summary of Change from Baseline of Mean HRV LF/HF (All data)	Same as above	SAC
2.107.	FAS	EFF_T1	Summary of Relative Rate of Decline of Mean HRV LF/HF (All data)	Same as above	SAC
2.108.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Mean HRV LF/HF (All data)	Same as above	SAC
2.109.	FAS	EFF_T1	Summary of Mean RMSSD (All data)		SAC
2.110.	FAS	EFF_T1	Summary of Mean RMSSD (Quality data)		SAC
2.111.	FAS	EFF_T1	Summary of Change from Baseline of Mean RMSSD (All data)		SAC
2.112.	FAS	EFF_T1	Summary of Change from Baseline of Mean RMSSD (Quality data)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.113.	FAS	EFF_T1	Summary of Relative Rate of Decline of Mean RMSSD (All data)		SAC
2.114.	FAS	EFF_T1	Summary of Relative Rate of Mean RMSSD (Quality data)		SAC
2.115.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Mean RMSSD (Quality data)		SAC
2.116.	FAS	EFF_T1	Summary of Variance HRV LF/HF (All data)	Include: • Variance HRV Lying minus active • Variance HRV Lying minus 'sedentary not lying' • Variance HRV Lying (average) • Variance HRV Active(average) • Variance HRV 'sedentary not lying'(average)	SAC
2.117.	FAS	EFF_T1	Summary of Change from Baseline of Variance HRV LF/HF (All data)	Same as above	SAC
2.118.	FAS	EFF_T1	Summary of Relative Rate of Decline of Variance HRV LF/HF (All data)	Same as above	SAC
2.119.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Variance HRV LF/HF (All data)	Same as above	SAC
2.120.	FAS	EFF_T1	Summary of Variance RMSSD (All data)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.121.	FAS	EFF_T1	Summary of Variance RMSSD (Quality data)		SAC
2.122.	FAS	EFF_T1	Summary of Change from Baseline of Variance RMSSD (All data)		SAC
2.123.	FAS	EFF_T1	Summary of Change from Baseline of Variance RMSSD (Quality data)		SAC
2.124.	FAS	EFF_T1	Summary of Relative Rate of Decline of Variance RMSSD (All data)		SAC
2.125.	FAS	EFF_T1	Summary of Relative Rate of Variance RMSSD (Quality data)		SAC
2.126.	FAS	EFF_T1	Summary of Monthly Rate of Decline of Variance RMSSD (Quality data)		SAC
2.127.	FAS	EFF_T3	Statistical Analysis of Relationship between Absolute Values of of HRV endpoints (LF/HF) and Absolute Value of Total ALSFRS-R		SAC
2.128.	FAS	EFF_T3	Statistical Analysis of Relationship between Absolute Values of of RMSSD and Absolute Value of Total ALSFRS-R		SAC
2.129.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of HRV endpoints (LF/HF) and Change from Baseline of Total ALSFRS-R		SAC
2.130.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of RMSSD and Change from Baseline of Total ALSFRS-R		SAC
2.131.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of HRV endpoints (LF/HF) and Slope of Total ALSFRS-R		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.132.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of RMSSD and Slope of Total ALSFRS-R		SAC
Speech					
2.133.	FAS	EFF_T1	Summary of Speech Endpoints	Categorise by Test	SAC
2.134.	FAS	EFF_T1	Summary of Change from Baseline of Speech Endpoints	Categorise by Test	SAC
2.135.	FAS	EFF_T1	Summary of Relative Rate of Decline of Speech Endpoints	Categorise by Test	SAC
2.136.	FAS	EFF_T1	Summary of Monthly Rate of Speech Endpoints	Categorise by Test	SAC
2.137.	FAS	EFF_T3	Statistical Analysis of Relationship between Absolute Values of Speech endpoints and Absolute Value of ALSFRS-R	Paginate by Total Score of ALSFRS, Bulbar Domain and Respiratory Domain	SAC
2.138.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of Speech endpoints and Change from Baseline of ALSFRS-R	Paginate by Total Score of ALSFRS, Bulbar Domain and Respiratory Domain	SAC
