NOVARTIS

Medical Affairs

[Exelon/Rivastigmine]

Clinical Trial Protocol [CENA713DJP02]
NCT02703636

[A 24-week, open-label, multicenter study to evaluate the efficacy, safety and tolerability of Exelon patch (Rivastigmine) with 1-step titration in patients with mild to moderate Alzheimer's disease (MMSE 10–23) switched directly from cholinesterase inhibitors (Donepezil, Galantamine)]

Statistical Analysis Plan (SAP)

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Document type:	SAP Documentation
Document status:	Addendum 1
Release date:	23-January-2019
Number of pages:	35

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-Mar-16	Prior to FPFV	NA	Final 2.0	NA
7-June-2018	Prior to DBL	-Calculation of Compliance data updated -Added imputation rules for AE and CM -Added SAS code for Step-wise Regression Model -Updated PD list	Amendment 1	Section 2.4.1 Section 5.1 Section 5.3.4 Section 5.2
12-June-2018	Prior to DBL	- 2 subgroup analysis categories added for patients satisfying inclusion criteria	Amendment 2	Section 2.2.1.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
23-January-2019	Post DBL	-Removed the screening time point from the subgroup analysis for Patients satisfying protocol inclusion criteria in Section 2.2.1.1 and also updated the categories for the same.	Addendum 1	Section 2.1.1.5 Section 2.2.1.1
		-Added subgroup 'weight' in the 2nd point in Amongst AE's of Special Interest in Section 2.2.1.2		Section 2.2.1.2
		-Added analysis for Only concomitant medications in Section 2.4.2.		Section 2.4.2.
		-Added change from baseline for laboratory parameters in section 2.7.1.		Section 2.7.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		- Divided the Patient-reported outcomes into Patient reported outcomes, Caregiver reported outcomes and clinical reported outcomes.		Section 2.8 Added section 2.9 and 2.10
		-Removed the word 'Stepwise' from the analysis described in Section 2.8.1.1 for QOL-AD total score		Section 2.8.1.1
		-Added details Section 4.		Section 4

Table of contents

Table of contents 6
List of abbreviations 8
1 Introduction 9
1.1 Overall study design 9
1.2 Study objectives and endpoints 10
2 Statistical methods 12
2.1 Data analysis general information 12
2.1.1 General definitions 12
2.2 Analysis sets 13
2.2.1 Subgroup of interest 14
2.3 Patient disposition, demographics and other baseline characteristics 16
2.3.1 Patient disposition 16
2.3.2 Medical history/current medical condition 16
2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance) 16
2.4.1 Study treatment exposure / compliance 16
2.4.2 Prior, concomitant and post therapies 17
2.5 Analysis of the primary objective 18
2.5.1 Primary endpoint 18
2.5.2 Statistical hypothesis, model, and method of analysis 18
2.5.3 Handling of missing values/censoring/discontinuations 18
2.5.4 Supportive analyses 18
2.6 Analysis of secondary objectives 19
2.6.1 Efficacy endpoints 19
2.6.2 Safety analyses 19
2.7 Other safety data 21
2.7.1 Laboratory data 21
2.7.2 Vital signs 22
2.7.3 ECG 23
2.8 Patient-reported outcomes 23
2.9 Caregiver-reported outcomes 23
2.10 Clinician-reported outcomes 24
2.11 Other analyses 24
2.11.1 Treatment retention during the last 8 weeks of maintenance period: 24
[redacted] 25

[redacted] [redacted] 25
[redacted] [redacted] 25
2.13 Interim analysis 25
3 Sample size calculation 26
4 Change to protocol specified analyses 26
5 Appendix 26
5.1 Imputation rules 26
5.2 Rule of exclusion criteria of analysis sets 29
5.3 SAS codes for statistical analyses 34
5.3.1 Mixed Model Repeated Measures (MMRM) analysis 34
5.3.2 MMRM model of subgroup analysis 34
5.3.3 Student's t-test 35
5.3.4 Regression Model 35

List of abbreviations

AE	Adverse event
CSR	Clinical Study report
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
o.d.	Once Daily
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods which will be used in the phase IV post-marketing clinical trial CENA713DJP02. The statistical analysis described in this SAP is based on the final study protocol and will be presented in the Clinical Study Report. This is a 24-week, open-label, multicenter study to evaluate the efficacy, safety and tolerability of Exelon patch (Rivastigmine) with 1-step titration in patients with mild to moderate Alzheimer's disease (MMSE 10 – 23) switched directly from cholinesterase inhibitors (donepezil, galantamine) in Japan.

1.1 Overall study design

This study will have three phases:

Screening phase [2-4 weeks: week -4 (Day -28) to week -2 (Day -14 to Day -1)].

The Screening Visit (Visit 1) has to take place 2 – 4 weeks before the planned start of rivastigmine patch treatment. After signing the informed consent, all patients will undergo a preliminary evaluation (Screening Visit) to assess eligibility (Appendix 16.1.1-Protocol-Section 4.1). Patients will continue their ChE inhibitors (donepezil or galantamine) during the Screening period, and patients are eligible to take their ChE inhibitors until the evening prior to start day of rivastigmine patch. For those patients who are eligible to enroll the study by the preliminary evaluation at Screening Visit, MMSE score during previous 6 months should be collected and recorded as much as possible. Their ChE inhibitors are discontinued on Baseline visit (Day 1). At the baseline visit (Visit 2), the patient will also undergo safety and efficacy assessments as per Appendix 16.1.1-Protocol-Table 6-1, and eligibility will be confirmed. Day 1 will be the day on which treatment with rivastigmine patch will be started. Patients will be starting on treatment with rivastigmine patch on the same day of the baseline visit (Day 1). When the patients already took their ChE inhibitors at the baseline visit (Visit 2, Day -1), the patients will start on treatment with rivastigmine patch the next day (Day 1) after the baseline visit.

Titration phase [8 weeks: week 1 (Day 1) to week 8 (Day 56)].

