National Institute for Health Research

CHIEF PD

CHOLINESTERASE INHIBITORS TO PREVENT FALLS IN PARKINSON'S DISEASE

CHIEF-PD (**CH**olinesterase **I**nhibitor to pr**E**vent **F**alls in **P**arkinson's **D**isease): A phase 3 randomised, double-blind placebo-controlled trial of rivastigmine to prevent falls in Parkinson's disease.

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University of BRISTOL

Bristol Randomised Trials Collaboration

This protocol has regard for the HRA guidance

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Contents

GLOSSARY OF ABBREVIATIONS

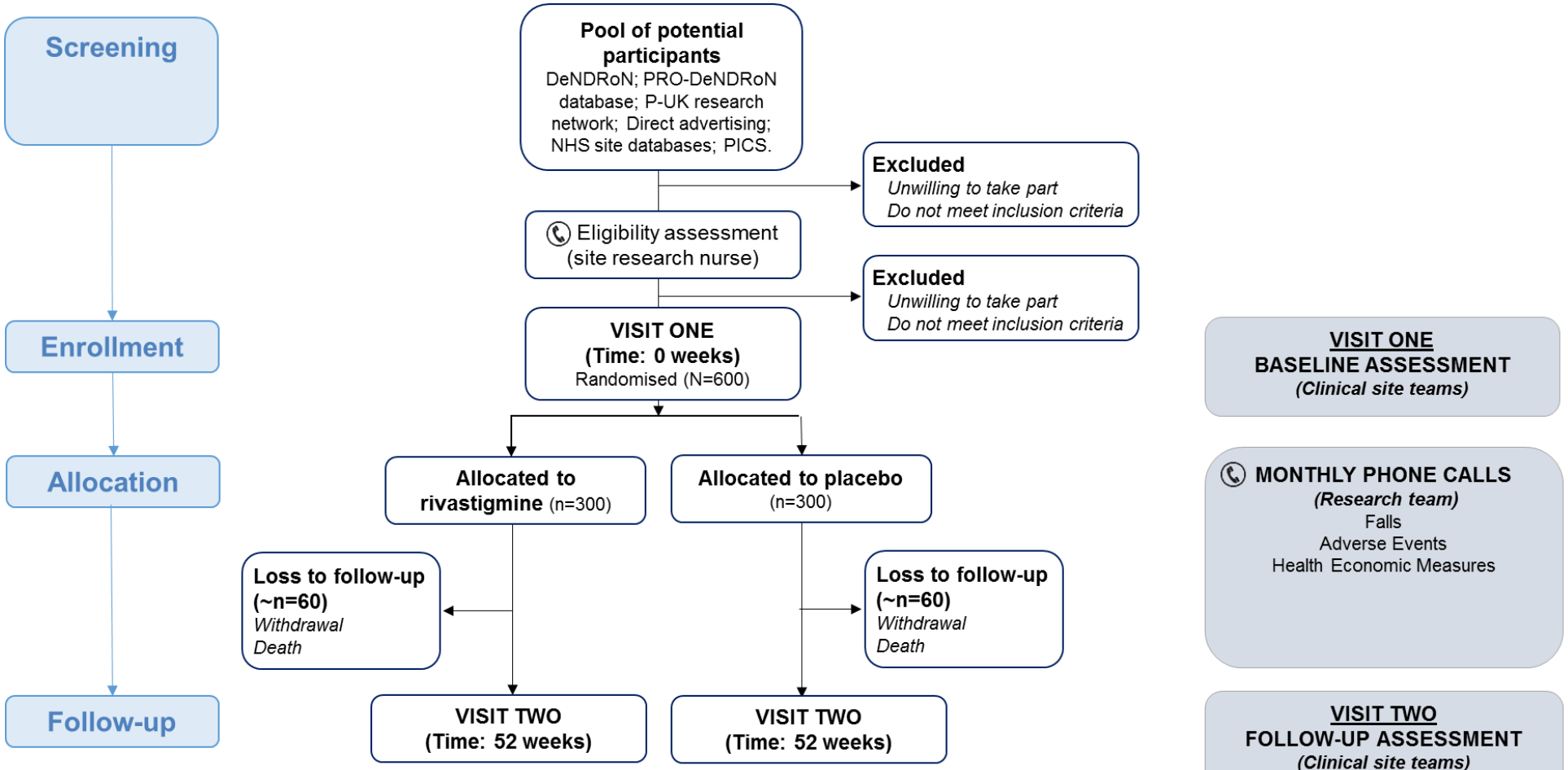
AE	Adverse Event
AR	Adverse Reaction
BTC	Bristol Trials Centre
ChEi	Cholinesterase inhibitor
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
DSUR	Development Safety Update Report
EC	European Commission
EU	European Union
FOG	Freezing of Gait
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
MDS	Movement Disorders Society
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS R&D/R&I	National Health Service Research & Development/Research & Innovation
NIHR CRN	National Institute of Health Research Clinical Research Networks
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PDG	Portfolio Development Group
PIB	Participant Information Booklet
PPI	Patient and Public Involvement
PQ	Participant Questionnaires
QALY	Quality Adjusted Life Years
RCT	Randomised Control Trial
RDSF	Research Data Facility Storage
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UH Bristol	University Hospitals Bristol and Weston NHS Foundation Trust
UoB	University of Bristol