2.139.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of Speech endpoints and Slope of ALSFRS-R	Paginate by Total Score of ALSFRS, Bulbar Domain and Respiratory Domain	SAC
2.140.	FAS	EFF_T3	Statistical Analysis of Relationship Absolute Values of Speech endpoints and Absolute Values of FVC		SAC
2.141.	FAS	EFF_T3	Statistical Analysis of Relationship between Change from Baseline of Speech endpoints and Change from Baseline of FVC		SAC
2.142.	FAS	EFF_T3	Statistical Analysis of Relationship between Slope of Speech endpoints and Slope of FVC		SAC
Data Quality Deviator					
2.143.	FAS	EFF_T2	Summary of Data Quality Deviators of Actigraphy Data	Footnote the 3 Rules	SAC
2.144.	FAS	EFF_T2	Summary of Data Quality Deviators of HRV Data	Footnote the 3 Rules	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Reconciliation of Actigraphy and Diary Data					
2.145.	FAS	EFF_T2	Summary of Reconciliation of Actigraphy and Diary Data	Footnote: 3 Rules N is the number of subjects at each visit	SAC
Actigraphy Diary – Feasibility Measures					
2.146.	FAS	EFF_T4	Summary of Actigraphy Diary (Feasibility) Data		SAC
Device Impact– Feasibility Measures					
2.147.	FAS	EFF_T5	Summary of Device Impact		SAC
ALSFRS-R					
2.148.	FAS	EFF_T1	Summary of ALSFRS-R Score	Paginate by Total Score, Gross Motor Domain, Fine Motor Domain, Bulbar Domain and Respiratory Domain	SAC
2.149.	FAS	EFF_T1	Summary of Change from Baseline of ALSFRS-R Score	Same as Above	SAC
2.150.	FAS	EFF_T1	Summary of Relative Rate of Decline of ALSFRS-R Score	Same as Above	SAC
2.151.	FAS	EFF_T1	Summary of Monthly Rate of Decline of ALSFRS-R Score	Same as Above	SAC
FVC					
2.152.	FAS	PD1	Summary of FVC		SAC
2.153.	FAS	PD1	Summary of Change from Baseline of FVC		SAC
2.154.	FAS	PD1	Summary of Relative Rate of Decline of FVC		SAC
2.155.	FAS	PD1	Summary of Monthly Rate of Decline of FVC		SAC

9.11.5. Exploratory Figures

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Actigraphy					
2.1.	FAS	EFF_F1	Plot of Absolute Values of Time Spent Active and Absolute Value of ALSFRS-R v/s Time (All data)	Plot Time on X Axis, Endpoint on Y axis and ALSFRS on RHS of Y axis ALSFRS: Total, Fine Motor and Gross Motor	SAC
2.2.	FAS	EFF_F1	Plot of Absolute Values of Time Spent Active and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.3.	FAS	EFF_F1	Plot of Relative Rate of Decline of Time Spent Active and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.4.	FAS	EFF_F1	Plot of Relative Rate of Decline of Time Spent Active and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.5.	FAS	EFF_F1	Plot of Absolute Values of Overall Time Spent Sedentary Not Lying and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.6.	FAS	EFF_F1	Plot of Absolute Values of Overall Time Spent Sedentary Not Lying and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.7.	FAS	EFF_F1	Plot of Relative Rate of Decline of Overall Time Spent Sedentary Not Lying and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	FAS	EFF_F1	Plot of Relative Rate of Decline of Overall Time Spent Sedentary Not Lying and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.9.	FAS	EFF_F1	Plot of Absolute Values of Time Spent Lying and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.10.	FAS	EFF_F1	Plot of Absolute Values of Time Spent Lying and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.11.	FAS	EFF_F1	Plot of Relative Rate of Decline of Time Spent Lying and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.12.	FAS	EFF_F1	Plot of Relative Rate of Decline of Time Spent Lying and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.13.	