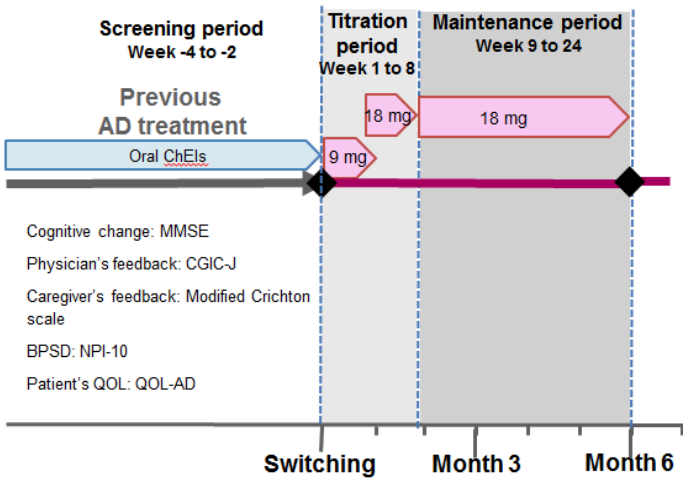
On the same day or next day (Day 1) following baseline visit, patients will begin treatment with a rivastigmine patch 9.0 mg/day and will be up-titrated after 4 weeks to reach the maintenance dose of 18 mg/day. Should tolerability problems occur, the investigators can decide to interrupt the treatment temporarily or to reduce the dose (see Appendix 16.1.1-Protocol-Section 5.5.5). The highest well-tolerated dose for each individual patient should be established within the titration period. The investigators also can use their clinical judgement to switch those patients to slower 3-step titration scheme in order to reach the maintenance dose of 18 mg/day or find the highest well-tolerated dose for each individual patient. Those patients will be allowed to stay in the study. During the titration period, visits will take place every 4 weeks.

Maintenance phase [16 weeks: week 9 (Day 57) to week 24 (Day 168)].

The patients will be maintained on the maintenance dose of rivastigmine patch 18 mg/day (or highest well-tolerated dose) during the remaining period of the study and will undergo safety and efficacy assessments as per protocol. If 18 mg/day is not achieved at maintenance period,

it will be increased up to 18 mg/day if possible. Patients not tolerating the 18 mg/day will stay on their highest tolerated dose in the study and will undergo safety and efficacy assessment as per protocol.

Figure 1-1 Study design



The planned number of patients to be enrolled in the study is 97. There are no planned interim analyses.

1.2 Study objectives and endpoints

Objectives	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Protocol Statistical Analysis Section
Primary		
To evaluate the efficacy of rivastigmine patch with 1-step titration on cognitive function measured as change from baseline to week 24 in the total score of MMSE in mild to moderate AD patients who failed to benefit from other cholinesterase inhibitors (ChEIs)	Endpoint Title: Change from baseline to week 24 in the total score of MMSE Time Frame : Up to week 24	Appendix16.1.1-Protocol-Section 9.4
Secondary		
To evaluate the safety, tolerability of Exelon® patch with 1-step titration for up to 24 weeks.	Endpoint Title: Monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs). Time Frame: Up to week 24.	Appendix 16.1.1-Protocol-Section 9.5

Objectives	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Protocol Statistical Analysis Section
To evaluate the efficacy of Exelon® patch with 1-step titration measured as the MMSE score at week 8.	Endpoint Title: Change from baseline to Week 8 in MMSE total score. Time Frame : Week 8	
To evaluate the efficacy of Exelon® patch with 1-step titration measured as the NPI-10 score at week 8 and week 24.	Endpoint Title: Change in NPI-10 score from baseline to week 8 and week 24 Time Frame : Week 8 and Week 24	
To evaluate the efficacy of Exelon® patch with 1-step titration measured as QOL-AD score at week 24.	Endpoint Title: Change in QOL-AD score from baseline to week 24 Time Frame : Week 24	Appendix 16.1.1-Protocol-Section 9.5
To evaluate the efficacy of Exelon® patch with 1-step titration measured as the J-CGIC score at week 4, week 8, week 16, and week 24.	Endpoint Title: Change in J-CGIC score from baseline to week 4, 8, 16 and 24 Time Frame : Week 4, 8, 16, 24	
To evaluate the efficacy of Exelon® patch with 1-step titration measured as Modified Crichton Scale score week 4, week 8, week 16, and week 24.	Endpoint Title: Change in as Modified Crichton Scale score from baseline to week 4, 8, 16 and 24 Time Frame : Week 4, 8, 16, 24	
To evaluate the formulation usability of Exelon® patch for up to 24 weeks as measured by the formulation usability questionnaire answered by caregiver.	Endpoint Title: Formulation usability score up to week 24 Time Frame : Up to week 24	
[redacted]		

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

All data will be analyzed by Novartis using the statistical software SAS version 9.4 according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

In general, the continuous variables will be summarized using standard descriptive statistics (mean, median, standard deviation, first (Q25) and third (Q75) quartile, minimum and maximum) and the categorical variables will be summarized in terms of the number and percentage of patients in each category.

2.1.1 General definitions

2.1.1.1 Study treatment

In this study aims to evaluate the tolerability, safety and efficacy of rivastigmine patch with 1-step titration in applicable patients with mild to moderate AD switched directly from cholinesterase inhibitors (donepezil, galantamine). Therefore, for these patients who had 1-step titration, study treatments are:

Form	Size
Exelon® patch 9 mg	5 cm^2
Exelon® patch 18 mg	10 cm^2

However, for patients who cannot tolerate 1-step titration method to reach the maintenance patch dose of 18 mg/day, the investigators will use their clinical judgement to switch those patients to slower 3-step titration method in order to reach the maintenance dose of 18 mg/day or find the highest well-tolerated dose for each individual patient. Once the dose started at 4.5 mg of rivastigmine once a day, as a general rule, the dose should be increased to 4.5 mg a day at 4-week intervals to 18 mg once a day. Therefore for these patients, study treatments are:

Form	Size
Exelon® patch 4.5 mg	2.5 cm^2
Exelon® patch 9 mg	5 cm^2
Exelon® patch 13.5 mg	7.5 cm^2
Exelon® patch 18 mg	10 cm^2

Patients who cannot tolerate 1-step titration will be allowed to participate in the study but will be excluded from the per protocol analysis only.

No control treatment is planned in this study.

2.1.1.2 Study day

Study day is defined with respective to the first day on which treatment with rivastigmine patch starts. The date of first administration of study medication is defined as Day 1 and the day before is defined as Day -1. There is no Day 0 is a study.

Therefore, for any particular date, study day will be calculated as follows:

- for dates on or after the first date of study medication administration,

  Study day = Assessment date – Date of first administration of study medication + 1;

- for dates prior to the first date of study medication administration,

  Study day = Assessment date – Date of first administration of study medication.

2.1.1.3 Baseline definition

Baseline visit (typically Visit 2) is defined as the day on which patients discontinue their prior ChE inhibitors. The baseline visit (Visit 2) may or may not be the same as Day 1. .