TRIAL SUMMARY

Trial Title	A multicentre, phase III, double blind, randomised control trial of the cholinesterase inhibitor, rivastigmine versus placebo to prevent falls in Parkinson's disease
Short title	(Cholinesterase inhibitors to prevent falls in Parkinson's Disease) CHIEF-PD
Chief Investigator	Dr Emily Henderson
Sponsor	University of Bristol
Funder	NIHR Health Technology Assessment Programme
Trial Design	Randomised, participant and assessor blinded, placebo-controlled study
Trial Participants	Adults with a diagnosis of Parkinson's disease
Trial population and size	600 participants randomised with Parkinson's disease who have fallen in the past year
Number of study sites	>26
Intervention	Transdermal rivastigmine 4.6mg / 9.5mg / 13.3mg versus placebo (1:1 ratio)
Treatment duration	12 months
Inclusion criteria	a. Diagnosis of idiopathic Parkinson's disease. b. Modified Hoehn and Yahr stage 1-4 disease. c. Have experienced a fall in the previous year. d. Able to walk ≥10m without aids or assistance. e. 18 years of age or above.
Exclusion criteria	a. Previous ChEi use in 12 months prior to enrolment. b. Hypersensitivity to rivastigmine c. Dementia diagnosed according to Movement Disorder Society (MDS) criteria. d. Inability to attend or comply with treatment or follow-up scheduling. e. Non-English-speaking patients (cognitive tests performed in English). f. Falling ≥4x per day. g. Unwillingness to use an acceptable method of contraception for the duration of the trial if they are of childbearing potential. h. Pregnancy and/or breastfeeding
Primary objective	To determine the difference in fall rate between people with Parkinson's disease treated for 12 months with a cholinesterase inhibitor and those treated with placebo.
Primary outcome	Fall rate over 12 months

Secondary objective	a) To determine the effect of 12 months of treatment with ChEi versus placebo on: i. PD severity ii. Freezing of gait iii. Frailty and physical performance iv. Cognition v. Depression vi. Apathy vii. Fear of falling viii. Dysphagia ix. Participant health related quality of life and capability x. Carer quality of life xi. Mortality xii. NHS, social service, and informal care costs and hospital admissions. b) To determine the overall cost-effectiveness of the treatment measured with EQ-5D-5L.
Study duration	From April 2018 to the last patient last visit + 3months

TRIAL FLOWCHART



DeNDRoN: Dementia and Neurodegenerative Diseases Research Network; PRO-DeNDRoN: Parkinson's Register of the Dementias and Neurodegenerative Diseases Research Network; P-UK: Parkinson's UK; NHS: National Health Service; PICS: Patient Identification Centers; HES: Hospital Episode Statistics; Telephone calls

TRIAL PROTOCOL TITLE

CHIEF-PD (Cholinesterase Inhibitor to prEvent Falls in Parkinson's Disease): A phase 3, randomised double-blind, placebo-controlled trial of rivastigmine to prevent falls in Parkinson's disease.

1. BACKGROUND AND RATIONALE

Cognitive impairment and gait dysfunction commonly coexist and are potent antecedents of falls in other neurodegenerative conditions including dementia, stroke, frailty and ageing. Parkinson's disease (PD) is second only to Alzheimer's disease, as the most common neurodegenerative disease.

There is a high incidence of falls in patients with PD. A quarter of people with PD fall at least once a month and they are twice as likely to fall on recurrent occasions compared to older people. Falls lead to hospital admissions, hip fracture, fear of further falling, increased dependency and nursing home placement. Reduced mobility is associated with constipation, pressure sores, poor sleep and osteoporosis.

