

[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)]**

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## List of abbreviations

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AChE	Acetylcholinesterase
AD	Alzheimer's disease
AE	Adverse event
BuChE	Butyrylcholinesterase
CFR	Code of Federal Regulations
ChE	Cholinesterase
ChEI	Cholinesterase inhibitors
eCRF	electronic Case Report Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
DS&E	Drug Safety & Epidemiology
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EDC	Electronic Data Capture
EMA	European Medicine Agency
FDA	Food and drug administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
J-CGIC	Japanese version of the Clinical global impression of change
MedDRA	Medical dictionary for regulatory activities
MMSE	Mini – Mental State Examination
NPI-10	Neuropsychiatric Inventory-10
PD	Premature discontinuation
PDD	Parkinson's disease dementia
QOL-AD	Quality of Life- Alzheimer's Disease
SAE	serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reactions
WHO	World Health Organization

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## Glossary of terms

Assessment	A procedure used to generate data required by the study
Dementia of the Alzheimer's Type	This is defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria.
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This <i>includes</i> any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally <i>does not include</i> protocol-specified concomitant background therapies when these are standard treatments in that indication
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Probable Alzheimer's Disease (AD)	Probable Alzheimer's Disease is defined according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria. This is the term which will be used in this protocol when defining the study population.
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
1-step titration	1-step titration begins treatment with a rivastigmine patch 9 mg/day for 4 weeks, followed by a dose increase to 18 mg/day.

## Amendment 1

### Amendment rationale

The main purpose of this amendment is to revise and provide clarity on one of the key inclusion criteria for AD patients who have lack or loss of efficacy with previous ChEIs. For the first item of inclusion criteria 9-1, definition of “in initial 3-month” will be revised to clarify as within initial 3-month because it is not always necessary to take 3-month to decide the decline of MMSE. For the second item of inclusion criteria 9-1, definition of “last 6-month” will be supplementary explained by additional description, stating that it is “during 6-month prior to at screening visit. Exclusion criteria point 13 has also been updated to reflect patients with complication of gastrointestinal adverse events caused due to oral ChE inhibitors treatment are not eligible for inclusion in the study. These changes are briefly summarized in below section.

This study is in the start-up phase and enrolled/screened 16 / 28 patients at the time of this amendment. Changes mentioned below will not impact the study population, drug administration, objectives, endpoints, or study results.

### Changes to the protocol

All changes to the protocol are summarized below.

In [Section 1.2](#) (Purpose) and [Section 4.1](#) (Inclusion criteria, point 9-1), criteria for lack or loss of efficacy with previous ChEIs are revised and defined as follows:

- Patients who declined  $\geq 2$  points MMSE within the initial 3-month treatment with oral ChEIs, and continued to show insufficient treatment effect until at baseline (*lack of efficacy*), and
- During 6 months prior to screening visit, patients who declined  $\geq 2$  points MMSE with oral ChEI treatment and continued to show insufficient treatment effect until at baseline (*loss of efficacy*).

These changes are also made in synopsis, page 12 to be consistent with the protocol body.

[Section 4.2](#) (Exclusion criteria, point 13) is revised to reflect ‘patients with complication (instead of the term ‘a past medical history’ as per the previous protocol version) of gastrointestinal adverse events such as nausea and vomiting during oral ChE inhibitors treatment except for such gastrointestinal adverse events if it is apparent to be caused by other than oral ChE inhibitors are not eligible for inclusion in the study.

[Section 4.2](#) (Exclusion criteria, point 22) is revised to reflect ‘serum creatinine (instead of the plasma creatinine as per the previous protocol version) and to align with protocol Japanese version.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do NOT affect the trial specific model ICF.



## Protocol summary

Protocol number	CENA713DJP02
Title	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)
Brief title	Phase IV study of rivastigmine patch with 1 step titration
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	It is unknown whether a patient gets a treatment benefit from switching other ChEIs to rivastigmine patch with 1 step titration. Our hypothesis is that rivastigmine patch with 1 step titration can be a suitable treatment option for patients with AD who failed to benefit from other ChEIs.
Primary Objective(s)	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).
Secondary Objectives	<p>To evaluate the safety, tolerability of rivastigmine patch with 1-step titration for up to 24 weeks.</p> <p>To evaluate the efficacy of rivastigmine patch with 1-step titration measured as the MMSE score at week 8.</p> <p>To evaluate the efficacy of rivastigmine patch with 1-step titration measured as the NPI-10 score at week 8 and week 24.</p> <p>To evaluate the efficacy of rivastigmine patch with 1-step titration measured as QOL-AD score at week 24.</p> <p>To evaluate the efficacy of rivastigmine patch with 1-step titration measured as the J-CGIC score at week 4, week 8, week 16, and week 24</p> <p>To evaluate the efficacy of rivastigmine patch with 1-step titration measured as Modified Crichton Scale score week 4, week 8, week 16, and week 24.</p> <p>To evaluate the formulation usability of rivastigmine patch for up to 24 weeks as measured by the formulation usability questionnaire answered by caregiver.</p>
Study design	This is a 24-week, multi-center, open-label, single-arm (1-step titration) study in patients with mild to moderate AD (MMSE 10-23) switched directly from cholinesterase inhibitors (donepezil, galantamine) for AD.
Population	The study population will consist of a representative group of male and female Japanese patients (50-85 years of age) with probable AD Mini – Mental State Examination (MMSE 10-23), treated with donepezil or galantamine.
Key Inclusion criteria	<p>Patient's with 50-85 years of age at baseline.</p> <p>Outpatient status at baseline.</p> <p>Males, and females not of child-bearing potential (surgically sterile, or one year or more from last menses).</p> <p>A diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria.</p>

	<p>A clinical diagnosis of probable AD according to National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.</p> <p>Brain scan (magnetic resonance imaging [MRI], or computed tomography [CT]) were met diagnosis criteria conducted within 3 years prior to baseline.</p> <p>Positron emission tomography (PET) or single photon emission computed tomography (SPECT) was met diagnosis criteria conducted within 3 years prior to baseline visit, as long as in the past a brain scan (MRI or CT) also was met.</p> <p>MMSE score of <math>\geq 10</math> and <math>\leq 23</math> at screening and baseline.</p> <p>Patients are currently on the oral monotherapy (donepezil, 5 mg), or galantamine (16-24 mg) for 4 weeks prior to baseline visit.</p> <p>Patients who failed to receive enough treatment benefit from the previous treatment can be defined if the patients meet at least one of following conditions at screening and baseline (multiple choices allowed)</p> <p>Patients who declined <math>\geq 2</math> 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.</p> <p>During 6 months prior to screening visit, patients who declined <math>\geq 2</math> points of MMSE with other oral ChE inhibitors and continued to show insufficient treatment effect until at baseline.</p> <p>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</p> <p>Patients having difficulties being treated orally with ChEIs (donepezil or galantamine) by physician's judgement.</p> <p>Poor compliance or adverse event except GI symptoms</p> <p>Patients with swallowing difficulties.</p>
Key Exclusion criteria	<p>Any medical or neurological condition other than AD that could explain the patient's dementia (e.g., abnormal thyroid function tests, vitamin B12 or folate deficiency, posttraumatic conditions, syphilis, head injury, Huntington's disease, Parkinson's disease, subdural hematoma, normal pressure hydrocephalus, brain tumor) at baseline;</p> <p>Any other DSM-IV Axis 1 diagnosis that may interfere with the evaluation of the patient's response to study medication, including other primary neurodegenerative dementia, schizophrenia, or bipolar disorder.</p> <p>An advanced, severe, progressive, or unstable disease of any type that may interfere with efficacy and safety assessments or put the patient at special risk.</p> <p>Current diagnosis of an active skin lesion/disorder.</p> <p>Patients with a history of hypersensitivity to any ingredients of rivastigmine or carbamate derivatives.</p> <p>Each patient will be required to have a primary caregiver willing to accept responsibility for supervising treatment, assessing the patient's condition throughout the study, and for providing input into efficacy assessments.</p>
Study treatment	Rivastigmine patch: 9 and 18 mg patch (5 and 10 cm <sup>2</sup> , respectively)
Efficacy assessments	MMSE (primary), NPI-10, J-CGIC, QOL-AD and Modified Crichton Scale

Key safety assessments	Adverse Events, Serious Adverse Events (SAE)
Other assessments	Formulation usability questionnaire Treatment compliance
Data analysis	<p>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 will be used to model the within-subject error. The estimated mean change at Week 24 along with a two-sided 95% confidence interval and p-value will be presented. In addition, as sensitivity analyses, the following will also be performed. The change from baseline to Week 24 in MMSE total score will be analyzed using a t-test. The estimated mean change along with 95% confidence interval and p-value will be presented. This analysis will be performed on study completers only without any imputation of missing data.</p> <p>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. The estimated mean change along with 95% confidence interval and p-value will be presented.</p>
Key words	Alzheimer, Dementia

## 1 Introduction

### 1.1 Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive dysfunction including memory impairment. Within Japan 1.17 million patients, aged 65 and older, were reported with AD in 2005, and it is estimated that there will be 1.82 million patients by 2015 and 2.40 million patients by 2025, respectively ([Shimokata 2008](#)). The symptoms of AD are directly related to the degeneration of cholinergic neurons of the cortex and hippocampus, which results in lower levels of acetylcholine and a reduction of cholinergic transmission ([Davies and Maloney 1976](#)). This cholinergic hypothesis led to the development of cholinesterase (ChE) inhibitors, which act by inhibiting the two enzymes responsible for the degradation of acetylcholine: acetylcholinesterase (AChE) or butyrylcholinesterase (BuChE). Cholinesterase inhibitors which act by inhibiting the degradation, and therefore elevating levels, of acetylcholine in functionally intact cholinergic synapses and in the brain parenchyma - form the mainstay of therapy for mild to moderate AD. Exelon<sup>®</sup> (rivastigmine) is widely approved for the treatment of mild to moderate AD, and differs from other cholinesterase inhibitors by its shorter serum half-life and its slowly reversible inhibition of both enzymes involved in the breakdown of acetylcholine in the brain. It is a relatively brain-selective AChE and BuChE inhibitor of the carbamate type that does not induce upregulation of its target enzymes ([Lane et al, 2006](#)).