FAS	EFF_F1	Plot of Absolute Values of Time Spent Sedentary and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.14.	FAS	EFF_F1	Plot of Absolute Values of Time Spent Sedentary and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.15.	FAS	EFF_F1	Plot of Relative Rate of Decline of Time Spent Sedentary and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.16.	FAS	EFF_F1	Plot of Relative Rate of Decline of Time Spent Sedentary and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.17.	FAS	EFF_F1	Plot of Absolute Values of Total Activity Score Day/Night and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.18.	FAS	EFF_F1	Plot of Absolute Values of Total Activity Score Day/Night and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.19.	FAS	EFF_F1	Plot of Relative Rate of Decline of Total Activity Score Day/Night and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.20.	FAS	EFF_F1	Plot of Relative Rate of Decline of Total Activity Score Day/Night and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.21.	FAS	EFF_F1	Plot of Absolute Values of Total Activity Score – 24 Hour and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.22.	FAS	EFF_F1	Plot of Absolute Values of Total Activity Score – 24 Hour and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.23.	FAS	EFF_F1	Plot of Relative Rate of Decline of Total Activity Score – 24 Hour and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.24.	FAS	EFF_F1	Plot of Relative Rate of Decline of Total Activity Score – 24 Hour and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.25.	FAS	EFF_F1	Plot of Absolute Values of Maximum Score (1 min – 24 Hour Window) and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.26.	FAS	EFF_F1	Plot of Absolute Values Maximum Score (1 min – 24 Hour Window) and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.27.	FAS	EFF_F1	Plot of Relative Rate of Decline of Maximum Score (1 min – 24 Hour Window) and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.28.	FAS	EFF_F1	Plot of Relative Rate of Decline of Maximum Score (1 min – 24 Hour Window) and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.29.	FAS	EFF_F1	Plot of Absolute Values of Active Periods (Number) and Absolute Value of ALSFRS-R v/s Time (All data)	5-day time lines (1 for each category) vs ALSFRS on 1 page 5-night time lines vs ALSFRS on 2nd page	SAC
2.30.	FAS	EFF_F1	Plot of Absolute Values of Active Periods (Number) and Absolute Value of ALSFRS-R v/s Time (Quality data)	5-day time lines (1 for each category) vs ALSFRS on 1 page 5-night time lines vs ALSFRS on 2nd page	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.31.	FAS	EFF_F1	Plot of Active Periods (Number)	Plot of number (y) over time (x)	SAC
2.32.	FAS	EFF_F1	Plot of Active Periods (Number) and ALSFRS-R v/s Time	5-day time lines (1 for each category) vs ALSFRS on 1 page 5-night time lines vs ALSFRS on 2nd page	SAC
2.33.	FAS	EFF_F1	Plot of Absolute Values of Active Periods (Duration) and Absolute Value of ALSFRS-R v/s Time (All data)	Plot Time on X Axis, Endpoint on Y axis and ALSFRS on RHS of Y axis ALSFRS: Total, Fine Motor and Gross Motor	SAC
2.34.	FAS	EFF_F1	Plot of Absolute Values of Active Periods (Duration) and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.35.	FAS	EFF_F1	Plot of Relative Rate of Decline of Active Periods (Duration) and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.36.	FAS	EFF_F1	Plot of Relative Rate of Decline of Active Periods (Duration) and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.37.	FAS	EFF_F2	Scatter Plot of Absolute Values of Actigraphy endpoints and Absolute Value of Total ALSFRS-R	Plot the individual values as dots	SAC