To compensate for gait slowing and instability people with PD need to pay more attention to their walking in order to not fall. However, even in early disease, executive dysfunction attenuates the cognitive attentional resource that is available. Stability is particularly compromised during the execution of complex motor activities (e.g. turning) or whilst walking and performing concurrent tasks where demands on attention outweigh available resource. Gait therefore becomes unstable and falls occur.

The propensity to fall results from underlying loss of cholinergic function in cognitive (frontocortical) and gait (mesencephalic locomotor area) critical brain areas. Animal studies have established that the dual loss of dopaminergic and cholinergic networks precipitates gait instability, freezing of gait and falls in PD (1). Amelioration of this underlying cholinergic deficient with cholinesterase inhibitors (ChEis) represents a promising strategy, targeting the aetiology of falls in PD. Efficacy has been suggested in 3 small, phase 2 trials (2–4) .

A phase 3 trial is required with a larger sample to definitively estimate the clinical and cost effectiveness of ChEis in this population. This will determine whether the reduction in falls achieved in small single centre studies can be matched in a larger multi–centre trial delivered in standard NHS clinics. Unlike phase 2 trials, the treatment will be delivered as in clinical practice (transdermally, over a longer time, at higher doses). The trial will specifically determine a) clinical and cost -effectiveness b) the impact of treatment on health and Quality of Life measures and c) whether the intervention operates through cognitive improvement. Emergent evidence suggests that there may a relationship between gait, falls and dysphagia with exploratory data showing a correlation between dysphagia severity and falls efficacy (15). Quantification therefore of the degree of dysphagia will be undertaken as these axial symptoms that are refractory to dopaminergic therapy may share non-dopaminergic pathophysiology in the brain that can be targeted with ChEi therapy.
This multi-centre double-blind Randomised Control Trial (RCT) will establish whether ChEi compared to placebo prevents falls. CHIEF-PD will provide definitive evidence that can be immediately translated into clinical practice. Powered to detect a treatment effect that is meaningful to clinicians and patients it will also establish the cost-effectiveness of the treatment in preventing falls which are potentially devastating for patients and expensive for the NHS. Positive findings will provide robust evidence to change clinical practice.

2. AIMS AND OBJECTIVES

2.1. Aim

To determine whether ChEi treatment reduce the rate of falls in Parkinson's and is cost-effective.

2.2. Primary objective

To determine the difference in fall rate over 12 months between people with PD treated for 12 months with a ChEi and those treated with a placebo.

2.3. Secondary objectives

a) To determine the effect of 12 months of treatment with ChEi versus placebo on
   i. PD severity
   ii. Freezing of gait
   iii. Frailty and physical performance
   iv. Cognition
   v. Depression
   vi. Apathy
   vii. Fear of falling
   viii. Dysphagia
   ix. Participant health related quality of life and capability
   x. Carer quality of life
   xi. Mortality
   xii. NHS, social service, and informal care costs and hospital admissions.
b) To determine the overall cost-effectiveness of the treatment measured with EQ-5D-5L.

2.4. Primary outcome measure

The primary outcome is fall rate measured using monthly diaries and telephone calls prospectively over 12 months from the day the IMP is commenced. A fall is defined as "unintentionally coming to rest on the ground or other lower surface without overwhelming external force or a major internal event" (5).

2.5. Secondary outcomes: (measured at baseline and 12 months unless otherwise stated)

Outcome	Tool / method
Parkinson's Disease (PD)	MDS-UPDRS total score in the practically defined 'ON' state and each individual subscale (1-4)
Freezing of gait	New Freezing of Gait Questionnaire (NFOGQ)
Frailty and physical performance	Short physical performance battery (SPPB), gait speed and frailty status
Cognition	Montreal Cognitive Assessment (MoCA) and
Depression	Geriatric Depression Scale (GDS)
Apathy	Starkstein Apathy Scale (SAS)
Fear of falling	Iconographical Fall Efficacy Scale (ICON-FES)
Dysphagia	Swallowing Disturbance Questionnaire (SDQ)
Participant health related quality of life	EuroQoL 5D-5L health status questionnaire (EQ-5D-5L) (at baseline,1,3,6 9 and 12 months)
Care-related quality of life	Carer Experience Scale (CES)
Capability of older people	ICEpop CAPability measure for Older people (ICECAP-O)
Mortality (all cause and PD-related)	Office of National Statistics (ONS) data (at 12 months)
Cost effectiveness and NHS resource use	EQ-5D-5L and NHS Hospital Episode Statistics (HES) data

3. TRIAL DESIGN

A multicentre, phase 3, RCT of the ChEi rivastigmine versus placebo to prevent falls in PD.