In addition to the oral formulations (capsule and liquid oral concentrate), a transdermal patch formulation for rivastigmine has been developed to reduce adverse drug reactions such as nausea and vomiting, which had been observed with the oral formulation. Pharmacokinetic studies conducted with rivastigmine patch have shown that transdermal administration of rivastigmine prolongs  $t_{max}$ , lowers  $C_{max}$  and reduces fluctuation in plasma concentration ([Lefevre et al, 2008](#)).

The only approved AD treatment in Japan was donepezil hydrochloride (5 mg o.d. for mild to moderate AD, 10 mg o.d. for severe AD) until 2010. Rivastigmine patch (18 mg o.d. for mild to moderate AD) and galantamine (8 mg, 12 mg b.i.d. for mild to moderate AD) were approved in 2011 along with memantine (20 mg o.d for moderate to severe AD). Rivastigmine is the only patch formulation among these approved AD medications. Japanese pivotal PhIIb/III clinical study (CENA713D1301 study), a 24-week, double-blind, randomized, placebo control, in AD patients (MMSE 10-20) demonstrated that the rivastigmine patch 18 mg/day was statistically significant over placebo on the ADAS-J cog at week 24 ([Nakamura. et al, 2011](#)).

On the other hand, CENA713D1301 study showed that the most frequent adverse events (AEs) were related to skin/application site reactions. The AEs that lead to study discontinuation, application site pruritus, dermatitis contact, and application site erythema in rivastigmine patch groups were higher than in the placebo group. Nausea and vomiting resulting in study discontinuation were reported in < 1% in treatment groups.

In the current Japanese label, treatment with rivastigmine patch starts at 4.5 mg/day, and the dose should be further increased by 4.5 mg/day at 4-week intervals up to the maintenance dose of 18 mg/day (3-step titration scheme: 4.5 mg, 9 mg, 13.5 mg, 18 mg). As the rest of the world including Korea, Malaysia, and Hong Kong adopts 1 step titration scheme (9 mg, 18 mg), the 3

step titration scheme is particularly developed in Japan to ease gastrointestinal adverse events while maximizing the effective dosage exposure among AD patients. On the other hand, the 3 step titration scheme requires a minimum of 12 weeks before reaching the effective dose, and a concern has been raised on a potential long-term use at doses below the effective dose.

Therefore, these circumstances lead to conduct another clinical study (CENA713D1303/ONO code: 2540-04) to further evaluate the tolerability of the shorter titration (1-step titration) in a Japanese AD population.

### **Phase IIIb clinical study (CENA713D1303)**

A 24-week, multicenter, parallel-group, randomized, double-blind study to evaluate the tolerability, safety and efficacy of 2 different titration methods of rivastigmine patch (CENA713D/ONO-2540) in patients with mild to moderate Alzheimer's disease (MMSE 10-20). The purpose of this study was to compare the tolerability, safety and efficacy of 3-step titration\* (the current approved titration schedule in Japan) to those of 1-step titration\*\* (the approved titration schedule in many countries worldwide including US and EU) in the mild to moderate AD Japanese patients. Data from this study was used to support a supplemental New Drug Application to allow the 1-step titration to be included into the label in Japan.

The study results showed the safety and tolerability of the 1-step titration scheme is comparable to the 3-step titration scheme in the Japanese mild to moderate AD population. The proportion of patients who discontinued the study drug treatment due to AEs were 15.0% (16/107) in the 1-step titration group and 18.5% (20/108) in the 3-step titration group. The observed difference between treatments of the proportion of discontinuation due to AEs were -3.6% (95% CI: -17.0, 9.6, Exact method). Since the point estimate of the observed difference falls within the pre-specified acceptance range (i.e. [-9.0%, 9.0%]), the study met its primary objective. The study showed similar efficacy between the 1-step titration and the 3-step titration group at week 24. At week 8, the 1-step titration group showed a slightly greater improvement compared to the 3-step titration group in ADAS-J cog, potentially suggesting an earlier efficacy onset. Overall, the 1-step titration is comparably safe and efficacious to the currently approved the 3-step titration for Japanese patients with mild to moderate AD during the 24 week assessment period.

\* 3-step titration schedule: 4.5 mg/day for 4 weeks, 9 mg/day for 4 weeks, 13.5 mg/day for 4 weeks, 18 mg/day (maintenance dose).

\*\* 1-step titration schedule: 9 mg/day for 4 weeks, 18 mg/day (maintenance dose).

Based on the results of Study 1303, 1 step titration scheme is approved in addition of 3 step titration scheme in Japan.

## **1.2 Purpose**

The purpose of this study is to further 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). As rivastigmine patch with 1-step titration was approved in Aug 2015 in addition of 3-step titration, physicians in Japan may be allowed considering 1-step titration method besides 3-step titration, depending on condition and tolerability of a patient, which allow AD patients to reach the maintenance dose (18 mg/day) after 4 weeks of loading dose (9 mg/day). Although it can be expected to

improve AD treatment with both titration methods depending on conditions of patients, treatment benefits of rivastigmine patch with 1-step titration when AD patients switch from other ChEIs have not fully evaluated. One of many reasons for switching between ChE inhibitors is declining of cognitive function or worsening of demential symptoms despite of treatments. Therefore, this study aims at enrolling those AD patients as non-responders against the previous ChE inhibitors' treatment by defining as lack and loss of efficacy\* in terms of cognitive function and other dementia symptoms. It is beneficial for AD patients to evaluate if switching therapy from oral ChE inhibitors to rivastigmine patch with 1 step titration could be a suitable treatment option.

\*: AD patients who have lack or loss of efficacy with previous ChEIs are defined as following criteria; 1) Patients who declined  $\geq 2$  points MMSE within the initial 3-month treatment with oral ChEIs, and continued to show insufficient treatment effect until at baseline (lack of efficacy), 2) During 6 months prior to screening visit, patients who declined  $\geq 2$  points MMSE with oral ChEI treatment and continued to show insufficient treatment effect until at baseline (loss of efficacy), 3) Both in the above 1 and 2, patients who showed marked worsening of ADL, or BPSD judged by a physician.

Each Exelon<sup>®</sup> patch of 5 cm<sup>2</sup> contains 9 mg of rivastigmine that delivers 4.6 mg/24 hours.

Each Exelon<sup>®</sup> patch of 10 cm<sup>2</sup> contains 18 mg of rivastigmine that delivers 9.5 mg/24 hours.

## **2 Study objectives and endpoints**

### **2.1 Primary objective(s)**

- 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 ChEIs.

### **2.2 Secondary objective(s)**

- To evaluate the safety, tolerability of rivastigmine patch with 1-step titration for up to 24 weeks.
- To evaluate the efficacy of rivastigmine patch with 1-step titration measured as the MMSE score at week 8.
- To evaluate the efficacy of rivastigmine patch with 1-step titration measured as the NPI-10 score at week 8 and week 24.
- To evaluate the efficacy of rivastigmine patch with 1-step titration measured as QOL-AD score at week 24.
- To evaluate the efficacy of rivastigmine patch with 1-step titration measured as the J-CGIC score at week 4, week 8, week 16, and week 24
- To evaluate the efficacy of rivastigmine patch with 1-step titration measured as Modified Crichton Scale score week 4, week 8, week 16, and week 24.
- To evaluate the formulation usability of rivastigmine patch for up to 24 weeks as measured by the formulation usability questionnaire answered by caregiver.

## 2.4 Objectives and related endpoints

**Table 2-1 Objectives and related endpoints- Objectives**

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
<b>Primary</b>		
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	<a href="#">Section 9.4</a>
<b>Secondary</b>		
To evaluate the safety, tolerability of rivastigmine 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.	<a href="#">Section 9.5</a>
To evaluate the efficacy of rivastigmine 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 rivastigmine 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 rivastigmine 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	<a href="#">Section 9.5</a>
To evaluate the efficacy of rivastigmine 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	

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
To evaluate the efficacy of rivastigmine 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 rivastigmine 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	

### 3 Investigational plan

#### 3.1 Study design

This is a 24-week, multi-center, open-label, single-arm (1-step titration) study in patients with mild to moderate AD (MMSE 10-23) switched directly from cholinesterase inhibitors (donepezil, galantamine) for AD.

The study will have three phases

##### 1. 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 (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 [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.