- It will be same as Day 1 if the patients already stop their ChE inhibitors prior to Day 1 and starts treatment with revastigmine patch from Day 1.
- on the otherhand, baseline visit (Visit 2, Day -1) will be one day before the Day 1 start of study treatment if the patients already took their ChE inhibitors at Visit 2.

In general, all assessments taken prior to the start of study treatment at Visit 2 will be considered as the baseline assessment. However, if the baseline assessments for MMSE, vital signs and laboratory parameters at Visit 2 are missing, then the measurements taken at Visit 1 (if available, as per protocol assessment schedule Table 6-1) will be used as baseline.

2.1.1.4 Post-baseline assessments

Post-baseline values are defined as assessments taken after the start of study treatment.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available: **Change from baseline = post-baseline value – baseline value.**

2.2 Analysis sets

Full Analysis Set (FAS)

The FAS will include all patients who received at least one dose of study treatment and had at least a baseline and any post-baseline assessment on treatment. This is the primary analysis population and will also be used for all efficacy analyses.

Per protocol Set (PP set)

The per protocol set will include all patients in the FAS who had only 1 step titration without any major deviations from the protocol procedures. The major protocol deviations will be specified prior to database lock.

Safety Set (SAF)

The safety set will consist of all patients who received at least one dose of drug and had at least one post-baseline safety assessment.

2.2.1 Subgroup of interest

[redacted]

2.2.1.1 Subgroup analyses for efficacy endpoints

The following subgroup analyses will be performed for the change from baseline in the total MMSE score at each post-baseline visit (i.e., Week 8 and Week 24):

- age (≤ 60 years, > 60 years)*
- weight (≤ median, > median, in kg, to be determined from the data)
- MMSE at baseline (10-14, 15-23 and further 15-23 into 15-19 and 20-23)*
- treatment regimen (e.g., overall, 1-step and 3-step titration)
- reason for switching to 3-step titration (as captured in the DAR page of CRF, e.g., adverse events, lab or test abnormality, lack of efficacy)
- Overall compliance to study medication (<75% and 75-100%)
- Patient profile analysis1a: Use of skin moisturizer at baseline (yes/no)*
    - ♦ Total
    - ♦ Compliance to study medication (<75% and 75-100%)

  Note: skin moisturizer will be identified using the data captured in the prior and concomitant medication CRF page and confirmed by the clinical team.
- Patient profile analysis 1b: Use of skin management at least one time during study period (yes/no)*
    - ♦ Total
    - ♦ Compliance to study medication (<75% and 75-100%)

  Note: skin management will be identified using the data captured in the prior and concomitant medication CRF page and confirmed by the clinical team.
- Patients satisfying protocol inclusion criteria 9-1 only, 9-2 only and both, respectively captured in the CRF page, are specified below:*
    - ♦ Inclusion criteria 9-1: Patients who are not responding to the previous treatment can be defined if the patients meet at least one of these conditions at baseline:
        - Patients who declined ≥ 2 points of MMSE despite of treatment of other oral ChE inhibitors within initial 3-month and continued to show insufficient treatment effect until at baseline.
        - During 6 months prior to screening visit, Patients who declined ≥2 points of MMSE with other oral ChE inhibitors and continued to show insufficient treatment effect until at baseline.
        - Patients who show marked worsening of BPSD, or ADL (can be defined by 1 state progression of FAST) judged by a physician despite

of treatment of other oral ChE inhibitors in initial 3-month or last 6-month with other oral ChE inhibitors

- ♦ Inclusion criteria 9-2: Patients having difficulties being treated orally with ChEIs (donepezil or galantamine) by physician's judgement. Difficulties are defined if the patients meet at least one of these conditions at baseline:*
  - Inadequate compliance with the ChE inhibitors at screening and baseline
  - Inadequate treatment (efficacious dose was not reached or inadequate compliance) with the ChE inhibitors because of AEs except gastrointestinal (GI) symptoms (nausea and vomiting) at screening and baseline
  - Patients with swallowing difficulties at screening and baseline

Further, a subgroup analysis will be presented for patients satisfying inclusion criteria

- 9-1 only, 9-2 only and both 9-1 and 9-2
- 9-1-1 only, 9-1-2 only, 9-1-3 only, and 9-1-1 and 9-1-3, and 9-1-2 and 9-1-3
- (9-1-1 or 9-1-2) versus (9-1-2 and 9-1-3) versus 9-1-3 only
- 9-1 versus 9-2
- (9-1 only) versus (9-1 and 9-2) or (9-2 only)
- (9-2 only) versus (9-1 and 9-2) or (9-1 only)

- Patients with concomitant use of memantine (yes/no)
- Patients satisfying treatment retention criteria as in Section 2.9.1 (yes/no)

Note: * items will also be illustrated using figures for the CSR.

2.2.1.2 Subgroup analyses for safety endpoints

The following subgroup analyses will be performed for all adverse events summaries as mentioned in Section 2.6.2.1:

- age (≤ 65 years, > 65 years)
- weight (</≥ 40 kg, </≥ 50 kg, </≥ 60 kg)
- treatment regimen (overall, 1-step and 3-step titration)
- reason for switching to 3-step titration (as captured in the DAR page of CRF, e.g., adverse events, lab or test abnormality, lack of efficacy etc.)
- Patients satisfying treatment retention criteria as in Section 2.9.1 (yes/no)
- overall compliance to study medication (<75% and 75-100%)
- Patient profile analysis1a: Use of skin moisturizer at baseline (yes/no)*
  - ♦ Total
  - ♦ Compliance to study medication (<75% and 75-100%)

  Note: skin moisturizer will be identified using the data captured in the prior and concomitant medication CRF page and confirmed by the clinical team.
- Patient profile analysis 1b: Use of skin management at least one time during study period (yes/no)*

- Total
- Compliance to study medication (<75% and 75-100%)

Note: skin management will be identified using the data captured in the prior and concomitant medication CRF page and confirmed by the clinical team.

Amongst AEs of special interest,

1. Gastrointestinal symptoms will be summarized by age, weight and patient profile analysis 1a and 1b subgroups as described above,
2. Application site skin reactions and irritations will be summarized by age, weight and patient profile analysis 1a and 1b subgroups as described above.

2.3 Patient disposition, demographics and other baseline characteristics

Patient demographic and baseline characteristics will be captured at Visit 1 or Visit 2 (only if the variable is not already captured at Visit 1). All the baseline and demographic characteristics will be summarized using the FAS in the CSR.