4. TRIAL SETTING

This trial will be delivered in a secondary care setting across ≥26 sites in the United Kingdom.

Sites will be selected based on their research capacity and capability.

5. ELIGIBILITY CRITERIA

5.1. Subject population

People with PD residing in the community and care homes recruited across the UK.

5.2. Inclusion criteria

a. Diagnosis of idiopathic Parkinson's disease.
b. Modified Hoehn and Yahr stage 1-4 disease as determined at baseline.
c. Have experienced a fall in the previous year.
d. Able to walk ≥10m without aids or assistance.
e. 18 years of age or above.

5.3. Exclusion criteria

a. Previous ChEi use in 12 months prior to enrolment.
b. Hypersensitivity to rivastigmine
c. Dementia diagnosed according to MDS criteria (6).
d. Inability to attend or comply with treatment or follow-up scheduling.
e. Non-English-speaking patients (cognitive tests performed in English).
f. Falling ≥4x per day.
g. Unwillingness to use an acceptable method of contraception for the duration of the trial if they are of childbearing potential.
h. Pregnancy and/or breastfeeding

5.4. Operationalisation of criteria

Clinically probable PD is defined as bradykinesia in combination with at least 1 of rest tremor or rigidity, the absence of absolute exclusion criteria and the balance of red flags counterbalanced by supportive criteria as detailed in the trial manual.

Hoehn and Yahr staging range is 1 (Unilateral involvement only) through to 4 (Severe disability; still able to walk or stand unassisted)

A fall is defined as "unintentionally coming to rest on the ground or other lower surface without overwhelming external force or a major internal event" (5).

Hypersensitivity to rivastigmine is usually related to the development of allergic contact dermatitis.

Dementia diagnosed according to the MDS criteria requires Parkinson's disease diagnosed before the onset of dementia and decreased cognition, sufficient to impact daily living that cannot be attributed to motor or autonomic symptoms.

5.5. Potential participants who are at higher risk of adverse effects

Certain conditions (sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block; active or predisposition to gastric or duodenal ulcers; urinary obstruction, seizures; asthma or obstructive pulmonary disease and clinically significant hepatic impairment). These conditions are NOT exclusion criteria and no additional monitoring is required but the PI should consider this risk during the eligibility assessment process. The PIB explains this additional risk to potential participants.

5.6. Co-enrolment in other research studies

If potential participants are enrolled in other clinical trials, due care will be paid as to the burdens of co-enrolment in this trial. Enrolment will be considered on a case-by-case basis taking into consideration other factors such as comorbidities, social support and distances necessary to travel. Participants taking part in another CTIMP cannot be enrolled in this trial.

5.7. Prior and concomitant therapies

Treatment with other cholinesterase inhibitors or memantine are not permitted during the trial, with the exception of pyridostigmine bromide.
In the event of a participant requiring a general anaesthetic, participant will carry a card with them that will inform any medical professionals they encounter that the participant is part of the trial and potentially taking a ChEi.
Participants will be advised that there is a theoretical risk of interference with anticholinergic medications but that concomitant use is not contraindicated. The use of dietary and herbal supplements (including e.g. vitamin D and calcium supplements, cod liver oil) during the trial is NOT prohibited.

5.8. Emergency contact procedure for participants

Details of what a participant should do if they experience any problems or side effects whilst taking part in the trial is detailed in a “how to take your medications” booklet. If the participant experiences mild symptoms, they are advised to leave the patch in situ and inform the trial team. Participants are provided with contact details for the central research team and details of their local research site team.
If a symptom is troublesome or serious (explained in the PIB) they are advised to seek medical help in the normal way e.g. via 111, their GP, or in an emergency phoning 999 or via an Emergency Department. The central trial team will ONLY advise a participant action to take with respect to the IMP and will not provide any other medical advice.
Each participant will be given a card to carry indicating that they are participating in the CHIEF-PD trial which they can show to any health professionals involved in their care.

6. RECRUITMENT

6.1. Identification

Six hundred participants will be recruited and randomised. The following routes of recruitment will be used;

6.2. Clinical lists and local advertising

Potential participants will be identified locally at sites by PD specialists, PD specialist nurses, local and regional network staff reviewing clinical lists and /or local databases. Recruitment posters will be displayed locally.