2.38.	FAS	EFF_F2	Scatter Plot of Change from Baseline of Actigraphy endpoints and Change from Baseline of Total ALSFRS-R	Plot the individual values as dots	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.39.	FAS	EFF_F2	Scatter Plot of Slope of Actigraphy endpoints and Slope of Total ALSFRS-R	Plot the individual values as dots	SAC
2.40.	FAS	EFF_F2	Scatter Plot of Absolute Values of Actigraphy endpoints and Absolute Value of gross motor domain of ALSFRS-R	Plot the individual values as dots	SAC
2.41.	FAS	EFF_F2	Scatter Plot of Change from Baseline of Actigraphy endpoints and Change from Baseline of gross motor domain of ALSFRS-R	Plot the individual values as dots	SAC
2.42.	FAS	EFF_F2	Scatter Plot of Slope of Actigraphy endpoints and Slope of gross motor domain of ALSFRS-R	Plot the individual values as dots	SAC
2.43.	FAS	EFF_F2	Scatter Plot of Absolute Values of Actigraphy endpoints and Absolute Value of fine motor domain of ALSFRS-R	Plot the individual values as dots	SAC
2.44.	FAS	EFF_F2	Scatter Plot of Change from Baseline of Actigraphy endpoints and Change from Baseline of fine motor domain of ALSFRS-R	Plot the individual values as dots	SAC
2.45.	FAS	EFF_F2	Scatter Plot of Slope of Actigraphy endpoints and Slope of fine motor domain of ALSFRS-R	Plot the individual values as dots	SAC
Night Time Rest Endpoints					
2.46.	FAS	EFF_F1	Plot of Absolute Values of Number Night Time Movement and Absolute Value of ALSFRS-R v/s Time (All data)	Plot Time on X Axis, Endpoint on Y axis and ALSFRS on RHS of Y axis ALSFRS: Total	SAC
2.47.	FAS	EFF_F1	Plot of Absolute Values of Number Night Time Movement and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.48.	FAS	EFF_F1	Plot of Relative Rate of Decline of Number Night Time Movement and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.49.	FAS	EFF_F1	Plot of Relative Rate of Decline of Number Night Time Movement and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.50.	FAS	EFF_F1	Plot of Absolute Values of Night-time Rest Efficiency and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.51.	FAS	EFF_F1	Plot of Absolute Values of Night-time Rest Efficiency and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.52.	FAS	EFF_F1	Plot of Relative Rate of Decline of Night-time Rest Efficiency and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.53.	FAS	EFF_F1	Plot of Relative Rate of Decline of Night-time Rest Efficiency and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.54.	FAS	EFF_F1	Plot of Absolute Values of Rest Fragmentation Index and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.55.	FAS	EFF_F1	Plot of Absolute Values of Rest Fragmentation Index and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.56.	FAS	EFF_F1	Plot of Relative Rate of Decline of Rest Fragmentation Index and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.57.	FAS	EFF_F1	Plot of Relative Rate of Decline of Rest Fragmentation Index and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.58.	FAS	EFF_F1	Plot of Absolute Values of Duration Movement Episodes and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.59.	FAS	EFF_F1	Plot of Absolute Values of Duration Movement Episodes and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.60.	FAS	EFF_F1	Plot of Relative Rate of Decline of Duration Movement Episodes and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.61.	FAS	EFF_F1	Plot of Relative Rate of Decline of Duration Movement Episodes and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.62.	FAS	EFF_F2	Scatter Plot of Absolute Values of Night Rest Endpoints and Absolute Value of Total ALSFRS-R	Plot the individual values as dots	SAC
