Title: An open label, single site, 48 week, randomised controlled trial evaluating the safety and efficacy of Exenatide once-weekly in the treatment of patients with Multiple system Atrophy

NCT Number: NCT04431713

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The Exenatide MSA Trial
Statistical Analysis Plan

Version 1.0

6 April 2023

1 Administrative information

1.1 Trial full title

A Phase IIa, open label, single-site, 48 week randomised controlled trial evaluating the safety and efficacy of Exenatide once-weekly in the treatment of patients with Multiple System Atrophy.

1.2 Purpose

This Statistical Analysis Plan describes a protocol-specified analysis of the investigational medicinal product Trial.

1.3 Protocol version

This SAP has been written based on information contained in the study protocol version 4.0, dated 14 Sep 2021. Full details of the trial design, population, intervention, comparison and outcome variables may be found in the protocol.

1.4 Trial registration

This trial was prospectively registered with ClinicalTrials.gov (NCT04431713).

1.5 Authorship

This SAP has been written by Dr Chen Qu and Professor Gareth Ambler (Lead Statistician), following the guidelines of Gamble *et al* (JAMA 2017. doi:10.1001/jama.2017.18556).

1.6 SAP revisions

There have been no revisions. This is version 1.0.

1.7 Signatures

The undersigned confirm that the following Statistical Analysis Plan has been agreed and accepted and that the Trial Statistician agrees to conduct the analysis in compliance with the approved Statistical Analysis Plan. Major deviations from the Plan will be agreed in advance before implementation. All deviations from the Plan will be explained, documented and reported accordingly.

Authorised by:	**Signature**	**Date**
Professor Thomas Foltynie Chief Investigator		
Professor Gareth Ambler Lead Statistician		
Dr Christopher Kobylecki IDMC Chair		
Dr Alan Whone TSC Chair		

2 Table of Contents

3 Introduction

3.1 Background

Multiple System Atrophy (MSA) has a prevalence of 4.4 in 100,000 individuals and there are no effective treatments that can slow down or modify the course of disease progression. There is thus an urgent unmet need for novel treatments that may slow or halt disease progression in MSA. Recent studies have shown encouraging results of using Exenatide in further neurodegenerative diseases. A simple randomised trial was therefore needed to compare use of Exenatide against standard treatment option in MSA. A full description of the trial is contained in the protocol.

3.2 Principle research objectives

To collect pilot data from which to estimate the effectiveness of Exenatide in modifying disease progression of patients with MSA. The primary endpoint will be the difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks comparing exenatide to best medically treated patients. Secondary measures will include adverse event reports, self-completed questionnaires, and blood test results.

4 Study Method

4.1 Trial design

This is a non-commercial, open label trial of a licensed drug designed to primarily provide preliminary efficacy and safety data for the use of Exenatide in MSA. This will be a simple parallel group design and include a 48-week exposure period. Detailed evaluations will take place at Screening, Baseline, 12, 24, 36, 48 and 96 weeks.

4.2 Randomisation

Patients will be randomly assigned in a 1:1 ratio to receive the Exenatide together with standard treatment options or to receive the standard treatment options alone. Randomisation will be stratified by MSA phenotype strata using block randomisation to enable achievement of approximately equal numbers in each group. Full details can be found in the randomisation protocol.

4.3 Sample size

The recent rasagiline for MSA (MSA-Ras) trial evaluated rasagiline versus placebo using the UMSARS total (Parts 1 and II) as the primary efficacy measure after 48 weeks treatment. Patients in the placebo group declined by mean 7.8 points (SD 10.4 – Werner et al. 2015).

Therefore, on the basis of this previously collected data and with a two-sided 5% significance level, we estimated that a sample size of 40 patients (20 per group) would be required to detect a difference of 5 total UMSARS points between the two groups, assuming a correlation between baseline and final disease severity of 0.85. These calculations were based on a common SD of 10.4, 80% power and an

overall type 1 error rate of 5%. A 5-point difference between groups would be a clinically important effect size. Based on a 20% dropout rate as reported from previous trials, the sample size would be 50 (25 per arm).

5 Statistical Principles

5.1 Confidence intervals and p-values

All statistical tests and confidence intervals will be 2-sided. Significance will be considered at the 5% level and confidence intervals will be at the 95% level.

5.2 Adherence to intervention

Compliance will be assessed by directly questioning patients at each visit, and if applicable carers will also be asked to provide estimates of compliance, along with review of the drug administration diary. Reasons for non-compliance will be sought and addressed as far as possible at each follow up visit.

5.3 Analysis Populations

The 'intention-to-treat' population will include all randomised patients according to the treatment to which they were randomised to receive. Any patients that have withdrawn from the trial, and withdrawn permission to keep and use their data, will be necessarily excluded. The 'per-protocol' population will also exclude any patients randomised to standard treatment who have sourced exenatide outside of the trial.