6.3. Research registers

We will interrogate the ProDeNDRoN (Parkinson's Register of the Dementias and Neurodegenerative Diseases Research Network) database which is an inclusive register of research interested participants in South West England, who have agreed to be approached about new studies. We will utilise other organisations such as Parkinson's UK who host the Parkinson's UK Research Network and the Cure Parkinson's Trust.

6.4. National organisations and committees

We will utilise the established Parkinson's Portfolio Development Group (PDG) and the NIHR neurodegeneration network to further enhance recruitment. Leads for the UK Parkinson's Excellence Network and other local organisations such as National Institute for Health Research Clinical Research Networks (NIHR CRN) will disseminate the opportunity to participate to members in their regions.

6.5. Publicity

We will utilise various media outlets to publicise the opportunity to participate in the research. Details of the trial will be posted on the area of the relevant websites (such as Parkinson's UK, Fox Trial Finder, etc.) that advertise taking part in clinical trials. Potential participants may approach the central or site teams directly having read about the trial e.g. from online trial registries or through word-of-mouth. Posters will also be placed around participating sites especially within PD clinic areas. Participants that contact the central trial team will be directed towards their closest active site and the research team will ensure that the site has received the green light from the Sponsor before enrolling participant into the trial.

6.6. Screening and consent

Potential participants will be given a Participant Information Booklet (PIB) to read (via various routes including by post (including a covering letter) or website) and a pre-paid reply slip to return to the local site trials team indicating if they wish to take part or not. They will be given at least 24 hours (although in practice this is likely to be longer) to consider the information. If no reply slip is received the local site research staff may contact the participant by phone to see if they would like to take part in the trial.

Paper screening logs will be kept that include where possible, reason for non-participation. The details of the screening will be added to the database by site staff. This will ensure that participants are not approached more than once and will highlight participants that are willing to be contacted in future (e.g. due to an acute intercurrent illness at that time). Willing and potentially eligible participants will receive a screening phone call from the site team, or where appropriate a screening/baseline visit at their local site or at home. Formal eligibility screening will be conducted by the local research team, this will be documented in the participant CRF. Eligibility of participants will be confirmed by a medically qualified doctor. As a clinical safety precaution, pulse rate and ECG assessment may be undertaken prior to enrolment. Consent to undertake an ECG will be sought from the participant separate to the consent to take part in the trial. The ECG may be provided at home using mobile ECG technology such as the KardiaMobile (AliveCor, US) or other App-based technologies, or it may provided in the regular care setting such as a GP office, clinic or similar. The PI may on balance decide whether to enrol the participant for the trial based on their clinical judgement of the safety and ability of patient to comply with the treatment. Consent will be sought by the local research team by someone with the appropriate training and experience. A copy of the consent will be filed in the participant's hospital notes with a record of the discussion and copy of the PIB. A copy of the consent form will be sent to the central research team. Consent may be sought via telephone or video call. Where consent is sought via telephone or video call, the consent form will be sent to the participant and reviewed with a member of the local research team. The participant will always be given the chance to ask questions during the consent process. The signed consent form may be posted to the central team in a pre-paid envelope. A certified electronic copy will be provided to the relevant site. Where applicable, participants will be reimbursed for travel and parking related expenses. There will be no other financial incentive to participate.

6.7. Randomisation

The randomisation sequence will be generated by Sealed Envelope using their online randomisation system. Participants will only be randomised after eligibility and consent have been confirmed. Randomisation will be stratified by site and by the following three minimisation criteria (number of falls in previous year (1-4 falls low, 5+ high); age (18-64 low, 65 + high) and cognitive impairment measured using MoCA (1-25 low, 26-30 high)). Participants will be allocated to each treatment group using the minimisation method with a probability of 0.8.
The PI (or authorised delegate) will log onto the online randomisation system, enter the minimisation variables and then receive the code that allocates the participant to a treatment (active or placebo). They and the participant will remain blinded as to which treatment group this code refers to. The unblinded randomisation code will be held by the trial pharmacy, central pharmacy and BTC. Trial participants will be allocated to one of two treatment groups (active rivastigmine patch or matched placebo patch).