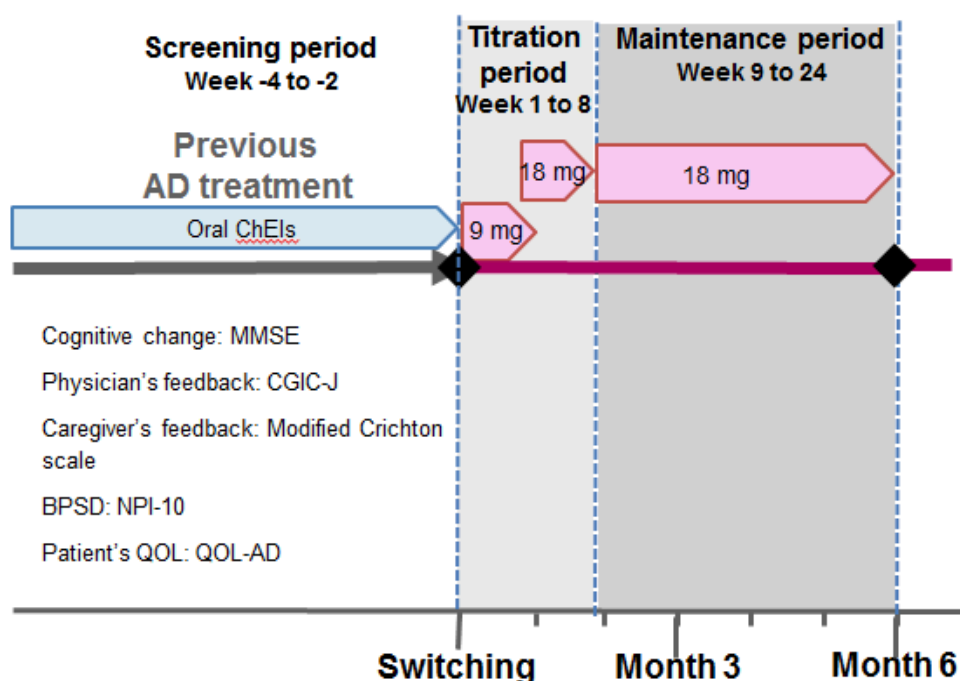
**2. Titration phase [8 weeks: week 1 (Day 1) to week 8 (Day 56)].**

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 [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.

**3. 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 3-1 Study design**



**3.2 Rationale for study design**

The patient population will be described in more detail in the [Section 4](#) below.

This study is a Phase IV study (post marketing study) to evaluate the efficacy, safety and tolerability of rivastigmine patch in patients with mild to moderate AD switching directly from oral ChE inhibitors (donepezil and galantamine) to rivastigmine patch with 1 step titration. Since the purpose of this study is not to prove superiority/non-inferiority, double-blind, placebo or active-controlled study is not needed.

The patients who are eligible to this study are those who are lack/loss of efficacy or having difficulties in administrating with previous oral ChE inhibitors. Active or placebo controlled study is not appropriate from an ethical point for patients.

In previous reported switch study, direct switching from donepezil to rivastigmine patch, was safe and well-tolerated ([Sadowsky 2010](#)). Another switching study in Japan, a 24-week, open-label, multicenter study to evaluate the efficacy, safety and tolerability of rivastigmine patch with 3-step titration in patients with mild to moderate Alzheimer's disease demonstrated the safety and well-tolerability of direct switch to rivastigmine patch for AD patients who have difficulties being treated with ChE inhibitors (donepezil and galantamine). Therefore, no washout period from the previous treatment is recommended for the study.

### **3.3 Rationale for dose/regimen, route of administration and duration of treatment**

Rivastigmine patch is a marketed drug, therefore the dose, dose regimen and titration scheme are in accordance with product label.

An AD patient who is applicable to 1 step titration method (initial loading dose is a rivastigmine patch 9.0 mg/day and will be up-titrated after 4 weeks to reach the maintenance dose of 18 mg/day) defined in [Section 4.1](#) is subject to the enrollment of this study. In principle, 1 step titration method should be applied to all of patients as long as tolerated.

The treatment period of 24-weeks is as per AD evaluation guideline EU ([EMA 2008](#)), and Japanese guideline research ([Homma 1998](#)). FDA guidelines ([Leber 1990](#)) specify that at least 3 months as treatment period is needed, and EU & Japanese guidelines mentioned that more than 6 months of treatment is required. Therefore, the treatment period for this study is also set for 24 weeks.

### **3.4 Rationale for choice of comparator**

No comparator will be included based on the rationale of study design.

### **3.5 Purpose and timing of interim analyses/design adaptations**

Not applicable.

### **3.6 Risks and benefits**

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring.

Rivastigmine patch is approved in more than 90 countries around the world. Approximately 17,144 patients received rivastigmine treatment in Novartis-sponsored investigational clinical trials. It is estimated from marketing experience (post-authorization exposure) that the

cumulative patient exposure of oral formulation is approximately 5,194,565 patient-years, and 3,912,326 patient-years of treatment with the transdermal formulation. Tests done in this study at each visit are standard medical tests. The risks of taking blood may include fainting, pain and/or bruising at the site of needle puncture or finger sticks. The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring.

Japanese pivotal Phase IIb/III clinical study (CENA713D1301 study), a 24-week, double-blind, randomized, placebo control, in AD patients (MMSE 10-20) demonstrated that rivastigmine patch 18 mg/day was statistically significant over placebo on the ADAS-J cog at week 24 (Nakamura. et al, 2011), and showed that most frequent observed AEs were application site erythema, application site pruritus, and contact dermatitis which developed regardless of starting dose and titration.

Overall, the incidence rate of skin reactions in the Japanese population was higher compared to the observed incidence rate in other global studies.

CENA713D1403 in Japan, a 24-week, open-label, multicenter study to evaluate the efficacy, safety and tolerability of rivastigmine patch with 3-step titration in patients with mild to moderate AD switched from ChE inhibitors (donepezil, galantamine) showed the safety and well-tolerability of direct switch to rivastigmine patch for those who had difficulties being treated with ChE inhibitors (donepezil and galantamine).

CENA713D1303 study results showed the safety and tolerability of the 1-step titration method is comparable to the slower 3-step titration method in the Japanese mild to moderate AD population. The tolerability of the 1-step titration method was evaluated by comparing the proportion of patients with AEs leading to discontinuation with the 3-step titration method. The proportion of patients who discontinued the study drug treatment due to AEs was 15.0% (16/107) in the 1-step titration group and 18.5% (20/108) in the 3-step titration group. The observed difference between treatments of the proportion of discontinuation due to AEs were -3.6% (95% CI: -17.0, 9.6, Exact method). Since the point estimate of the observed difference falls within the pre-specified acceptance range (i.e. [-9.0%, 9.0%]), the study met its primary objective. The study showed similar efficacy in ADAS-J cog and MMSE score between the 1-step titration and the 3-step titration group at week 24. At week 8, the 1-step titration group showed a slightly greater improvement compared to the 3-step titration group in ADAS-J cog, potentially suggesting an earlier efficacy onset with the quicker titration.

In conclusion, it is clinically meaningful to assess a benefit of quicker titration method to reach the maintenance dose of 18 mg/day and to explore if switching therapy from oral ChE inhibitors to rivastigmine patch with 1 step titration could be a suitable treatment option.

## 4 Population

The study population will consist of a representative group of male and female Japanese patients (50-85 years of age) with probable AD Mini – Mental State Examination (MMSE 10-23), treated with donepezil or galantamine.

This is the multicenter study that will enroll a total of approximately 120 patients which will be switched to rivastigmine patch with 1-step titration in Japan. Since a 30% screening failure rate is expected, 170 patients have to be screened.

#### 4.1 Inclusion criteria

Patients/subjects eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent of the patient and legal representative will be obtained before any assessment is performed (MUST be signed by the legal representative if a signed informed consent from patients is difficult, consent can only be obtained from the patients orally) at Screening.
2. Patients within the age of 50-85 years at Baseline.
3. Outpatient status at Baseline.
4. Males and females not of child-bearing potential.
  - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with/without hysterectomy) or tubal ligation at least six weeks previously.
5. A diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria.
6. A clinical diagnosis of probable AD according to National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and meeting any of following criteria.
  - Brain scan (magnetic resonance imaging [MRI], or computed tomography [CT]) were met diagnosis criteria conducted within 3 years prior to baseline (Imaging within 1 year prior to baseline is preferable).
  - Positron emission tomography (PET) or single photon emission computed tomography (SPECT) was met diagnosis criteria conducted within 3 years prior to baseline visit; as long as in the past a brain scan (MRI or CT) was also met (Imaging within 1 year prior to baseline is preferable).
7. An MMSE score of  $\geq 10$  and  $\leq 23$  at screening and baseline.
8. Patients are currently on the oral monotherapy (donepezil, 5 mg), or galantamine (16-24 mg) for 4 weeks prior to baseline visit.
9. Patients who could not receive treatment benefits of previous oral ChEIs can be defined by meeting the following criteria, either 9-1, 9-2, or both.
  - 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 screening and baseline
    - Patients who declined  $\geq 2$  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  $\geq 2$  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
- 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 screening and 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
- 10. Sufficient education to be able to read, write, and communicate effectively during the premorbid state
- 11. Cooperative, willing to complete all aspects of the study, and capable of doing so, either alone or with the aid of a responsible caregiver
- 12. Residing with someone in the community throughout the study or, if living alone, in contact with the primary caregiver every day
- 13. A primary caregiver willing to accept responsibility for supervising the treatment, (e.g., application and removal of the patch daily at approximately the same time of the day) assessing the condition of the patient throughout the study, and for providing input to efficacy assessments in accordance with all protocol requirements. The caregiver was required to be able to directly assess the condition of the patient during the day and night 4 or more days a week.