2.3.1 Patient disposition

The FAS will be used for the summary and listing of patient disposition.

The number and percentage of patients screened, completed and discontinued the study (and/or treatment) will be summarized for FAS population.

The overall number of patients who were screened, completed the study and discontinued from the study (and/or treatment) will also be summarized with reasons for premature discontinuation.

Patient identification number and whether they completed or discontinued from the study (and/or treatment) will be listed, with date of last dose and primary reason for premature discontinuation.

2.3.2 Medical history/current medical condition

Medical history will be coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA, current version at database lock). History/conditions will be summarized for the safety set by primary system organ class and preferred term, and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment exposure / compliance

Duration of exposure to the study treatment (rivastigmine patch) will be calculated as the number of days exposed to the treatment with rivastigmine patch over the specified period (expressed as: Duration of exposure = last known date of rivastigmine patch administration – first known date of rivastigmine patch administration + 1).

The duration of exposure (in days) will be summarized for the safety set as

- a continuous variable with the standard descriptive statistics, and
- a categorical variable classified into <=4 weeks, >4 to <=8 weeks, >8 to <=12 weeks, >12 to <=16 weeks, >16 to <=20 weeks and >20 to <=24 weeks.

A data listing of the drug doses administered by patients will be provided.

The number and percentage of patients who could stay on 1-step titration and switched 3 step titration will also be provided separately.

Investigator reported compliance from eCRF

Compliance will be calculated based on the DAR data. Compliance data will be summarized descriptively as a continuous and categorical variable.

The number and percentages of patients in each of the compliance categories mentioned in the eCRF, i.e., Poor (< 25%), Average (≥ 25% to < 50%), Good (≥ 50% to <75%), Very good (≥ 75% to ≤100%) and Overdose or misuse (>100%) will be summarized In case of over compliance (> 100%) the reason will be listed.

Additional summaries will be presented for each compliance category stated above for the following subgroups,

- use of skin moisturizer at baseline (yes/no)
- use of skin management at least one time during study period (yes/no)
- inadequate compliance with the ChE inhibitors at screening and baseline (yes/no)
- inadequate treatment (efficacious dose was not reached or inadequate compliance) with the ChE inhibitors because of AEs except gastrointestinal (GI) symptoms (nausea and vomiting) at screening and baseline (yes/no)
- swallowing difficulties at screening and baseline (yes/no)

2.4.2 Prior, concomitant and post therapies

Each medication has the start and end dates recorded. Prior medications are defined as those medications which were taken and stopped prior to the first dose of study drug. Concomitant medications are defined as those medications which were taken on or after the first dose of study drug but not prior to the first dose of study drug. Prior/concomitant medications are defined as those medications which were taken prior to and continued after the first dose of the study drug. All prior and concomitant medications will summarized by primary system organ class and preferred term. All prior/concomitant medications will be summarized as concomitant medications, and will not be included in prior medication outputs. All concomitant medications is also summarized by primary system organ class and preferred terms.

Surgical and medical procedures (non-drug therapies) will be summarized by primary system organ class and preferred term. All summaries will be on the safety set.

2.5 Analysis of the primary objective

The primary objective is to evaluate the efficacy of rivastigmine patch with 1-step titration on cognitive function for mild to moderate AD patients who failed to benefit from other ChEIs as change from baseline to Week 24 in the total score of Mini-Mental State Examination (MMSE).

2.5.1 Primary endpoint

The primary variable is change from baseline at Week 24 in the total score of 11 items included in the Mini-Mental State Examination (MMSE) for the FAS. Of note, the primary analysis will include all patients in the FAS population irrespective of the treatment regimen.

2.5.2 Statistical hypothesis, model, and method of analysis

The change from baseline in MMSE total score will be analyzed using a mixed model repeated measures (MMRM) model. The model will contain visit as a fixed effect, baseline MMSE score as a covariate and subject as a random effect. An unstructured covariance matrix should be used. The estimated mean change at Week 24 along with a two-sided 95% confidence interval and p-value will be tabulated and presented graphically. P-values will be used in descriptive manner.

Further, the MMSE total score and change from baseline will be summarized using standard descriptive statistics by visits.

In addition, the primary endpoint will be summarized and analyzed by subgroups specified in Section 2.2.1.1.

The MMRM model of subgroup analysis will contain visit, subgroup (categories) and visit*subgroup as fixed effects, baseline MMSE score as a covariate and subject as a random effect. An unstructured covariance matrix should be used. The estimated mean change at Week 24 along with a two-sided 95% confidence interval and p-value will be presented. P-values will be used in descriptive manner. Figures will only be provided for selected subgroup analysis as specified in Section 2.2.1.1.

2.5.3 Handling of missing values/censoring/discontinuations

The primary analysis will be performed using a MMRM model, which assumes that missing data is missing at random (MAR) given the preceding observed data.

The discontinuations data has been handled as explained in Section 4, point 3. No other imputation methods will be considered.

2.5.4 Supportive analyses

As supportive to the primary analysis,

1. The change from baseline at Week 24 in MMSE total score analysis will be repeated using the similar MMRM analysis for (1) the Per protocol set and (2) the FAS 3-step set. These two analyses will separately present the results for patients who has 1-step and 3-step titrations respectively. Tables and corresponding figures will be presented.
2. The change from baseline to Week 24 in MMSE total score will be analyzed using a t-test for the FAS. The estimated mean change along with 95% confidence interval and two-

sided p-value will be presented. This analysis will be performed on study completers only without any imputation of missing data.

3. The change from baseline to Week 24 in MMSE total score imputed with last observation carried forward (LOCF) method will be analyzed using a t-test for the FAS. The estimated mean change along with 95% confidence interval and p-value will be presented.

The p-values obtained in the supportive analyses will be descriptive in nature.

2.6 Analysis of secondary objectives

2.6.1 Efficacy endpoints

All following secondary efficacy variables will be analyzed using the FAS, PP set and subset of patients in FAS who had 3-step titration

2.6.1.1 MMSE score at Week 8

The change from baseline to Week 8 in MMSE total score will be summarized descriptively and analyzed using the same MMRM model used for the primary analysis. The estimated mean change along with two-sided 95% confidence interval will be presented.

Same figure will present the estimates and 95% confidence intervals of change from baseline in MMSE score at both Week 8 and Week 24.

2.6.2 Safety analyses

All safety variables will be reported using the safety set.

In addition, the adverse events, serious adverse events and adverse events of special interest summaries described in the following sub-sections will also be presented by the safety subgroups specified in Section 2.2.1.2.