6.8. Internal pilot

Participants will be recruited over a 2-year period. Participant and site recruitment will be reviewed at 9 months and assessed on an on-going basis. If >90% of expected participants and >50% sites have been recruited, the trial will continue. If 50%-89% of expected participants and / or <49% of expected sites have been recruited, then the TMG will identify remediable factors and discuss with the TSC and submit recovery plan to HTA with new targets for the following 6 months. If <50% of expected participants are recruited and/ or <25% of expected sites are actively recruiting, we will stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed after further discussion with the funder (Table 1).

Table 1 Internal pilot 'Stop / Amend / Go' criteria

	Participants		Sites	Anticipated action
GO (green)	>=90% of expected patients recruited (104 patients)	AND	>=50% of expected sites actively recruiting (13 sites)	Continue
AMEND (amber)	50%-90% of expected patients recruited (58 – 104 patients)	AND / OR	and/or <49% of expected sites actively recruiting (<13 sites)	Identify remediable factors, discuss with TSC and submit recovery plan to HTA with new targets for the following 6 months
STOP (red)	<50% of expected patients recruited (<58 patients)	AND / OR	<25% of expected sites actively recruiting (<7 sites)	Stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed

6.9. Planned recruitment rate

The aim is to recruit a conservative 1.18 participants per site / per month or 14 participants per site per year until we have reached our target recruitment of 600 participants. This considers staggered recruitment of sites.

7. TRIAL PROCEDURES

7.1. Schedule of assessments

Participants in the trial will undergo an assessment at baseline (0 months) and follow-up (12 months). The assessment may be carried out face-to-face and/or via video call. Where the latter is chosen, it may be necessary to video record the assessments.
Research staff at the sites will complete assessments at baseline (time 0), and final visit (12 months) unless otherwise agreed. That is, the assessments may be performed by a trained member of the central research team such as the central research nurse where agreed. The central nurse may undertake one or several of the scheduled assessments per site.

The participant is expected to start treatment within 7 days of the baseline visit, unless otherwise agreed.
The 12 month visit should be conducted at the end of the 12th treatment month ensuring that the participant is assessed whilst on the patches. As the treatment month is 30 days, the follow up should be aimed to be performed within 350-360 days from the first day of treatment.

For participants enrolled in the trial from September 2022 onwards the follow up period will be up to 12 months. If a costed extension is granted, participants will be enrolled in the trial for 12 months.

Pending a decision from NIHR regarding the extension, to continue recruitment and deliver the trial within the current funding envelope, participants who enrol in the trial from September 1st 2022 onwards will enrol for ***up to*** 12 months. This is shown in Table 2.

To ensure that NHS sites can manage the potential of several patients needing their follow-up assessment visit in the same month at the end of the trial (August 2023) the window for this testing will be extended to 330-360 days following the first day of treatment.

Months of enrolment													*Duration in the trial (months)*
	Sep 22	**Oct 22**	**Nov 22**	**Dec 22**	**Jan 23**	**Feb 23**	**Mar 23**	**Apr 23**	**May 23**	**Jun 23**	**Jul 23**	**Aug 23**	
Current trial participants	*Low*	*Medium*					*High*						*12*
The rows below shows the dosing schedule for people enrolled in September 2022 and beyond.													
Sep 22		***Low***	***Medium***					***High***					***11***
Oct 22			***Low***	***Medium***					***High***				***10***
Nov 22				***Low***	***Medium***					***High***			***9***
Dec 22					***Low***	***Medium***					***High***		***8***
Jan 22						***Low***	***Medium***					***High***	***7***
Feb 22							***Low***	***Medium***					***6***

Monthly phone calls to participants will be coordinated centrally by research staff, blinded to treatment status. These phone calls remind participants to return their fall diaries, screen for adverse events and collect data on health care use and quality of life.

Table 2 summarises the assessment schedule and outcomes measured at each time point.

Table 2 Schedule of assessment visits and outcomes measurement

Month	0	1	2	3	4	5	6	7	8	9	10	11	12
Activity													
Procedures													
Eligibility criteria review	●												
Informed consent	●												
Sociodemographics	●												●
Medical history	●												●
Drug history	●												●
Examination (HR, BP, height, weight, MDS-UPDRS III, frailty, gait, SPPB)	●												●
Falls	●	●	●	●	●	●	●	●	●	●	●	●	●
MoCA	●												●
GDS	●												●
SAS	●												●
MDS-UPDRS I, II, IV	●												●
NFOGQ	●												●
ICON-FES	●												●
SDQ	●												●
ICECAP-O	●												●
EQ5D-5L	●	●		●			●			●			●
CES**	○												○
Medication													
IMP dispensing	●		●					●					
IMP return													●
Safety													
Adverse events		●	●	●	●	●	●	●	●	●	●	●	●
ECG*	○		○				○						
Formal & informal care use		●		●			●			●			●
Hospital care and mortality	**(HES via NHS Digital and ONS data linkage)**												