2.63.	FAS	EFF_F2	Scatter Plot of Change from Baseline of Night Rest Endpoints and Change from Baseline of Total ALSFRS-R	Plot the individual values as dots	SAC
2.64.	FAS	EFF_F2	Scatter Plot of Slope of Night Rest Endpoints and Slope of Total ALSFRS-R	Plot the individual values as dots	SAC
Heart Rate Variability					
2.65.	FAS	EFF_F1	Plot of Absolute Values of Mean HRV LF/HF and Absolute Value of ALSFRS-R v/s Time (All data)	Plot Time on X Axis, Endpoint on Y axis and ALSFRS on RHS of Y axis ALSFRS: Total	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.66.	FAS	EFF_F1	Plot of Relative Rate of Decline of Mean HRV LF/HF and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.67.	FAS	EFF_F1	Plot of Absolute Values of Mean RMSSD and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.68.	FAS	EFF_F1	Plot of Absolute Values of Mean RMSSD and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.69.	FAS	EFF_F1	Plot of Relative Rate of Decline of Mean RMSSD and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.70.	FAS	EFF_F1	Plot of Relative Rate of Decline of Mean RMSSD and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.71.	FAS	EFF_F1	Plot of Absolute Values of Variance HRV LF/HF and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.72.	FAS	EFF_F1	Plot of Relative Rate of Decline of Variance HRV LF/HF and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.73.	FAS	EFF_F1	Plot of Absolute Values of Variance RMSSD and Absolute Value of ALSFRS-R v/s Time (All data)	Same as Above	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.74.	FAS	EFF_F1	Plot of Absolute Values of Variance RMSSD and Absolute Value of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.75.	FAS	EFF_F1	Plot of Relative Rate of Decline of Variance RMSSD and Relative Rate of Decline of ALSFRS-R v/s Time (All data)	Same as Above	SAC
2.76.	FAS	EFF_F1	Plot of Relative Rate of Decline of Variance RMSSD and Relative Rate of Decline of ALSFRS-R v/s Time (Quality data)	Same as Above	SAC
2.77.	FAS	EFF_F2	Scatter Plot of Absolute Values of HRV endpoints (LF/HF) and Absolute Value of Total ALSFRS-R	Plot individual values as dots	SAC
2.78.	FAS	EFF_F2	Scatter Plot of Absolute Values of RMSSD and Absolute Value of Total ALSFRS-R	Plot individual values as dots	SAC
2.79.	FAS	EFF_F2	Scatter Plot of Change from Baseline of HRV endpoints (LF/HF) and Change from Baseline of Total ALSFRS-R	Plot individual values as dots	SAC
2.80.	FAS	EFF_F2	Scatter Plot of Change from Baseline of RMSSD and Change from Baseline of Total ALSFRS-R	Plot individual values as dots	SAC
2.81.	FAS	EFF_F2	Scatter Plot of Slope of HRV endpoints (LF/HF) and Slope of Total ALSFRS-R	Plot individual values as dots	SAC
2.82.	FAS	EFF_F2	Scatter Plot of Slope of RMSSD and Slope of Total ALSFRS-R	Plot individual values as dots	SAC
Speech					
2.83.	FAS	EFF_F1	Plot of Absolute Values of Speech Endpoints and Absolute Values of ALSFRS-R v/s Time	Plot Time on X Axis, Endpoint on Y axis and ALSFRS on RHS of Y axis ALSFRS: Total Bulbar and Respiratory Domain	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.84.	FAS	EFF_F1	Plot of Relative Rate of decline of Speech Endpoints and Relative Rate of decline of ALSFRS-R v/s Time	Same as Above	SAC
2.85.	FAS	EFF_F2	Scatter Plot of Absolute Values of Speech endpoints and Absolute Value of ALSFRS-R	Plot individual values as dots	SAC
2.86.	FAS	EFF_F2	Scatter Plot of Change from Baseline of Speech endpoints and Change from Baseline of ALSFRS-R	Plot individual values as dots	SAC
2.87.	FAS	EFF_F2	Scatter Plot of Slope of Speech endpoints and Slope of ALSFRS-R	Plot individual values as dots	SAC