2.6.2.1 Adverse events (AEs)

All adverse events starting on or after the first treatment will be included in all summaries and will also be listed. Adverse events occurring after signing of the informed consent prior to the start of study treatment will be listed only.

These adverse events will also be summarized by overall, by study periods as Week 1 to Week 4, Week 4 to Week 8, Week 8 to Week 12, Week 12 to Week 16, Week 16 to Week 20 and Week 20 to Week 24 by the following variables.

Adverse events by SOC and PT

All adverse events starting on or after the first treatment will be coded utilizing the MedDRA dictionary, tabulated, and analyzed by primary system organ class and preferred term.

Primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency.

If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the

same primary system organ class, the patient will be counted only once at the system organ class level.

AEs by severity

All adverse events will be summarized by maximum severity, primary system organ class and preferred term. If a patient reports more than one adverse event within the same primary system organ class, only one adverse event will be counted for that patient at the highest severity level in the total row for each primary system organ class. If a patient reported more than one adverse event with the same preferred term, the highest (maximum) severity will be presented. Missing severity will be assumed to be severe in the summary table.

AEs suspected to be related to study drug

The treatment emergent adverse events suspected to be related to study drug (according to the investigators) will be summarized by primary system organ class and preferred term. Relationship to study drug is considered as suspected for those events where "Relationship to study drug" is answered by the investigator as "Suspected".

AEs leading to permanent study drug discontinuation

Treatment emergent adverse events leading to permanent study drug discontinuation, regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

AEs requiring dose adjustment or interruption

Treatment emergent adverse events requiring dose adjustment or interruption, regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

2.6.2.2 Serious adverse events (SAE)

Number and percentage of patients with serious adverse events, regardless of study drug relationship, will be presented by primary system organ class and preferred term. These SAEs will also be summarized by overall, by study periods as Week 1 to Week 4, Week 4 to Week 8, Week 8 to Week 12, Week 12 to Week 16, Week 16 to Week 20 and Week 20 to Week 24.

Additionally separate tables will be provided for SAEs occurring more than 30 days after the last treatment administration for patients who discontinued the study treatment but remained in the study for more than 30 days and for SAEs which happened between Visit 1 (screening) and the time of first treatment for all patients in the safety set.

SAEs will also be listed separately.

2.6.2.3 Adverse events of special interest / grouping of AEs

The adverse events of special interest (Gastrointestinal events and skin events) will be summarized separately for the safety set by overall and chronologically by study periods as Week 1 to Week 4, Week 4 to Week 8, Week 8 to Week 12, Week 12 to Week 16, Week 16 to Week 20 and Week 20 to Week 24. A listing of such AEs will also be presented including action taken and outcome.

AEs of special interest are defined as the following terms. These will be taken from the latest MedDRA dictionary at the time of database lock.

GI event ("Gastrointestinal symptoms")

-HLT "Diarrhoea (excl infective)"

-HLT "Nausea and vomiting symptoms"

Skin event ("Application site skin reactions and irritations")

-HLT "Application and instillation site reactions"

-PT "Dermatitis allergic"

-PT "Dermatitis contact"

-PT "Administration site reaction"

-PT "Administration site pain"

-PT "Administration site infection"

2.6.2.4 Deaths

All the deaths in the clinical database will be listed with the investigator-reported principal cause. Deaths occurring after the first administration of study treatment until 30 days after the date of last treatment will be summarized with numbers and percentages.

2.7 Other safety data

2.7.1 Laboratory data

Laboratory measurements will include Hematology (Erythrocyte count, leukocyte count, hemoglobin, hematocrit, platelet count); Blood chemistry (Total protein, uric acid, ALP, AST, ALT, LDH, cholinesterase, blood urea nitrogen, creatinine, Na, K, Cl, total cholesterol, triglycerides, CPK, albumin, Ca, P, total bilirubin, amylase) and Urinalysis (Glucose, protein, occult blood).

All data will be converted into SI units (except Cholinesterase, which will be reported as collected (in U/L)) listed for the safety set with abnormal values flagged. A listing of all patients in the safety set will be provided.

The change from baseline at Week 24 is provided for Hematology and Chemistry. For urinalysis, descriptive statiscs is provided for baseline and Week 24.

Liver function tests

The metabolism of a drug can have an impact on the safety profile of the drug. To evaluate potential drug-induced liver injury, the patients with newly occurring or worsening abnormalities in liver function tests at any time post-baseline will be listed based on the following criteria:

Notable Liver events:

	Definition/ threshold
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

2.7.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), pulse rate, and body weight. The following summaries will be presented for the safety set:

2.7.2.1.1 Summary of absolute values and change from baseline

Vital signs including the changes from baseline will be summarized at the scheduled visits and time points. The maximum and minimum post-baseline SBP, DBP, and pulse rate values will also be summarized including the respective changes from baseline.

Body weight will be summarized by scheduled visits.

2.7.2.1.2 Notable absolute values and change from baseline

The number and percentage of patients with newly occurring or worsening notable values, including notable change from baseline, will be summarized by vital sign parameter and post-baseline visit. An additional section will be included for abnormalities occurring at any time point over the treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Notable absolute values and notable changes from baseline for each vital sign parameter are defined as:

Table 2-1 FDA (DNDP) Criteria: Clinically Notable Vital Signs Abnormalities

Variable			Change Relative to Baseline
Pulse Rate	> 120 bpm	And an	Increase of >= 15 bpm
	< 50 bpm	And a	Decrease of >= 15 bpm
Systolic BP	> 180 mmHg	And an	Increase of >= 20 mmHg
	< 90 mmHg	And a	Decrease of >= 20 mmHg
Diastolic BP	> 105 mmHg	And an	Increase of >= 15 mmHg
	< 50 mmHg	And a	Decrease of >= 15 mmHg

Weight	Increase of >= 7%
	Decrease of >= 7%

A listing of all patients with notable vital sign values and changes will be provided for the safety set.

2.7.3 ECG

ECG measurements include heart rate, QT interval, RR interval, PR interval, QRS duration, QTcF and QTcB, taken in a supine position after rest will be summarize descriptively for safety set. Listing will be provided for all patients.

2.8 Patient-reported outcomes

The following secondary endpoint related to patient reported outcome will be analyzed:

2.8.1.1 QOL-AD score

The QOL-AD is a brief, 13-item measure designed to obtain a rating of the patient's Quality of Life from the caregiver. A lower score indicates more severe impairment.