## 4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Any medical or neurological condition other than AD that could explain the patient's dementia (e.g., abnormal thyroid function tests, vitamin B12 or folate deficiency, posttraumatic conditions, syphilis, head injury, Huntington's disease, Parkinson's disease, subdural hematoma, normal pressure hydrocephalus, brain tumor) at baseline;
2. A current diagnosis of probable or possible vascular dementia according to the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (NINDS-AIREN) at baseline;
3. 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;
4. Any other DSM-IV Axis 1 diagnosis that may interfere with the evaluation of the patient's response to study medication, including other primary neurodegenerative dementia, schizophrenia, or bipolar disorder at baseline;
5. A current diagnosis of active, seizure disorder at baseline;

6. A history or current diagnosis of severe cerebrovascular disease (e.g., stroke, transient ischemic attacks, aneurysms) at baseline;
7. A current diagnosis of severe or unstable cardiovascular disease (e.g., cardiac failure congestive, angina unstable), hypertension, diabetes at baseline;
8. 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;
9. A current diagnosis of acute, severe, or unstable asthmatoïd conditions (e.g., severe chronic obstructive pulmonary disease (COPD) at baseline;
10. A current diagnosis of active, uncontrolled peptic ulceration or gastro-intestinal bleeding within the last 3 months from baseline;
11. Clinically significant urinary obstruction at baseline;
12. Patients with extrapyramidal disorders (e.g., Parkinson's disease, Parkinson's syndrome).
13. Patients with complication of gastrointestinal adverse events such as nausea and vomiting during oral ChE inhibitors treatment except for such gastrointestinal adverse events if it is apparent to be caused by other than oral ChE inhibitors;
14. Patients with low body weight as judged by the investigators
15. Current diagnosis of an active skin lesion/disorder that would influence to the adhesion and potential skin irritation of the patch (e.g., atopic dermatitis, wounded or scratched skin in the area of the patch application) at baseline;
16. A disability that may prevent the patient from completing all study requirements (e.g., blindness, deafness, severe language difficulty) at baseline ;
17. Patients with a history of hypersensitivity to any ingredients of rivastigmine or carbamate derivatives;
18. Patients who have taken rivastigmine any time in the past;
19. Significantly change of content and frequency of rehabilitation, day care, day service during the 4 weeks prior to efficacy assessment at baseline;
20. 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;
21. Taken any of the following treatments (Potential topical or ophthalmic formulations of the following compounds will be allowed)
  - donepezil > 5 mg/day 4 weeks prior to baseline (Visit 2);
  - Any ChEIs (except for donepezil, galantamine), selegiline, centrally acting anticholinergic drugs, olanzapine or tricyclic and tetracyclic antidepressants during the 4 weeks prior to efficacy assessment at baseline;
  - Change of dosage and regimen of donepezil, galantamine, memantine (patients who have been on a stable dose of memantine during 4 weeks or more prior to efficacy assessment at baseline are allowed to enter the study and may continue to take memantine during the entire study without changing the dosage), psychotropic medication, antidepressants (except for tricyclic and tetracyclic antidepressants), anxiolytics (including benzodiazepine-type hypnotics), antiepileptics, drugs for Parkinson's disease, hypnotics (except for short-acting hypnotics such as zolpidem tartrate and zopiclone etc), agents which improve cerebral circulation/metabolism, vitamin E and estrogens and peripheral anticholinergic agents (except for oxybutynin

- hydrochloride and propiverine hydrochloride, tolterodine tartrate, solifenacin and imidafenacin etc), Yokukan-san, Yokukansankachimpihange during the 4 weeks prior to efficacy assessment at baseline;
- Succinylcholine-type muscle relaxants, lithium during the 2 weeks prior to efficacy assessment at baseline;
  - 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 baseline;
22. Result(s) of laboratory tests at the screening visit:
- total bilirubin 3.0 mg/dL or above;
  - AST (GOT) and/or ALT (GPT) 3 ×ULN or above;
  - serum creatinine 2.0 mg/dL or above;
23. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin;
24. Patients who, in the opinion of the investigator, will be otherwise unsuitable for inclusion in this clinical study (e.g., an advanced, severe, progressive, or unstable disease of any type that may interfere with efficacy and safety assessments or put the patient at special risk);

## 5 Treatment

### 5.1 Study treatment

#### 5.1.1 Investigational and control drugs

Rivastigmine transdermal patch will be supplied as marketed drugs (9 mg, 18 mg patch). Two different rivastigmine strengths 9 mg (5 cm<sup>2</sup>) and 18 mg (10 cm<sup>2</sup>) patch will be used in this study.

No control treatment is planned in this study.

**Table 5-1 Dosage form and drug content for 1 step titration**

Form	Loading dose / Content per one patch	Size
Exelon® patch 9 mg	9 mg rivastigmine	5 cm <sup>2</sup>
Exelon® patch 18 mg	18 mg rivastigmine	10 cm <sup>2</sup>

If patients cannot tolerate 1-step titration method to reach the maintenance patch dose of 18 mg/day, the investigators can 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. Those patients will be allowed to stay in the study. Patients with doses below the planned dose will continue to participate in the study.

**Table 5-2 Dosage form and drug content for 3 step titration**

Form	Loading dose / Content per one patch	Size
Exelon® patch 4.5 mg	4.5 mg rivastigmine	2.5 cm <sup>2</sup>
Exelon® patch 9 mg	9 mg rivastigmine	5 cm <sup>2</sup>
Exelon® patch 13.5 mg	13.5 mg rivastigmine	7.5 cm <sup>2</sup>
Exelon® patch 18 mg	18 mg rivastigmine	10 cm <sup>2</sup>

### **5.1.2 Additional treatment**

Not Applicable.

## **5.2 Treatment arms**

This is an open-label, single arm study; all of the patients will be assigned to 1-step titration treatment.

## **5.3 Treatment assignment and randomization**

Not Applicable.

## **5.4 Treatment blinding**

Treatment will not be blinded during the course of the study, as the study is open-label.

## **5.5 Treating the patient**

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

### **5.5.1 Patient numbering**

Each patient is uniquely identified in the study using 9-digit number which is combination of his/her 4-digit site number and a sequential 5-digit patient number. The site number is assigned by Novartis to the investigative site. Upon signing the ICF, the patient number is assigned a patient number by the investigator. At each site, the first patient is assigned the patient number 1, and subsequent patients are assigned consecutive numbers (e.g. second patient is assigned patient number 2, and third patient is assigned patient number 3). Once assigned to a patient, the Subject Number will not be reused. Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank eCRF available from the electronic data capture (EDC) system. If the patient fails to be registered for any reason, the reason for not being registered will be entered on the Screening Log, and the Demography CRF/eCRF should also be completed.

### **5.5.2 Dispensing the study drug**

Each patient will purchase the drugs from the local pharmacy.





### **5.5.3 Handling of study and additional treatment**

#### **5.5.3.1 Handling of study treatment**

Upon receipt, all drugs should be stored according to the instructions specified on the drug labels. Patients will be asked to bring all unused drug and packaging at the end of the study or at the time of drug discontinuation for evaluating the drug compliance.

Treatment compliance will be investigated by Physician in one of the following categories:

- $<25\%$  Poor
- $25 \leq \sim < 50\%$  Average
- $50 \leq \sim < 75\%$  Good
- $75 \leq \sim \leq 100\%$  Very good
- $> 100\%$  Reason to be specified (overdose or misuse)

In case of over compliance ( $> 100\%$  reason to be specified, e.g. patients who ran out of their drug due to overdose or misuse), the investigators record the reason (overdose or misuse) separately on eCRF.

#### **5.5.4 Instructions for prescribing and taking study treatment**

In general, one rivastigmine transdermal patch should be applied once daily by the caregiver on the back of the patient (alternatively, the patch can be applied to the upper arm or chest). The skin should be clean, and dry with no cuts, rashes, or other skin problems. The rivastigmine patch will be replaced every 24 hours and should be applied at approximately the same time. Additionally, the application site should be changed each time a new patch is applied to avoid skin irritation. When skin reactions appear, appropriate treatment including the use of topical steroids or topical antihistamines may be initiated. Also, other appropriate treatments including dose reductions, temporarily interruption or discontinuation of the treatment should be considered.

##### **Screening Period (Week -4 / -2 to -Day -1)**

During the screening period, patients will continue to receive donepezil or galantamine. At the baseline visit, patients discontinue previous treatment with donepezil or galantamine.

##### **Titration Period (Week 1 to 8)**

The day or following day (in case of a patient who takes his/her previous oral ChE inhibitors at the baseline visit) of the baseline visit (Day 1), all patients will start study treatment with one rivastigmine patch of 9 mg once a day. During the titration period, as a general rule, the dose should be increased to 18 mg once a day at 4 weeks later:

Week 1 – 4: Rivastigmine patch 9 mg/day

Week 5 – 8: Rivastigmine patch 18 mg/day

Should tolerability problems occur during the titration period, the dose can be adjusted in a range not exceeding 18 mg a day as appropriate depending on the clinical symptoms until the dose reaches the maintenance dose. In the event of gastrointestinal disorders (e.g., nausea, vomiting) or other tolerability problems, the dose should be reduced or treatment should be

temporarily interrupted until these adverse effects resolve. Patch treatment can be resumed at the same dose or previous well tolerated dose if interruption of treatment is around or within 4 days. Otherwise, treatment should be resumed at the initial starting dose (e.g. 4.5 mg or 9 mg). After treatment resumption, the dose at resumption should be maintained for a minimum of 2 weeks. If the dose is shown to be well-tolerated, the dose can be increased to the pre-resumption dose at intervals of 2 weeks or more.