6 Trial Population

6.1 Recruitment and retention

A CONSORT diagram will be presented to provide a detailed description of participant numbers at each time point during the trial. In addition, a table summarising the number of patients who have been lost to follow up at each stage of the trial and reasons for loss to follow up (if supplied) will be presented.

6.2 Baseline characteristics

The demographic information collected at baseline will be presented in a table summarised separately by study arm. Numerical variables will be summarised using either means and standard deviations or medians and interquartile ranges. Categorical variables will be summarised using numbers and proportions. The number of missing observations will be reported. No statistical tests will be performed to assess baseline differences between study arms.

The following baseline characteristics of patients will be summarised by randomised allocation:

a) Age
b) Sex
c) Ethnicity
d) Weight
e) Physical Examination
f) Neurological Examination
g) Vital Signs
h) HOMA index

7 Analysis

7.1 Outcomes

7.1.1 Primary outcome

The primary outcome is the total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks.

7.1.2 Secondary outcomes

- Patients with loss of independent ambulation by the end of the study, defined by a score of 4 in UMSARS-I item 7 (walking);
- Multiple System Atrophy health-related Quality of life (MSA-QoL) scale at week 48;
- UMSARS score (Parts III and IV) at week 48;
- Anti-parkinsonian or anti-orthostatic hypotension drugs comparing exenatide at week 48;
- The number of falls at week 48;
- Patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling) at week 48;
- Clinical global impression (CGI) at week 48;
- Montreal Cognitive Assessment (MoCA) scores at week 48;
- Safety of exenatide in MSA based on Adverse event reporting.

7.1.3 Exploratory outcomes

- UMSARS score (Parts I and II) at 96 weeks;
- MSA-QoL scale at 96 weeks;
- UMSARS score (Parts III and IV) at 96 weeks;
- The use of Anti-parkinsonian or anti-orthostatic hypotension drugs at 96 weeks;
- The number of falls at 96 weeks;
- Patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling) at 96 weeks;
- CGI and MoCA scores at 96 weeks.

Serum will be collected at baseline and 12 weeks, 24 weeks, 36 weeks, 48 weeks and 96 weeks for biomarker analysis. CSF will be collected at baseline and 48 weeks for biomarker analysis. Further details on the scoring and ranges of all outcomes can be found in the Appendix.

7.1.4 Timing of outcomes

Table 1 provides an overview of primary and secondary outcomes and the time points at which they will be collected.

Table 1: Data collection measures and time points.

Measure	0	4*	12	24	36	48	58*	96
Screening measures								
Physical Examination	✓		✓	✓	✓	✓		✓
Neurological Examination	✓			✓		✓		✓
Vital Signs including weight	✓		✓	✓	✓	✓		✓
Fasting blood test	✓			✓		✓		
Eligibility confirmation	✓							
Primary outcome								
UMSARS Part 1, 3 and 4	✓		✓	✓	✓	✓		✓
UMSARS Part 2	✓		✓	✓	✓	✓		✓
Secondary outcomes								
MSA-QoL scale	✓					✓		✓
MoCA	✓		✓	✓	✓	✓		✓
Serum collection	✓		✓	✓	✓	✓		✓
CSF collection	✓					✓		
Other measures								
BDI-II	✓		✓	✓	✓	✓		✓
COMPASS Select	✓			✓		✓		✓
COMPASS Change				✓		✓		✓
Timed Motor Tests	✓			✓		✓		✓
The Unified Dystonia Rating	✓		✓	✓	✓	✓		✓
IMP administration	✓			✓	✓	✓		
Adverse Events/SAEs review	✓	✓	✓	✓	✓	✓	✓	
Concomitant Medication	✓	✓	✓	✓	✓	✓		

*: Telephone call

7.2 Primary outcome Analysis

The primary outcome is the total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks. The primary analysis will compare exenatide patients to be best medically treated patients using a two-level mixed model that includes the total UMSARS scores from four time-points (12 weeks, 24 weeks, 36 weeks and 48 weeks) with interaction terms between the intervention and time-point indicator variables to enable estimation of the effect of intervention at 48 weeks. This model will also adjust for baseline UMSARS score and MSA subtype using fixed effects.