The change from baseline at Week 24 in the QOL-AD total and sub-item scores (by patients or caregivers) will be summarized along with 95% confidence interval of the mean for the FAS. Assessment of QOL of a given patient by his/her caregiver should be considered as primary measurement while assessment of QOL of a given patient by his/herself will be recorded as reference.

In addition, association between QOL-AD total score and each of MMSE total score, NPI-10 total score, J-CGIC and Modified Crichton Scale total score will be explored. A logistic regression will be considered to select the appropriate factors and thereafter to test whether or not the selected factors are associated with QOL-AD.

Similarly, the association between QOL-AD and number of gastrointestinal AEs and Application skin AEs will be explored using a regression analyses.

[redacted]

2.9 Caregiver-reported outcomes

The following secondary endpoints related to caregiver reported outcomes will be analyzed:

2.9.1.1 Neuropsychiatric Inventory (NPI) score

The neuropsychiatric symptoms will be assessed by the 10-item Neuropsychiatric Inventory (NPI). The NPI-10 total score is a sum of the 10 domains, where the score for a domain is defined as the product of frequency (range: 1-4) and severity (range: 1-3). Each domain has a maximum score of 12 and all domains are equally weighted for the total score (thus the range for the total score is 0 to 120). The NPI-10 total score and individual domain scores will be summarized descriptively at visits 2, 4 and 8 respectively. For where, N/A or absent has been marked in the crf, value 0 is considered for the same.

For change from baseline in NPI-10 total score at Week 24, summary statistics and 95% CI of the mean change will be derived for FAS.

2.9.1.2 Modified Crichton Scale

Modified Crichton Scale total score is defined as the sum of 7 items. If at least one missing item exists, the total score is set as missing..

Modified Crichton Scale total score will be summarized at visits 2, 3, 4, 6 and 8.

For change from baseline (visit 2), summary statistics and 95% CI of the mean will be derived for FAS at visits 3, 4, 6 and 8.

2.9.1.3 Formulation usability questionnaire

This questionnaire data is used to assess if the usability rivastigmine patch is preferred by the majority (greater than 50%) of AD patient caregivers or not. This will be assessed using the questionnaire in the CRF. The proportion of caregivers preferring the patch will be summarized with two-sided 95% confidence intervals for the FAS.

In addition, reasons for questionnaire answers will be summarized by presenting the frequencies of endorsed reasons.

2.10 Clinician-reported outcomes

The following secondary endpoint related to clinician reported outcome will be analyzed:

2.10.1.1 J-CGIC

J-CGIC is a global assessment scale to assess change of the patient's clinical symptoms, which are assessed subjectively by clinicians with seven grades. (1: Marked improvement, 2: Moderate improvement, 3: Mild improvement, 4: Unchanged, 5: Mild Worsening, 6: Moderated Worsening, 7: Marked Worsening). The number and percentage of patients in each grade will be displayed at visits 3, 4, 6 and 8. Also, proportion and 95% confidence interval for the proportions of the patients without worsening (1: Marked improvement, 2: Moderate improvement, 3: Mild improvement, 4: Unchanged) and with improvement (1: Marked improvement, 2: Moderate improvement, 3: Mild improvement) will also be provided.

2.11 Other analyses

2.11.1 Treatment retention during the last 8 weeks of maintenance period:

Treatment retention rate will be summarized for the FAS.

Here, "treatment retention" is considered to be successful when a patient meets all of the following condition:

- complete the study,
- receive rivastigmine 18 mg treatment during the last 8 weeks of maintenance period,
- never decrease the dose during the last 8 weeks of maintenance period,

- comply with drug application ≥ 75% during the last 8 weeks of maintenance period (compliance will be categorized as Poor (< 25%), Average (≥ 25% to < 50%), Good (≥ 50% to <75%), Very good (≥ 75% to ≤100%) and Overdose or misuse (>100%)).

  As stated in Section 2.2.1, Subgroup analysis, change from baseline in MMSE score at Week 24 and adverse events will be summarized by subgroup of patients satisfying treatment retention (yes/no).

  Further, treatment retention rate will be summarized in these subgroups as below:

  - Patient profile analysis 1a: Use of skin moisturizer at baseline (yes/no)*
    - ♦ Total
    - ♦ Compliance to study medication (<75% and 75-100%)
  - Patient profile analysis 1b: Use of skin management at least one time during study period (yes/no)*
    - ♦ Total
    - ♦ Compliance to study medication (<75% and 75-100%)

Note: skin moisturizer or other skin management will be obtained from the prior and concomitant medication CRF as captured in the database and confirmed by the study medical experts.

[redacted]

2.13 Interim analysis

Not applicable.

3 Sample size calculation

The sample size is determined as precision-based for the change from baseline in MMSE score at week 24. Ninety-seven patients will ensure that the half-width of 95% confidence interval for the change from baseline in MMSE score at week 24 would be 0.6, assuming SD=3.0 which is estimated from 1301, 1303 and 1403 studies. Assuming drop-outs, a total of 120 patients will be enrolled to achieve at least 97 evaluable patients.

4 Change to protocol specified analyses

The following are considered for the analysis which was not planned during the time of protocol development:

1. Rate of responses for change from baseline in MMSE total score has been provided based on Full Analysis Set, Per Protocol Set and subjects with 3-step titration.

   A responder is defined as those patients whose MMSE total score has remained unchanged from baseline till Week 24 or, patients whose MMSE total score has improved at Week 24 compared to baseline.

2. For Neuropsychiatric Inventory (NPI), the value 0 is considered wherever N/A or Absent has been marked in the eCRF page.

3. Visit Window for discontinuations: The study does not have a pre-defined visit windows for the entire study period. However, correct visit re-mapping for the discontinued patients was performed for summarizing and listing the efficacy and safety variables by visits. The last records of the discontinued patients are re-mapped to the actual visit when they discontinued rather than the Visit 8/discontinuation as per the assessment schedule of the protocol. Re-mapping was done for the discontinued patients to the nearest planned visit as per their actual discontinuation/ assessment date for each variable.

   The following efficacy assessments: MMSE, NPI-10, QOL-AD, J-CGIC and Modified Crichton Scale were re-mapped for the considered discontinued patients as described above.

   Under safety assessment, Vitals were considered for re-mapping for the discontinuation patients as described above. For other safety assessments, this re-mapping had no impact.

5 Appendix

This appendix gives details about statistical methods in addition to the report text. All analyses will be performed by using SAS version 9.4.