Rivastigmine patch dose adjustments required for tolerability problems will be according to the dose adjustment scheme defines in [Section 5.5.5](#).

#### **Maintenance Period (Week 9 to 24)**

The patients will be maintained on the maintenance dose of 18 mg/day rivastigmine patch at the time of Visit 4 (start of the maintenance period) and will undergo safety and efficacy assessments as per protocol. 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.

Decreasing the dose required for tolerability problems will be allowed at any time during the Maintenance Period and conducted according to the dose adjustment scheme defined in [Section 5.5.5](#).

After reducing the dose, investigators can try to increase up to dose of 18 mg/day according to the dose adjustment scheme defined in [Section 5.5.5](#).

All dosages prescribed to the patients and all dose changes during the study must be recorded to the Dosage Administration Record CRF (eCRF).

The investigator should promote compliance by instructing the patients and the caregivers to take the drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact their investigators if he or she is unable for any reason to take the drug as prescribed.

#### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

The dose can be adjusted in a range up to, but not exceeding 18 mg/day as appropriate depending on the clinical conditions until the dose reaches the maintenance dose.

In the event of gastrointestinal disorders (e.g. nausea, vomiting) and other tolerability problems, the dose should be reduced or treatment should be temporarily interrupted until these adverse effects resolve. The following treatment adjustments should be applied, and the actions to be taken in the event of consecutive days of interruption are described in detail in [Table 5-3](#).

**Table 5-3 Actions following dose interruption**

Consecutive days missed	Actions when patients with 9 mg/day patch
≤ 4 days	Can be resumed at the same dose (9 mg/day), and the dose at resumption should be maintained for a minimum of 2 week after treatment resumption. If the dose is shown to be well-tolerated, the dose can be increased to 18 mg/day.
≥ 5 days - ≤ 28 days	Treatment should be resumed at the initial starting dose (9 mg/day), and follow for 1 step titration method to reach the maintenance dose of 18 mg/day.

Consecutive days missed	Actions when patients with 9 mg/day patch
	<p>Patients who still have tolerability issues with 9 mg/day, consider to resume the treatment at the initial starting dose (4.5 mg/day)</p> <p>When resumed at the initial dose of 4.5 mg/day, follow for 3 step titration method.</p> <p>After treatment resumption, the dose at resumption should be maintained for a minimum of 2 weeks. If the dose is shown to be well-tolerated, the dose can be increased to the pre-resumption dose at intervals of 2 weeks or more.</p>
>28 days	Must discontinue study drug administration.
Consecutive days missed	Actions when patients with 18 mg/day patch
≤ 4 days	Can be resumed at the same dose, 18 mg/day
≥ 5 days - ≤ 28 days	<p>Treatment should be resumed at the initial starting dose (9 mg/day) and follow for 1 step titration method to reach the maintenance dose of 18 mg/day.</p> <p>In case of patients showing some tolerability issue with 9 mg/day at this time, repeat same procedure with 9 mg/day described above</p> <p>When resumed at the initial dose of 4.5 mg/day, follow for 3 step titration method.</p> <p>After treatment resumption, the dose at resumption should be maintained for a minimum of 2 weeks. If the dose is shown to be well-tolerated, the dose can be increased to the pre-resumption dose at intervals of 2 weeks or more.</p>
>28 days	Must discontinue study drug administration.

These changes must be recorded on the Dosage Administration Record CRF (eCRF).

### 5.5.6 Rescue medication

Not applicable.

### 5.5.7 Concomitant medication

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded.

### 5.5.8 Prohibited medication

The following medications are prohibited or restricted during specified periods (topical and ophthalmic formulations of the mentioned drugs below are allowed):

#### Prohibited concomitant medications

Use of the following treatments is NOT allowed after the start of study drug (Day 1):

1. Any investigational drug (including topical and ophthalmic investigational drugs).

2. Donepezil, galantamine.
3. Selegiline.
4. Centrally acting anticholinergic drugs.
5. Olanzapine.
6. Tricyclic and tetracyclic antidepressants.
7. Succinylcholine-type muscle relaxants.
8. Lithium.

### **Restricted concomitant medications / non-drug therapies**

The following medications / non-drug therapies are permitted, but with some limitations:

1. Initiation of the following concomitant medications should be avoided during the 4 weeks prior to efficacy assessment at baseline to Visit 8/discontinuation. Patients who have been on a stable dose of these drugs during the 4 weeks or more prior to efficacy assessment at baseline should continue on the dose without changing the dosage and administration:
  - Memantine
  - Yokukan-san
  - Yokukansankachimpihange
  - Agents which improve cerebral circulation/metabolism
  - Vitamin E- Estrogens
2. Initiation of the following concomitant medications should be avoided during the 2 weeks prior to efficacy assessment at Visit 8 if possible. Patients who have been on a stable dose of these drugs during the 4 weeks or more prior to efficacy assessment at baseline should continue on the dose without changing the dosage and administration:
  - Psychotropic medication
  - Antidepressants (tricyclic and tetracyclic antidepressants are prohibited)
  - Anxiolytics (except benzodiazepine-type hypnotics)
  - Antiepileptics
  - Drugs for Parkinson's disease
  - Hypnotics:
3. A new treatment should be limited to the following medications, but the treatment should be at the lowest effective dose and shortest duration possible. Accumulated duration must be 14 days or less during each visit.
  - Psychotropic medication: tiapride hydrochloride
  - Antidepressants : trazodone hydrochloride
  - Nonbenzodiazepine hypnotic of short duration : zolpidem tartrate zopiclone and eszopiclone . Additionally new initiation of treatment and irregular treatment such as on-demand use are prohibited during the 24 hours prior to efficacy assessment at Visit 2, 4, and 8.
4. The following drugs are allowed to use, but not recommended to use.
  - Benzodiazepine anxiolytic (Newly initiation of treatment is prohibited during the previous 24 hours prior to efficacy assessment at Visit 2, 4, and 8): rilmafafone hydrochloride, brotizolam , lormetazepam, triazolam.

5. The following new medication for atypical psychotropic must not be started after starting the study drug (Day1)
  - Risperidone, quetiapine fumarate, perospirone hydrochloride
6. Peripheral anticholinergic agents:  
Patients who have been on a stable dose of these drugs during the 4 weeks or more prior to efficacy assessment at baseline should continue on the dose without changing the dosage and administration. When new-onset urinary urgency or urinary incontinence during the study constitutes an intolerable symptom that cannot be overcome by non-pharmacological measures, initiation of treatment with peripheral anticholinergics such as oxybutynin hydrochloride, propiverine hydrochloride, tolterodine tartrate solifenacin and imidafenacin are permitted.
7. Antitussive agents, cold medicine or antihistaminic anti-allergy agents:  
As a rule, these agents are prohibited 1 week prior to efficacy assessment at baseline and Visit 8.
8. Rehabilitation, day care and day service:  
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).
9. Short stay (hospital / nursing home):  
Short stay should be limited during the previous 2 weeks prior to efficacy assessment at baseline and Visit 8.

#### **5.5.9 Emergency breaking of assigned treatment code**

Emergency breaking is not applicable as this is an open-label study.

### **5.6 Study Completion and Discontinuation**

#### **5.6.1 Study completion and post-study treatment**

At a minimum, caregivers of the patients who complete this study or discontinue the drug, including those who refuse to return for a final visit, will confirm the onset (or no onset) of a SAE during at least 30 days following the last dose of study drug or at the patient's last visit, and the result should be recorded in the source document & in eCRF.

#### **5.6.2 Discontinuation of Study Treatment**

The drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances require drug discontinuation:

1. Where an adverse event has occurred that, in the judgment of the investigator, warrants discontinuation of treatment;
2. Where an abnormal laboratory value has been found that, in the judgment of the investigator, warrants discontinuation of treatment;
3. Where aggravation of the condition has occurred that, in the judgment of the investigator, warrants discontinuation of treatment;

4. Where necessary observation and examination after the initiation of treatment has become impossible for the patient's or his/her caregiver's personal reasons;
5. Where any important deviation from the protocol has become clear;

In addition to these requirements for drug discontinuation, the investigator should discontinue the drug for a given patient if, on balance, he/she thinks that continuation would be detrimental to the patient's well-being.

The investigator should record the last known date a patient takes the drug and select primary reason for premature discontinuation from the following reasons on the study completion page in eCRF.

1. Adverse Event(s)
2. Abnormal lab value(s)
3. Abnormal test procedure result(s)
4. Unsatisfactory therapeutic effect
5. Subject's condition no longer requires study
6. Protocol deviation
7. Subject withdrew consent
8. Lost to follow-up
9. Administrative problem
10. Death

Patients who discontinue the drug should NOT be considered withdrawn from the study. See [Section 6](#) for the required assessments of these patients after discontinuation of the treatment.

### **5.6.3 Withdrawal of informed consent**

Patients/subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information on medical chart.

The drug must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

#### **5.6.4 Loss to follow-up**

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

#### **5.6.5 Early study termination by the sponsor**

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

## **6 Visit schedule and assessments**

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients must be seen for all visits on the designated day, or as close to it as possible as allowed "visit window" of "x" days. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all drugs should be reconciled for compliance purpose and the adverse event and concomitant medications reconciled on the eCRF.