2.88.	FAS	EFF_F2	Scatter Plot of Absolute Values of Speech endpoints and Absolute Values of FVC	Plot individual values as dots	SAC
2.89.	FAS	EFF_F2	Scatter Plot of Change from Baseline of Speech endpoints and Change from Baseline of FVC	Plot individual values as dots	SAC
2.90.	FAS	EFF_F2	Scatter Plot of Slope of Speech endpoints and Slope of FVC	Plot individual values as dots	SAC
ALSFRS-R					
2.91.	FAS	EFF_F1	Mean (SE) Plot of ALSFRS-R Score	• Paginate by Total Score, Gross Motor Domain, Fine Motor Domain, Bulbar Domain and Respiratory Domain • Only 1 y axis	SAC
2.92.	FAS	EFF_F1	Mean (SE) Plot of Relative Rate of Decline of ALSFRS-R Score	• Paginate by Total Score, Gross Motor Domain, Fine Motor Domain, Bulbar Domain and Respiratory Domain • Only 1 y axis	SAC

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
FVC					
2.93.	FAS	EFF_F1	Mean (SE) Plot of FVC	Only 1 y axis	SAC
2.94.	FAS	EFF_F1	Mean (SE) Plot of Relative Rate of FVC	Same as above	SAC

9.11.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE1CP	Summary of All Adverse Events	Add a Footnote: Only those AEs and SAEs which, in the opinion of the investigator, are related to a protocol-mandated procedure or one of the devices used in the study will be reported	SAC
3.2.	Safety	AE1CP	Summary of Serious Adverse Events		SAC
3.3.	Safety	AE1CP	Summary of Adverse Events Leading to Withdrawal from Study		SAC
3.4.	Safety	AE5A	Summary of Adverse Events by Maximum Intensity		SAC
3.5.	Safety	SAFE_T1	Summary of Deaths		SAC

9.11.7. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screen Failure	ES7	Listing of Reasons for Screen Failure		SAC
2.	FAS	ES2	Listing of Reasons for Study Withdrawal		SAC
Protocol Deviations					
3.	FAS	DV2	Listing of Important Protocol Deviations		SAC
4.	FAS	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
5.	Enrolled	SA3a	Listing of Subjects Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
6.	FAS	DM2	Listing of Demographic Characteristics		SAC
7.	FAS	DM10	Listing of Race		SAC
Prior and Concomitant Medications					
8.	FAS	MH3	Listing of Medical Conditions		SAC
9.	FAS	CP_CM3	Listing of Concomitant Medications		SAC
Adverse Events					
10.	Safety	CP_AE8	Listing of All Adverse Events		SAC
11.	Safety	CP_AE8	Listing of Drug Related Adverse Events		SAC
12.	Safety	CP_AE8	Listing of Serious Adverse Events		SAC
13.	Safety	CP_AE8	Listing of Adverse Events Leading to Withdrawal from Study		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
14.	Safety	CP_AE8	Listing of Adverse Events by Maximum Intensity		SAC
Death					
15.	Safety	SAFE_L1	Listing of Deaths		SAC

9.11.8. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
16.	Safety	AE2	Listing of Relationship between System Organ Class and Verbatim Text		SAC
Actigraphy					
17.	FAS	PD11	Listing of Wear Time - Derived Data (All data)		SAC
18.	FAS	PD11	Listing of Wear Time - Derived Data (Quality Data data)		SAC
19.	FAS	PD11	Listing of Duration of Day Time Wear Time (All data)		SAC
20.	FAS	PD11	Listing of Duration of Day Time Wear Time (Quality data)		SAC
21.	FAS	PD11	Listing of Duration of Night Time Wear Time (All data)		SAC
22.	FAS	PD11	Listing of Duration of Night Time Wear Time (Quality data)		SAC
23.	FAS	PD11	Listing of Time Spent Active – Raw Data		SAC
24.	FAS	PD11	Listing of Time Spent Active – Derived Data (All data)		SAC
25.	FAS	PD11	Listing of Time Spent Active – Derived Data (Quality data)		SAC
26.	FAS	PD11	Listing of Over All Time Spent sedentary not Lying – Raw Data		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
27.	FAS	PD11	Listing of Over All Time Spent sedentary not Lying – Derived Data (All data)		SAC