5.1 Imputation rules

1. Adverse events

AE START DATE IMPUTATION (CENA713D2340)

where AE start date is XX-MON-YYYY and Treatment start date is XX-TRTM-TRTY,

If YYYY<TRTY and MON missing, then AE start date=1-JULY-YYYY which is prior to start of trt
If YYYY<TRTY and MON<TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY<TRTY and MON=TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY<TRTY and MON>TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY=TRTY and MON missing, then AE start date=TRTSTDT+1
If YYYY=TRTY and MON<TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY=TRTY and MON=TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY=TRTY and MON>TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY>TRTY and MON missing, then AE start date=1-JAN-YYYY
If YYYY>TRTY and MON<TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY>TRTY and MON=TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY>TRTY and MON>TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)

AE END DATE IMPUTATION (CQVA149A2340)

AE end date = min (last visit date, last know date of contact for discontinued patients, DEC 31, date of death), if MON is missing and YYYY is present.

AE end date = min (last visit date, last know date of contact for discontinued patients, last day of the Month, date of death), if day is missing, MON and YYYY present.

Impute Date Flag (CQVA149A2340)

If not a complete date:

• If year of the imputed date <> YYYY then date flag = Y (not possible since missing dates will not be imputed),
• else if month of the imputed date <> MON then date flag = M,
• else if day of the imputed date <> day of original date then date flag = D,
• else date flag = null.

---

2. Concomitant medication

CM start date imputation

Rules for imputing the CMD start date:

Here TRTSTDT = treatment start date,

1. If the CMD start date year value is missing, the imputed CMD start date is set to TRTSTDT-1, if not after the CMD end date. Thus the imputed CMD start date = minimum (TRTSTDT-1, CMD end date).
2. If the CMD start date year value is less treatment start date year value, the CMD started before treatment start. Therefore:
    a) If the CMD year is less than treatment start year and the CMD month is missing, the imputed CMD start date is set to 01JulYYYY.
    b) Else if the CMD year is less than the treatment start year and the CMD month is not missing, the imputed CMD start date is set to 15MONYYYY.
3. If the CMD start date year value is greater than treatment start date year value, the CMD started after treatment start. Therefore:
    a) If the CMD year is greater than the treatment start year and the CMD month is missing, the imputed CMD start date is set to 01JanYYYY.
    b) Else if the CMD year is greater than the treatment start year and the CMD month is not missing, the imputed CMD start date is set to 01MONYYYY.
4. If the CMD start date year value is equal to treatment start date year:
    a) If the CMD month is missing or the CMD month is equal to treatment start month, then the imputed CMD start date is set to the minimum (TRTSTDT-1, CMD end date).
    b) Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to 15MONYYYY.
    c) Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to 01MONYYYY.

CMD end date imputing:

1. If the CMD end date is completely missing (and "Ongoing at final examination" was not answered "Yes"), the CMD end date will be the maximum of treatment end date +1 day and CMD start date.
2. If a partial CMD end date is reported (day is missing or day and month are missing), the CMD end date will be imputed by the maximum possible date, i.e.,
    - the end of the reported month if day is missing, or

- the end of the reported year if day and month are missing provided that the imputed date is not before the CMD start date,
- otherwise CMD end date will be equal to CMD start date.

3. CMTime since first symptoms of AD noticed by patient/caregiver (in years), for the partial dates in the data, the dates will be imputed as:

- If month and year are present, the 1st of the month is considered as the date. For example, if March 2015 is present, it will be imputed as 1st March 2015.
- If only year is present, January will be considered as the month and 1st as the date. For example, only 2015 is present, it will be imputed as 1st January 2015.

5.2 Rule of exclusion criteria of analysis sets

The protocol deviations defined for this study are the followings:

Table 1 Protocol deviations that cause patients to be excluded

Deviation Code	Text Description	Severity/ Analysis Classify action Code
E01	Any medical or neurological condition other than AD that could explain the patient'sdementia at baseline.	1
E02	Current diagnosis of probable vascular dementia according to National Institute of Neurological Disorders & Stroke and AIREN criteria at baseline.	1
E03	A current DSM-IV diagnosis of major depression, unless successfully treated with a stable dose of an antidepressant without anticholinergic properties for at least 4 weeks at baseline	49
E04	Any other DSM-IV Axis1 diagnosis interfering with evaluation of patient's response to study medication including other primary neurodegenerative dementia,schizophrenia or bipolar disorder at baseline.	49
E05	A current diagnosis of active, seizure disorder at baseline	49
E06	A history or current diagnosis of severe cerebrovascular disease at baseline	49
E07	A current diagnosis of severe or unstable cardiovascular disease, hypertension, diabetes at baseline	49
E08	A current diagnosis of bradycardia (< 50 bpm), sick-sinus syndrome, or conduction defects (sino-atrial block, second or third degree atrio-ventricular block) at baseline	49
E09	A current diagnosis of acute, severe, or unstable asthmatoid conditions at baseline	49
E10	A current diagnosis of active, uncontrolled peptic ulceration or gastro-intestinal bleeding within the last 3 months from baseline	49
E11	Clinically significant urinary obstruction at baseline	49
E12	Patients with extrapyramidal disorders	49
E13	Patient with complication of gastrointestinal (GI) adverse events during oral ChE inhibitors treatment except for GI adverse events caused by drugs other than oral ChE inhibitors	49
E14	Patients with low body weight as judged by the investigators at Visit 1 and/or 2 date	49
E15	Current diagnosis of an active skin lesion/disorder that would influence to the adhesion and potential skin irritation of the patch at baseline	49
E16	A disability that may prevent the patient from completing all study requirements at baseline	49
E17	Patients with a history of hypersensitivity to any ingredients of rivastigmine or carbamate derivatives	49