Patients/subjects will be contacted for safety evaluations during the 30 days following the last administration of study treatment.



**Table 6-1 Assessment schedule**

Period	Screening <sup>g)</sup>		Titration		Maintenance			
Visit number	1 (Screening)	2 (BL) <sup>g)</sup>	3	4	5	6	7	8/disc ontinu ation <sup>h)</sup>
Visit Day	-28 ~ -14	1	28	56	84	112	140	168
Visit week	-4 ~ -2	1	4	8	12	16	20	24
Visit Window	-56 ~ -14	-7 ~ 1	21 ~ 35	49 ~ 63	77 ~ 91	105 ~ 119	126 ~ 154	161 ~ 182
Inclusion/Exclusion criteria	X	X						
Obtain Informed consent	X							
Patient demographics/other baseline characteristics	X	X						
Problem of previous ChE inhibitors treatment <sup>a)</sup>	X	X						
Medical history	X							
Previous treatment/concomitant medication/therapy	X	X	X	X	X	X	X	X
Brain scan if required <sup>b)</sup>	X							
MMSE	X	X		X				X <sup>e)</sup>
NPI-10		X		X				X <sup>e)</sup>
QOL-AD		X						X <sup>e)</sup>
J-CGIC			X	X		X		X <sup>e)</sup>
Modified Crichton Scale		X	X	X		X		X <sup>e)</sup>
Adverse events		X	X	X	X	X	X	X
Vital sign	X	X	X	X	X	X	X	X
Laboratory evaluation Regular hematology, blood chemistry, cholinesterase, urine test	X							X
Additional Screening blood test for differential diagnosis if necessary	X							
ECG		X						X
Formulation usability questionnaire <sup>c)</sup>								X
Treatment compliance <sup>d)</sup>			X	X	X	X	X	X

(a) Based on the short interview to caregiver by the physician, however, inclusion and exclusion will be judged by physician. This is confirmatory information from caregiver for screening the patients.

(b) Imaging test can be performed at screening visit if latest imagings of a patient are more than 3 years old from baseline.

(c) Based on answer of questionnaire from the caregiver

(d) Based on the interview and assessment by investigators

(e) These assessments are not mandatory at discontinuation due to adverse events

(f) During the screening period, patients will continue receiving their previous medication (donepezil or galantamine)

(g) At the baseline visit, patients discontinue their previous ChE inhibitors (donepezil, galantamine) and could start the initial dose of 9 mg/day rivastigmine patch after cleared all necessary assessment for enrollment. If patients already take their previous ChE inhibitors on the day of baseline visit, the patients should start the initial dose of 9 mg/day rivastigmine patch on the following day (Day 1).



(h) If a patient discontinues the study, scheduled assessment should be performed as soon as possible, but visit window is not set.

## **6.1 Information to be collected on screening failures**

For patients who provided written informed consent but did not complete the baseline visit (withdrawn during the screening period), the investigator will record the withdrawal until baseline visit on the Screening Log, and will record the patient identifier, age, gender and the reason for not being registered on the eCRF.

## **6.2 Patient demographics/other baseline characteristics**

The following items should be investigated at the day of obtaining informed consent to baseline visit or before. Then, the other necessary items such as prior medication, MMSE, vital signs, ECG, and laboratory tests should be investigated or conducted for confirming eligibility.

### **Patient demographics**

Investigate the following items, and record the results in the clinical record and the eCRF. About medical history, only diseases which are related to the Inclusion/Exclusion Criteria or which are judged significant by investigator will be investigated and recorded. Record the problems associated with prior use of oral anti-AD medications

### **Investigation items**

Sex, date of birth, family history, relation of caregiver, date of diagnosis, date of disease onset, years of education, living situation, height, weight, current medical condition, medical history, problems with administration of oral anti-AD medications, [REDACTED].

Additionally, diagnosis of dementia of Alzheimer's type (DSM-IV, NINCDS-ADRDA, NINDS-AIREN) and MHIS should be investigated and recorded in the source document.

### **Brain scan**

A brain scan (MRI or CT) is required at screening but only if one has not been performed in the last three years prior to baseline although the brain scan within one year prior to baseline is preferable. Taking into account the patient burden, these previous brain scan data can be used to confirm diagnosis if the signed informed consent of the patient and legal representative allow the use of this data. Alternatively, if at screening a PET or SPECT is available, which had been performed in the last three years, any MRI or CT conducted in the past will be sufficient.

These scans are performed to establish that entry criteria are met. As outlined above, with the consent of the patient, scans performed before the study will be allowed to reduce the patient burden.

### **Screening Test (Laboratory test) if necessary**

The special laboratory tests are to be performed to exclude non-Alzheimer type dementias during the screening period.

### **Investigation items**

[REDACTED]

Folic acid, vitamin B12, triiodothyronine (T3), total thyroxine (T4), and thyroid stimulating hormone (TSH)

### **Methods of collection, processing and storage of blood samples**

Approximately 9-mL sample of venous blood will be collected in an AutoSep vacutainer for each patient. After blood sampling, each investigator should follow the blood test procedure of each study site where he/she belongs to.

## **6.3 Treatment exposure and compliance**

### **Previous treatment**

At screening and baseline visit, all treatments which had been received within 4 weeks before and during the screening period, will be reviewed and record name of drug and therapy, dosage and administration, period/duration and reasons for use in the eCRF.

### **Concomitant medication/therapy**

Record the drug names, dosage and administration, period/duration and reasons for use in the eCRF for all treatment used concomitantly during treatment period.

## **6.4 Efficacy**

To ensure the sensitivity and reliability of the efficacy assessments, the same rater for a given instrument will, whenever possible, assess the status of a given patient in every evaluation. All efficacy assessments will be conducted as specified in [Table 6-1](#). The result of these assessments will be recorded in the eCRF. All efficacy assessments at discontinuation will not be conducted if patients discontinue because of an adverse event.

### **6.4.1 Mini-Mental state examination (MMSE)**

MMSE will be conducted at Visit 1, 2, 4 and 8 (refer [Table 6-1](#)). MMSE at premature discontinuation will not be conducted if patient discontinues because of adverse event.

### **Assessment Items**

The MMSE is a brief, practical screening test for cognitive dysfunction. The MMSE consists of 2 parts: language (time orientation, registration and attention) and performance (recall, response to written/verbal commands, writing ability and reproduction of complex polygons), and the total possible score is 30. Lower score indicates more severe impairment ([Folstein MR et al, 1975](#)).

### **Method of assessment**

Throughout the study, the same rater (an attending physician of a given patient, a psychologist, or a medical staff who has been trained in psychologist equivalent and carried out MMSE scoring more than 50 times) will assess the status of a given patient whenever possible.

#### **6.4.2 Neuropsychiatric Inventory-10 (NPI-10):**

NPI-10 will be conducted at Visit 2, 4 and 8 (refer [Table 6-1](#)). NPI-10 at premature discontinuation will not be conducted if patient discontinues because of adverse event.

##### **Assessment Items**

The NPI-10 is a scale for neuropsychiatric symptoms. The NPI assesses a wide range of behaviors encountered in dementia patients to provide a means of distinguishing frequency and severity of behavioral changes, and facilitates rapid behavioral assessment through the use of screening questions ([Cummings et al. 1994](#)). Ten behavioral domains are evaluated through an interview of the caregiver. The scale includes both frequency and severity ratings of each domain as well as a composite domain score (frequency x severity). The sum of the composite scores for the 10 domains yields the NPI-10 total score. A higher score indicates more severe impairment.

##### **Method of assessment**

Throughout the study, the same rater (e.g. an attending physician of a given patient, a psychologist, or a medical staff who has been trained in psychologist equivalent ) will assess the status of a given patient whenever possible.

#### **6.4.3 J-CGIC (Japanese version of the Clinical global impression of change)**

J-CGIC will be conducted at Visit 2, 3, 4, 6 and 8 (refer [Table 6-1](#)). J-CGIC at premature discontinuation will not be conducted if patient discontinues because of adverse event.

##### **Assessment Items**

The J-CGIC is simple 7 grade investigator's impression scale (1. Markedly improved, 2. Improved, 3. Slightly improved, 4. No change, 5. Slightly aggravated, 6. Aggravated, 7. Markedly aggravated) ([Homma et al, 2000](#)). The J-CGIC is an assessment which requires a clinician to make a judgment of severity or change with minimal guidelines. This rating instrument is based upon the clinician's experience.

##### **Method of assessment**

Throughout the study, the same rater (an attending physician) will assess the status of a given patient.

#### **6.4.4 Quality of Life- Alzheimer's Disease (QOL-AD)**

QOL-AD will be conducted at Visit 2, and 8 (refer [Table 6-1](#)). QOL-AD at premature discontinuation will not be conducted if patient discontinues because of adverse event.

##### **Assessment Items**

QOL-AD is a 13-item questionnaire to assess the quality of life of Alzheimer's patients from the perspectives of patients and their caregivers. It covers several aspects, for example, the perception of health status, mood, functional capacity, personal relationships and leisure, financial situation, and life as a whole ([Logsdon et al, 1999](#)). Each item is quantified using a Likert scale with score one classified as poor, and score four as excellent where total scores range from 13 to 52.