*IMP: Investigational Medicinal Product, SPPB: Short Performance Physical Battery MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale NFOGQ: New Freezing of Gait Questionnaire ICON-FES: Iconographical Falls Efficacy Scale GDS: Geriatric Depression Scale SAS: Starkstein Apathy Scale MoCA: Montreal Cognitive Assessment CES: Carer Experience Scale. SDQ: Swallowing Disturbance Questionnaire *ECG as per arrhythmia safety protocol **Completed by carer*

7.2. Pre-baseline visit (month -1)

Potentially eligible participants identified from clinic lists and other recruitment strategies (see section 6.1-6.5) will be given an invitation letter and participant information booklet (PIB). The site research staff are encouraged to obtain a pulse reading to determine whether an ECG will be needed to ensure participant safety prior to enrolment. Where an ECG is requested, the participant should be consented to the ECG using the ECG consent form. Failure to enrol a participant following consent to ECG will be considered a screening failure and not a withdrawal. The participant is considered to be fully enrolled only after full informed consent has been obtained.

When eligibility has been confirmed, the potential participant will be invited to attend the baseline visit (face-to-face or remote).

With their appointment letter they will be sent the following self-completed questionnaires to complete (ideally but not essentially) **prior** to the visit to minimise fatigue and burden. If they are unable to self-complete these can be facilitated by the researcher during the visit. In respect to consent, the cover of this questionnaire booklet clearly articulates that if the questionnaires are completed pre-visit but the participant declines to participant or is ineligible these data will not be retained. This arrangement is explained in the PIB.

- Appointment Letter
- +/- consent form.
- +/- video workbook (for remote appointments, optional).
- MDS-UPDRS Parts Ib and II performed in the practically defined ON state (defined as patients taking their normal daily medications in the optimally medicated state)
- NFOGQ
- ICON-FES
- ICECAP-O
- GDS
- SAS
- SDQ
- EQ5D-5L

7.3. Baseline visit (month 0)

Prior to the baseline assessments, the eligibility criteria will be reviewed by a medically qualified doctor, the trial explained, and informed consent obtained. The following assessments and procedures will be completed at the baseline visit:

- Review eligibility criteria
- Obtain written informed consent
- Collection of sociodemographic data, medical and drug history including previous falls
- Neuropsychometry: MoCA
- Brief examination: heart rate (+/-ECG as per the trial specific instructions. Note that ECG should not be repeated where obtained pre-baseline), lying and standing blood pressure, height and weight, MDS-UPDRS Ia, III, IV, frailty and dual task gait assessment (consisting of timed walks as tolerated, one of which will be performed with a dual (naming) task, and 1 performed with turns to examine freezing of gait), SPPB.
- Quality of life and cost effectiveness: EQ-5D-5L

Where the participant carries out the assessments at home, a risk assessment will be undertaken to ensure the safety of the participants. A pragmatic approach will be taken with response to achieving all secondary outcome measures.

7.4. Diaries and telephone calls (monthly)

Falls and concordance with the IMP will be recorded using a diary. Participants will receive a diary on entry to the trial that includes detailed instructions. The fall calendars will be returned monthly to the central trial team in pre-paid envelopes provided. Participants will be telephoned monthly and asked to corroborate information returned in the diary. In the event of a diary not being returned the team will prompt the participant at the next phone call or record the information during the call.
In the case where participants are unable or prefers not to communicate via telephone (e.g. due to speech impairment), alternative methods such as email communication may be used if the participant agrees.
Where necessary to assess e.g. an adverse event, the team will collect data on concomitant medication. Side effects reporting, including those overlapping with the IMP's RSI should be evaluated in the usual way. Participants will be asked about the occurrence of any adverse events and where necessary, advised according to clinical judgement and in liaison with the local research team (blind to treatment allocation), in conjunction with the relevant trial specific instructions about adjustment of dose (see section 8.8 Titration side effects). This information will be communicated securely to the site team. Additional phone calls may be required to support dose changes, arrange deliveries/collection and to follow up on adverse events. Participants will be given telephone numbers of their local study team and the central research team to seek advice at any point during the trial.

7.5. Dispensing timepoints

Participants will be provided with the active or placebo patches at baseline, at the end of 2 and 7 months. This is covered in detail in Section 8.6.