E18	Patients who have taken rivastigmine anytime in the past (Please consider partial dates)	49
E19	Any rehabilitation day care and day service during 4 weeks or more prior to efficacy assessment at baseline must not be changed significantly with content and frequency (new start/discontinuation)	49
E20	Taken any investigational drug (including investigational biologics) in the 90 days prior to baseline or within 5 half-lives of the compound, whichever is longer;	49
E21A	Use of donepezil > 5 mg/day 4 weeks prior to baseline (Visit 2)	1
E21B	Any ChEIs(except donepezil,galantamine),selegiline,centrally acting anticholinergic drug,olanzapine or tricyclic & tetracyclic antidepressants,lithium during 4 weeks prior to efficacy assessment at V2	1
E21C	Change of dosage, frequency of donepezil, galantamine, memantine during the 4 weeks prior to efficacy assessment at baseline (V2)	1
E21D	Succinylcholine-type muscle relaxants, lithium during the 2 weeks prior to efficacy assessment at Visit 2	49
E21E	Newly used benzodiazepine-type hypnotics of short duration, newly used or irregularly used zolpidem tartrate and zopiclone within 24 hours prior to efficacy assessment at Visit 2	49
E21F	Change of dosage and frequency of other specified drugs during the 4 weeks prior to efficacy assessment at baseline (V2)	49
E22A	Total bilirubin 3.0 mg/dL or above at Visit1	49
E22B	AST (SGOT) and/or ALT (SGPT) 3 x ULN or above at Visit 1	49
E22C	Plasma creatinine 2.0 mg/dL or above at Visit1	49
E23	History of malignancy treated or untreated within past 5 years with exception of localized basal cell carcinoma of skin.	49
E24	Patients diagnosed by investigator as unsuitable for inclusion in this clinical study	49

I01	No written informed consent from patient and/or his/her Caregiver at V1	8
I02	Aged ≤49 or ≥86	49
I03	Out patient status at baseline	49
I04	Female with child- bearing potential	49
I05	No diagnosis of mild to moderate AD (dementia of the Alzheimer's type) according to DSM-IV criteria	1
I06	No clinical diagnosis of probable mild to moderate AD as per NINCDS-ADRDA criteria	1
I07	A MMSE score of < 10 or > 23 at Visit1 & V2	1
I08A	Patients are not currently on the oral monotherapy (donepezil, 5 mg), within 4 weeks prior to baseline visit.	49
I08B	Patients are not currently on the galantamine (16-24 mg) within 4 weeks prior to baseline visit.	49
I09	"Date of MMSE examination " provided must be within six months and 14 days prior to screening visit date.	49
I09A	Patients who could not receive treatment benefits of previous oral ChEIs as defined by meeting either 9-1 and 9-2 or both, of Inclusion criteria 9 of protocol	49
I10	Unable to read, write, and communicate effectively during the premorbid state	49
I11	Could not complete all aspects of the study alone or without care giver help	49
I12	Not Residing with someone/ not having daily caregiver support /living alone throughout the study	49
I13	Primary caregiver un-willing to accept responsibility for supervising treatment, assessing condition of patient & providing input to efficacy assessment	49
M01A	Newly initiation or use prohibit concomitant medications/non- drug therapies during the study	1
M01B	Newly initiation or use of prohibit concomitant medications (Donepezil and/or Galantamine) during the study.	1
M02	New initiation or use/change in restricted concomitant medications/non-drug therapies/rehabiliation/day care and day service/short stay during study, more than prescibed dose or duration.	49
O02	Different rater from baseline perform QOL-AD at the visit	49
O03	Different rater from visit 3 perform J- CGIC at the visit	49
O04	Labelling details of the sample collected	49
O05	Modified Crichton Scale evaluation was not completed by caregiver at visits 2,3,4,6 and 8	49

O06	Additional screening blood test for differrential diagnosis not performed even though required	49
S01	Applied patch location on body other than back, shoulder or chest	49
S02	1-step titration begins treatment with a rivastigmine patch 9 mg/day for 4 weeks, followed by a dose increase to 18 mg/day.	1
S03	Dose was not maintained for 2 weeks after reducing the dose due to safety or tolerebility	49
S04	Patient who decreased more than two-dose- levels without doctors prescription	1
S05	Different Dose Level applied from protocol specified or doctor prescribing. ex) wrong DL was used, more than three patches / prescribed number of patches were applied,	49
S06	Treatment was not discontinued incase of >28 days interruption	6
S07	Restart study drug without prescribed dose adjustment after interruption	49
S08	Decrease in the dose- level without prescribed dose adjustment by doctor	49
S09	Treatment Not discontinued in case of unfavorable events/results	49
S10	Non-adherence to patch treatment for less than 50 percent of study period	1
S11	No rivastigmine medication administered during the study period	0
S12	Use expired study drug during study period	49

Table 2 Subject Classification

Analysis Set	PD severity codes that cause a subject to be excluded	Criteria that cause a subject to be excluded
FAS	0, 6, 8	Enrolled but no study drug received
PPS	0, 1, 6, 8	NA
SAF	8	

Table 3 Severity codes with action taken

Code	Action
0	Exclude from all efficacy analysis
1	Exclude from per protocol analysis
6	Exclude from Main Analysis Set

8	Exclude from all analysis
49	Report relevant protocol deviation – include in all analyses

5.3 SAS codes for statistical analyses.

5.3.1 Mixed Model Repeated Measures (MMRM) analysis

The change from baseline in MMSE total score will be analyzed using a mixed model repeated measures (MMRM) model. The model will contain visit as a fixed effect, baseline MMSE score as a covariate and subject as a random effect. An unstructured covariance matrix should be used.

```
proc mixed data = xxx ;
class visit subjid;
model chg = visit base /noint ddfm =KR alpha = 0.05;
repeated visit /type =UN subject =subjid ;
lsmeans visit /cl;
run;
```

where,

chg: change from baseline in MMSE total score

visit: study visits as per protocol assessment schedule,

base: baseline MMSE score

subjid: subject identifier.

5.3.2 MMRM model of subgroup analysis

The MMRM model of subgroup analysis will contain visit, subgroup (categories) and visit*subgroup as fixed effects, baseline MMSE score as a covariate and subject as a random effect. An unstructured covariance matrix should be used.

```
proc mixed data = xxx ;
class visit subgrcat subjid;
model chg = visit subgrcat visit*subgrcat base / noint ddfm = KR alpha = 0.05;
repeated visit /type =UN subject =subjid ;
lsmeans visit*subgrcat /cl;
run;
```

where

chg: change from baseline in MMSE total score,

visit: study visits as per protocol assessment schedule,

subgrcat: subgroup categories,

visit*subgrcat: interaction effect of visit and subgrcat,

base: baseline MMSE score,

subjid: subject identifier.

5.3.3 Student's t-test

The change from baseline to Week 24 in MMSE total score will be analyzed using a t-test.

proc ttest *data=xxx;*

var chg;

run;

where

chg: change from baseline in MMSE total score.

5.3.4 Regression Model

Regression Model: `QOL-AD total score = MMSE total score + NPI-10 score + J-CGIC grade + Modified Crichton total score.`

Use SAS code:

proc reg data = xxxx;

model QOL-AD total score = MMSE total score NPI-10 score J-CGIC grade Modified Crichton total score / selection = forward slentry = 0.95;

run;