In detail, the primary analysis will involve fitting the model

$$UMSARS_{ij} = \beta_0 + \beta_1 TRT_i + \beta_{2j} TIME_j + \beta_{3j} TRT_i \times TIME_j + \beta_4 UMSARS0_i + \beta_5 MSA_i + u_i + \epsilon_{ij}$$

to patients $i = 1, .., 48$ and time-points $j = 12, 24, 38 \text{ and } 48$ weeks, where $UMSARS_{ij}$ and $UMSARS0_i$ are the UMSARS total scores for patient i at time-point j and baseline respectively, TRT_i is the intervention group indicator (0=standard; 1=Exenatide), $TIME_j$ are time-point indicators, MSA_i is a MSA subtype indicator, and $\mathrm{u_i} \sim N(0, \sigma_u^2)$ and $\epsilon_{\mathrm{ij}} \sim N(0, \sigma^2)$ are error terms. All modelling assumptions will be checked.

7.3 Secondary outcome analyses

The effect of the intervention on secondary outcomes will be assessed using appropriate single-level regression models, i.e. linear regression models for numerical outcomes, logistic regression models for binary outcomes, and Poisson models for count outcomes (or negative binomial models, if their use is indicated). All models will be adjusted for MSA subtype; models for numerical outcomes will also be adjusted for baseline outcomes if available. All analyses of secondary and other outcomes should be considered as supportive analyses.

7.4 Exploratory outcome analyses

The effect of the intervention on exploratory outcomes will be assessed using the same models as used for the secondary outcomes.

7.5 Sensitivity analyses

Several sensitivity analyses will be performed for the primary outcome. These are:

- The effect of the intervention will be assessed using a single-level linear regression model, adjusted for MSA subtype and baseline severity.
- If adherence is deemed to be an issue, per-protocol and complier average causal effect (CACE) analyses will be performed.

7.6 Subgroup analyses

There are no planned subgroup analyses.

7.7 Missing data

Withdrawals from the study, loss to follow up and other missing outcome data will be summarised separately by randomised arm. Potential bias due to missing data will be investigated by comparing the baseline characteristics of patients with and without missing values. From this, predictors of missingness may be identified and used to perform an additional analysis that includes these predictors as covariates in the primary analysis model.

Multiple imputation may also be performed, if deemed appropriate. The imputation model will include outcome data from all time-points, as well as baseline characteristics.

In addition, imputation may be performed under the assumption that the missing data are MNAR. Two strategies may be investigated:

- Delta-adjustment: This approach initially uses (standard) multiple imputation to impute missing values but then the imputed values are modified using a 'delta-adjustment'. Different values of delta may be specified, and these can differ by trial arm.
- Reference-based sensitivity analyses: A range of different assumptions regarding the missing data can be investigated using this approach, which is implemented in the Stata package mimix (Cro et al, 2016).

7.8 Adverse event reporting

The number, nature and severity of serious adverse events (if any) will be reported separately by study arm at each follow up time point. The number of patients who experience adverse events will likewise be reported separately by study arm.

7.9 Software

All the statistical analysis will be performed using Stata version 17 (or above).

8 Summary of Changes

This Statistical Analysis Plan does not propose any major changes to the statistical approach described in the protocol. Of note, is that the primary analysis proposed in this document uses outcomes from four time-points; however, the effect of intervention will still be estimated at 48 weeks. Any changes to the Statistical Analysis Plan made after this document has been signed off need to be recorded. In addition, significant changes will need to be approved before implementation.

9 Appendix - Questionnaires scoring

9.1 The Unified Multiple System Atrophy Rating Scale (UMSARS) score

The Unified MSA Rating Scale (UMSARS) comprises four components: a historical review of disease-related impairments (Part I, 12 items), motor examination (Part II, 14 items), autonomic examination (Part III), and global disability scale (Part IV). A single score using a 0 (no impairment) to 4 (severe impairment) scale was generated for each item. UMSARS total is calculated as the sum of the Part I and Part II items; all items must be answered to have a score.

- Wenning GK, Tison F, et al.. Multiple System Atrophy Study G (2004) Development and validation of the unified multiple system atrophy rating scale (UMSARS). Mov Disord 19:1391–1402.

9.2 MSA health-related Quality of life (MSA-QoL) scale

MSA-QoL is a validated 40 item self-completed questionnaire (on a 5-point scale ranging from 0-4). Score is calculated as the sum of the items. Missing values for MSA-QoL will be scored as zero unless more than four items are missing, in which case the participant is to be excluded.

- Schrag A, et al.. Measuring health-related quality of life in MSA: the MSA-QoL. Mov Disord. 2007;22(16):2332–2338.

9.3 Clinical Global Impression - Improvement (CGI-I)

CGI-I is an observer-rated score (on a 8-point scale ranging from 0-7).

- https://en.wikipedia.org/wiki/Clinical_Global_Impression

9.4 Montreal Cognitive Assessment (MoCA)

MoCA is a screening test for assessing cognitive impairment. It is a 30-question test and cover eight cognitive domains. Total scores on the MoCA range from 0 to 30, a score of 26 and above is considered to be normal.

- Nasreddine ZS, Phillips NA, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–699