28.	FAS	PD11	Listing of Over All Time Spent sedentary not Lying – Derived Data (Quality data)		SAC
29.	FAS	PD11	Listing of Over All Time Spent Lying – Raw Data		SAC
30.	FAS	PD11	Listing of Over All Time Spent Lying – Derived Data (All data)		SAC
31.	FAS	PD11	Listing of Over All Time Spent Lying – Derived Data (Quality data)		SAC
32.	FAS	PD11	Listing of Over All Time Spent Sedentary – Raw Data		SAC
33.	FAS	PD11	Listing of Over All Time Spent Sedentary – Derived Data (All data)		SAC
34.	FAS	PD11	Listing of Over All Time Spent Sedentary – Derived Data (Quality data)		SAC
35.	FAS	PD11	Listing of Total Activity Score Day/Night – Raw Data		SAC
36.	FAS	PD11	Listing of Total Activity Score Day/Night – Derived Data (All data)		SAC
37.	FAS	PD11	Listing of Total Activity Score Day/Night – Derived Data (Quality data)		SAC
38.	FAS	PD11	Listing of Total Activity Score – 24 Hour – Raw Data		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
39.	FAS	PD11	Listing of Total Activity Score – 24 Hour – Derived Data (All data)		SAC
40.	FAS	PD11	Listing of Total Activity Score – 24 Hour – Derived Data (Quality data)		SAC
41.	FAS	PD11	Listing of Maximum Score from 1 – 24 Hour Window -Raw Data		SAC
42.	FAS	PD11	Listing of Maximum Score from 1 – 24 Hour Window - Derived Data (All data)		SAC
43.	FAS	PD11	Listing of Maximum Score from 1 – 24 Hour Window - Derived Data (Quality data)		SAC
44.	FAS	PD11	Listing of Active Periods (Numbers) – Raw Data		SAC
45.	FAS	PD11	Listing of Active Periods (Numbers) – Derived Data (All data)		SAC
46.	FAS	PD11	Listing of Active Periods (Numbers) – Derived Data (Quality data)		SAC
47.	FAS	PD11	Listing of Active Periods (Duration) – Raw Data		SAC
48.	FAS	PD11	Listing of Active Periods (Duration) – Derived Data (All data)		SAC
49.	FAS	PD11	Listing of Active Periods (Duration) – Derived Data (Quality data)		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Night Time Rest Endpoints					
50.	FAS	PD11	Listing of Number Night Time Movement Episodes/Hr (All data)		SAC
51.	FAS	PD11	Listing of Number Night Time Movement Episodes/Hr (Quality data)		SAC
52.	FAS	PD11	Listing of Percent Time Night-time Rest Efficiency (All data)		SAC
53.	FAS	PD11	Listing of Percent Time Night-time Rest Efficiency (Quality data)		SAC
54.	FAS	PD11	Listing of Rest Fragmentation Index (All data)		SAC
55.	FAS	PD11	Listing of Rest Fragmentation Index (Quality data)		SAC
56.	FAS	PD11	Listing of Average Duration Movement Episodes (All data)		SAC
57.	FAS	PD11	Listing of Average Duration Movement Episodes (Quality data)		SAC
Heart Rate Variability					
58.	FAS	PD11	Listing of Mean HRV LF/HF (All data)		SAC
59.	FAS	PD11	Listing of Mean RMSSD (All data)		SAC
60.	FAS	PD11	Listing of Mean RMSSD (Quality data)		SAC
61.	FAS	PD11	Listing of Variance HRV LF/HF (All data)		SAC
62.	FAS	PD11	Listing of Variance RMSSD (All data)		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
63.	FAS	PD11	Listing of Variance RMSSD (Quality data)		SAC
64.	FAS	PD11	Listing of HRV data from McLaren		SAC
Speech					
65.	FAS	PD11	Listing of Speech Endpoints	Also include comments	SAC
Actigraphy Diary Data					
66.	FAS	PD11	Listing of Actigraphy Diary (Feasibility) Data	For categorical data add the test and the categorical results	SAC
Device Impact					
67.	FAS	PD11	Listing of Device Impact	For categorical data add the test and the categorical results	SAC
Neurological Exam					
68.	FAS	PD11	Listing of Neurological Exams	For categorical data add the test and the categorical results, add location and laterality	
ALSFRS-R					
69.	FAS	PD11	Listing of ALSFRS-R		SAC
FVC					
70.	FAS	PD11	Listing of FVC		SAC