## **Method of assessment**

Caregivers complete the measure as a questionnaire about their patients' QOL, while patients complete it in interview format about their own QOL. The form should be handed to the participant, so that he or she may look at it as a rater gives the instructions. 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. Throughout the study, the same rater (e.g. an attending physician of a given patient, a psychologist, or a medical staff who has been trained in psychologist equivalent) will give the instructions to both caregivers and patients.

### **6.4.5 Modified Crichton Scale**

Modified Crichton scale will be conducted at Visit 2, 3, 4, 6 and 8 (refer [Table 6-1](#)). Modified Crichton scale at premature discontinuation will not be conducted if patient discontinues because of adverse event.

#### **Assessment Items**

The following 7 items will be evaluated by caregiver. Total score is in the 0 to 56 range. Higher score means more severe impairment.

Orientation, Conversation, Cooperation with family and caregiver, Restlessness, Dressing and clothes, Job and social activities/roles, Leisure activities ([Homma 2000](#)).

A higher score means more severe impairment.

## **Method of assessment**

The assessment will be performed by caregiver with using the care diary and the results will be recorded on the eCRF.

### **6.4.6 Appropriateness of efficacy assessments**

The MMSE is a brief, practical screening test for cognitive dysfunction. It is the most common and simple cognitive scale for AD ([Folstein 1975](#)).

To confirm whether worsening AD symptom is observed after switching from ChE-inhibitors, assessment of J-CGIC is scheduled at every 4-week for the first 2 months and at every 8-week for the rest of the study. J-CGIC is simple 7 grade investigator's impression scale ([Homma 2000](#)).

Modified Crichton Scale is to assess basic activation of daily living, communication functions, and quality of life ([Homma 2000](#)).

Neuropsychiatric Inventory (NPI) is developed to assess neuropsychiatric symptoms and psychopathology of patients with Alzheimer's disease and other neurodegenerative disorders through the use of screening questions ([Cummings et al. 1994](#)). NPI is commonly used in both clinical trials and clinical practices for assessing behavioral and psychological symptoms of dementia.

QOL-AD is a 13-item questionnaire to assess the quality of life of Alzheimer's patients from the perspectives of both patients and their caregivers. It is simple to administer and rating

consistency of score between patients and their caregivers has been validated ([Logsdon et al. 2002](#)). In addition, multinational translational version of original QOL-AD including Japanese has been validated ([Matsui et al. 2006](#)).

## **6.5 Safety**

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs).

### **6.5.1 Physical examination**

Medical examination will be conducted at patient visit. The investigator will check the patient's condition by direct medical examination. Subjective symptoms will be monitored for at length by direct medical interview with the patients. The care diary will be referred in medical examination. Any abnormality recognized as such compared to pre-administration will be recorded as an adverse event.

### **6.5.2 Vital signs**

The following items will be measured at patient visit (refer to [Table 6-1](#)).

#### **Examination items**

Systolic/diastolic blood pressure, pulse rate, body weight

#### **Methods of monitoring**

Systolic/diastolic blood pressure and pulse rate will be measured in a sitting position. Body weight will be measured.

### **6.5.3 Laboratory evaluations**

The following items will be measured at patient visit (refer to [Table 6-1](#)).

#### **Laboratory items**

Hematology;

Erythrocyte count, leukocyte count, hemoglobin, hematocrit, platelet count.

Blood chemistry;

Total protein, uric acid, ALP, AST, ALT, LDH, cholinesterase, BUN, creatinine, Na, K, Cl, total cholesterol, triglycerides, CPK, albumin, Ca, P, total bilirubin, amylase.

Urinalysis

Glucose, protein, occult blood.

#### **Amounts of test samples to be collected as standard guidance**

- Hematology: App. 2.0-mL sample of blood will be collected at screening visit and Visit 8 or discontinuation for a total of app. 4.0 mL.

- Blood chemistry: At screening, app. 9.0 mL sample of blood, and app. 4.0 mL blood at Visit 8 or discontinuation will be collected in an AutoSep vacutainer for a total of app. 13 mL.

### **Methods of collection, processing and storage of test samples**

Samples of venous blood will be collected.

After blood sampling, each investigator should follow the blood test procedure of each study site where he/she belongs to.

### **Laboratory measuring these items**

The hematology and blood chemistry tests will be performed by the laboratory measurement described on [[Appendix 2](#)].

#### **6.5.3.1 Urinalysis**

- Urinalysis: App. 5-mL sample of urine will be collected at each of 2 points for a total of app. 10 mL
- For urinalysis, each investigator should follow urine sample procedure of each study site where he/she belongs to.

#### **6.5.4 Electrocardiogram (ECG)**

ECG will be measured at patient visit (refer to [Table 6-1](#)).

##### **Assessment items**

Standard 12-lead ECG, ECG readings (heart rate, PR interval, QRS duration, QT interval, QTcB\*, QTcF\*)

\*: These data will be calculated by EDC system, and the calculated data is input to eCRF automatically.

##### **Method of assessment**

ECG will be taken in a supine position after rest.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

#### **6.5.5 Pregnancy and assessments of fertility**

Please refer to [Section 7.6](#).

#### **6.5.6 Appropriateness of safety measurements**

The safety assessments selected are standard for this indication/patient population.

### **6.6 Other assessments**

Formulation usability questionnaire



The Formulation usability preference questionnaire will be used to compare the previous oral AD drugs versus the patch in this study and will be completed at Visit 8 (or discontinuation). The caregiver will select one of the following answers (1. Very easy to use, 2. Easy to use, 3. No change, 4. Not easy to use, 5. Not easy to use at all, 6. Unknown). The caregiver answer in the questionnaire should be recorded in eCRF. The reason for the answer should be recorded in eCRF as possible.

### **Treatment compliance**

The status of application of study drug patches will be investigated at every visit between Visit 3 and Visit 8 (or discontinuation).

### **Investigation Items**

The status of application of rivastigmine patches

### **Methods of investigation**

Treatment compliance will be investigated by Physician in one of the following category:

- $<25\%$  Poor
- $25 \leq \sim < 50\%$  Average
- $50 \leq \sim < 75\%$  Good
- $75 \leq \sim \leq 100\%$  Very good
- $> 100\%$  Reason to be specified (overdose or misuse)
- In case of over compliance ( $> 100\%$  Reason to be specified, e.g. patients who ran out of their drug due to overuse or misuse), the investigators record the reason (overdose or misuse) separately on eCRF.

The results of treatment compliance should be recorded in eCRF by the interview to either patients or caregivers. "Applied day" is defined as a date when patch has been applied for more than 16 hours.

#### **6.6.1 Resource utilization**

Not applicable.

#### **6.6.2 Pharmacokinetics**

Not applicable.

## **7 Safety monitoring**

### **7.1 Adverse events**

An adverse event (AE) is appearance of worsening of any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Study treatment includes the study medication under evaluation given during any phase of the study.

Medical conditions/diseases present before starting study treatment will only be considered AEs if they worsen after starting study treatment. Non-serious AEs occurring before starting study treatment but after signing the informed consent form will be recorded on the Medical History/Current Medical Conditions pages in eCRF. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events which were observed from the first treatment of the drug to the last treatment of the drug must be recorded on the Adverse Events eCRF with the following information:

The severity grade (mild, moderate, severe)

Its relationship to the drug(s) of interest (suspected/not suspected)

Its duration (start and end dates or if continuing at final exam)

Whether it constitutes a serious adverse event (SAE- see [Section 7.2](#) for definition of SAE)

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); the drug dosage adjusted/temporarily interrupted; the drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the AE pages in eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the drug can be found in the Package Insert (PI) or will be communicated between PI updates in the form of individual safety report or periodic safety update report and others. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

## **7.2 Serious adverse events**

### **7.2.1 Definition of SAE**

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:



- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcome listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the SAE definition criteria and not resulting in hospitalization.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the eCRF, SAEs also require individual reporting to Novartis Drug Safety & Epidemiology department (DS&E) as per [section 7.2.2](#).

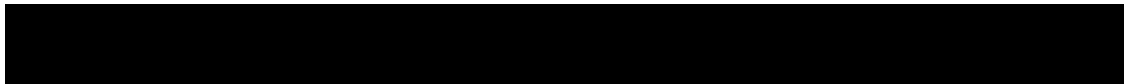
### **7.2.2 SAE reporting**

Each Serious Adverse Event (SAE), regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of drug taken or last visit whichever is later) will be reported by the investigator to Novartis DS&E by FAX within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The principle investigator must assess the relationship of any SAE to the drug, complete the SAE Report Form, and send the completed, signed form by fax within 24 hours to Novartis Drug Safety and Epidemiology Department. In case of emergency, investigator other than principle investigator or staff can act for it instead of the principle investigator. The telephone and telecopy number of the contact persons in the local department of Clinical -Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The principle investigator must submit to Novartis monitor the original SAE report. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Any SAEs experienced after this 30 day period should only be reported to Novartis DS&E by FAX if the investigator suspects a causal relationship to the drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information by the principle investigator. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.



Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report by FAX. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is thought to be related to the drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an individual safety report and others to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### 7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of the drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to [Table 14-1 in Appendix 2](#) for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in [Table 14-1 of Appendix 2](#) should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in [Table 14-2 in Appendix 2](#).

For the liver laboratory trigger:

- Repeating the liver function test (LFT) to confirm elevation as appropriate.

Repeat laboratory tests must be entered on the appropriate unscheduled local laboratory CRF page.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)

- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

## **7.4 Renal safety monitoring**

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - Confirmed (after  $\geq 24$ h) increase in serum creatinine of  $\geq 25\%$  compared to baseline during normal hydration status
- Urine event
  - New onset ( $\geq 1+$ ) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - New onset ( $\geq 1+$ ), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in [Table 15-1 in Appendix 3](#) should be followed up by the investigator or designated personnel at the trial site as summarized in [Appendix 3](#).

## **7.5 Reporting of study treatment errors including misuse/abuse**

Not applicable

## **7.6 Pregnancy reporting**

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the drug.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took the drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

## **8 Data review and database management**

### **8.1 Site monitoring**

Before study initiation, at a site initiation visit, a CRO working on behalf of Novartis will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol, to Good Clinical Practice (GCP) and Good Post-marketing Study Practice (GPSP), the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. *[Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs.]* The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

### **8.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the EDC system (OC/RDC system). Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

### **8.3 Database management and quality control**

A CRO working on behalf of Novartis reviews the data entered into the eCRFs by investigational staff for completeness and accuracy, and instructs the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Japan Head of Medical Division.

#### **8.4 Data Monitoring Committee**

Not required.

#### **8.5 Adjudication Committee**

Not required.

### **9 Data analysis**

The analysis will be conducted on all subject data at the time the trial ends.

#### **9.1 Analysis sets**

##### **Full Analysis Set (FAS)**

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

##### **Per protocol Set (PP)**

The per protocol set will include all patients in FAS 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.

#### **9.2 Patient demographics and other baseline characteristics**

Descriptive statistics for background and demographic characteristics will be summarized.

The number and percentage of patients according to reasons of study participation should be provided (based on inclusion criteria: lack/loss efficacy or intolerability to previous ChE inhibitors).

#### **9.3 Treatments**

A data listing of the drug doses administered by patients will be provided. The number and percentage of patients exposed will be provided as well as the summary statistics for the duration of exposure.



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

The number and percentage of patients receiving concomitant medications and significant non-drug therapy will be summarized by preferred term (coded by World Health Organization [WHO] and Anatomic Therapeutic Chemical classification [ATC]).

## **9.4 Analysis of the primary variable(s)**

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).

### **9.4.1 Variable(s)**

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.

### **9.4.2 Statistical model, hypothesis, 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 will be used to model the within-subject error. 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.

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

### **9.4.3 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.

No other imputation methods will be considered.

### **9.4.4 Sensitivity analyses**

As supportive analysis, the primary endpoint will be analyzed for the FAS as follows:

1. The change from baseline to Week 24 in MMSE total score will be analyzed using a t-test. 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.
2. 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. 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.

Subgroup analyses will be performed as necessary. The details will be described in the Statistical Analysis Plan.

## **9.5 Analysis of secondary variables**

### **9.5.1 Efficacy variables**

All secondary efficacy variables will be analyzed using the FAS.

#### **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.

#### **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 items, 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 for each sub-item will be summarized descriptively at visits 4 and 8.

For change from baseline to Week 24, summary statistics and 95% CI of the mean will be derived for FAS.

#### **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 week 4, 8, 16 and 24. 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.

#### **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 4, 8, 16, 24.

For change from baseline, summary statistics and 95% CI of the mean will be derived for FAS at Week 4, 8, 16, and Week 24.

### **9.5.2 Resource utilization**

Not applicable.

### **9.5.3 Pharmacokinetics**

Not applicable.

## **9.6 Analysis of [REDACTED] variables**

### **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.

### **9.6.2 Safety variables**

All safety variables will be reported using the safety set.

### **Adverse events**

All adverse events will be coded utilizing the MedDRA dictionary, tabulated, and analyzed by primary system organ class and preferred term.

These adverse events will be summarized by overall, by study periods Week 1 to Week 4 (while on Rivastigmine 9 mg/day) and by every 4 week period starting Week 4 to Week 24 (while on Rivastigmine 18 mg/day), severity, relationship to study drug, death, serious adverse events (SAE), adverse event leading to study drug discontinuation, adverse event leading to study drug interruption/adjustment.

### **Vital signs**

Summary statistics of absolute value and change from baseline will be provided by visit. Abnormal values/changes will be summarized and listed.

### **9.6.3 Other assessment**

#### **Formulation usability questionnaire**

This questionnaire data is used to assess if the rivastigmine patch is preferred over the previous ChIE treatment by the majority (greater than 50%) of AD patient caregivers. This will be



assessed using the direct preference question in the follow-up questionnaire. The proportion of caregivers choosing the patch over the previous medication will be summarized with two-sided 95% confidence intervals for the FAS.

In addition, reasons for medication preference in the questionnaire will be summarized by presenting the frequencies of endorsed reasons for those preferring the previous pill medication and for those preferring the patch.

### **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  $\geq 75\%$  during the last 8 weeks of maintenance period (compliance will be categorized as  $>0\%$  to  $25\%$ ,  $>25\%$  to  $50\%$ ,  $>50\%$  to  $75\%$ ,  $>75\%$  to  $100\%$  and  $>100\%$ ).

## **9.7 Interim analyses**

Not applicable.

## **9.8 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 study. Assuming drop-outs, a total of 120 patients will be enrolled to achieve at least 97 evaluable subjects.

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare[GCP, GPSP]), and with the ethical principles laid down in the Declaration of Helsinki.

### **10.2 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient.



In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

### **10.3 Responsibilities of the investigator and IRB/IEC**

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

### **10.4 Publication of study protocol and results**

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **11 Protocol adherence**

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should



be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

## 11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in [Section 7](#) Safety Monitoring must be followed. Novartis should be notified of this action and the IRB at the study site should be informed within 10 working days.

## 12 References

References are available upon request

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## **13 Appendix 1: Severity of adverse events, causal relationship to drug, and action taken for adverse events**

### **Adverse Events**

#### **Severity of adverse events**

The severity of adverse events (signs and symptoms) should be assessed in the following 3 grades, based in principle on the indicated criteria, and recorded on the eCRF:

1. Mild: An adverse event that allows continued treatment without intervention.
2. Moderate: An adverse event that allows continued treatment with some intervention.
3. Severe: An adverse event that requires discontinuation of treatment.

#### **Causal relationship to study drug**

The causal relationship of adverse events to the study drug should be assessed according to the following 2 categories. When it is assessed as not suspected, the reason should be documented on the eCRF:

0. Not suspected: Time relationship to the study drug is indefinite, and the occurrence can be fully explained by concomitant medication, other therapeutic intervention or patient background factors.
1. Suspected: Time relationship to the study drug exists, and the occurrence cannot be fully explained by concomitant medication, other therapeutic intervention or patient background factors.

#### **Action taken for adverse events**

When any action is taken for adverse events, its content should be specified from among the following 5 categories (More than one may be chosen):

1. Study drug dosage adjusted/temporarily interrupted.
2. Study drug permanently discontinued due to the adverse event.
3. Concomitant medication taken.
4. Non-drug therapy given.
5. Hospitalization/prolonged hospitalization

## 14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

**Table 14-1 Liver Event and Laboratory Trigger Definitions**

	Definition/ threshold
LIVER LABORATORY TRIGGERS	<ul style="list-style-type: none"> <li>3 x ULN &lt; ALT / AST ≤ 5 x ULN</li> <li>1.5 x ULN &lt; TBL ≤ 2 x ULN</li> </ul>
LIVER EVENTS	<ul style="list-style-type: none"> <li>ALT or AST &gt; 5 x ULN</li> <li>ALP &gt; 2 x ULN (in the absence of known bone pathology)</li> <li>TBL &gt; 2 x ULN (in the absence of known Gilbert syndrome)</li> <li>ALT or AST &gt; 3 x ULN and INR &gt; 1.5</li> <li>Potential Hy's Law cases (defined as ALT or AST &gt; 3 x ULN and TBL &gt; 2 x ULN [mainly conjugated fraction] without notable increase in ALP to &gt; 2 x ULN)</li> <li>Any clinical event of jaundice (or equivalent term)</li> <li>ALT or AST &gt; 3 x ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia</li> <li>Any adverse event potentially indicative of a liver toxicity*</li> </ul>

\*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

**Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers**

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case <sup>a</sup>	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> <li>Hospitalize, if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
<b>ALT or AST</b>		
> 8 x ULN	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 x ULN and INR > 1.5	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> <li>Hospitalize, if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, continue follow-up monitoring</li> <li>If elevation persists for more than 2 weeks, discontinue the study drug</li> <li>Establish causality</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	<ul style="list-style-type: none"> <li>Complete liver CRF</li> </ul>	
> 3 × ULN accompanied by symptoms <sup>b</sup>	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks
<b>ALP (isolated)</b>		
> 2 × ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
<b>TBL (isolated)</b>		
> 2 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> <li>Hospitalize the patient</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> <li>Consider study treatment interruption or discontinuation</li> <li>Hospitalization if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion

<sup>a</sup> Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

<sup>b</sup> (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

<sup>c</sup> Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

## 15 Appendix 3: Specific Renal Alert Criteria and Actions

**Table 15-1 Specific Renal Alert Criteria and Actions**

<b>Serum Event</b>	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
<b>Urine Event</b>	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR )≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
<b>For all renal events:</b>	
<p><u>Document contributing factors in the CRF:</u> co-medication, other co-morbid conditions, and additional diagnostic procedures performed</p> <p>Monitor patient regularly (frequency at investigator's discretion) until either:</p> <p>Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or</p> <p>Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.</p>	