7.6. End of treatment visit

The 12 month visit should be performed whilst the participant is on the patches in as far as possible and unless the participant has discontinued treatment. The visit should take place approximately 350-360 days after the first patch was applied.
For participants who have enrolled in the trial after September 2022, their follow up visit will take place *up to* 12 months after enrolment.
In the same manner as the baseline visit, participants will be sent questionnaires in the post to complete prior to the end of treatment visit. The following assessments will be performed as per Table 2. The participants bring the completed questionnaires to their visit or send them to the research team via post. If they are unable to complete them independently then the research nurse can assist at the visit.

Completed pre-appointment

- MDS-UPDRS Parts Ib and II performed in the practically defined ON state (defined as patients taking their normal daily medications in the optimally medicated state)
- NFOGQ
- ICON-FES
- ICECAP-O
- GDS
- SAS
- SDQ
- EQ5D-5L

Completed at visit (telephone call, video call and/or face-to-face as applicable)

- Review of medical and drug history and falls sustained (if required)
- Review of sociodemographic history
- Brief examination: heart rate, lying and standing blood pressure, height and weight, MDS-UPDRS Ia, III, IV, frailty and dual task gait assessment (consisting of 3 x timed walks, one of which will be performed with a dual (naming) task, one of which will be performed with turning to assess freezing of gait), SPPB.
- Neuropsychometry: MoCA
- Quality of life and cost effectiveness: EQ-5D-5L

Post-trial follow up

The central team will telephone the participant in the month following the 12 month visit to collect information on aspects including withdrawal effects, experience in the trial and to understand whether the participant has been prescribed the rivastigmine after the trial.

7.7. Blinding

The central research team, investigator site staff and participants will be blinded to the allocation of treatment group, except for the Junior Trial Statistician and Data Manager, and the trial pharmacists and/or pharmacy technicians.
Blinding will be assessed at the end of the trial using the Schultz questions with the Bang Blinding Index.

7.8. Unblinding

Treatment codes will only be released to the investigative team once written confirmation has been received that the trial database has been locked. Participants will be informed of their allocation by the central trial team after the trial has concluded. Following each randomisation, blinded coding information will be sent to the central research team to ensure protocol deviations and stock control are managed.

7.9. Emergency Unblinding

The safety profile of the IMP within the trial is well established, therefore unblinding should not be expected unless clear clinical need dictates this. In the event of a medical emergency the participant's treating physician will contact the central pharmacy at the University Hospitals Bristol and Weston NHS Foundation Trust who will hold the unblinding codes. Sites will follow the trial specific instructions for unblinding.

7.10. Withdrawal from the trial

Participants can choose to withdraw for any reason at any time during their involvement in the trial. The PI can also decide to withdraw participants based on clinical opinion at any time during the trial. This section does **not** include treatment discontinuation (see 8.8)
Examples *of a complete withdrawal from all trial related activity could be:*

- Participants who become ineligible due to some of the exclusion criteria listed in section 5.3 of the protocol, namely criterion (c), Dementia diagnosed according to MDS criteria, (d) Inability to attend or comply with treatment or follow-up scheduling, (g) Unwillingness to use an acceptable method of contraception for the duration of the trial if they are of childbearing potential (h) pregnancy or breast feeding.
- Inability to complete assessments that in the opinion of the investigator warrants withdrawal from the trial
- Intercurrent illness as determined by the PI.

In the event of withdrawal, participants will be requested to return the treatment packs in accordance with the trial specific instruction. Data obtained up to this point will be retained for analysis.

7.11. End of Trial

The end of trial for CHIEF-PD will be when the last patient has completed their 12 month visit which includes completion of the 12 month questionnaire and diary, and subsequent data analysis.

7.12. Carer Involvement

Primary carers will be recruited concurrently to assess the impact of treatment on the participant's care needs on carers. Their involvement is detailed in Appendix 1. A carer is defined as an individual who undertakes informal or formal care responsibility for the participant. The carer will be approached only with the agreement of the participant and be consented separately. If carers do not wish to consent to take part, or if there is no carer, the participant is still eligible to participate in the trial.

8. INTERVENTION / IMP

8.1. General information

Rivastigmine is a reversible non-competitive inhibitor of acetylcholinesterase. It is currently licensed for use in mild to moderate dementia in PD and in mild to moderate dementia in Alzheimer's disease. Further information on the IMP can be found in Appendix 3.

8.2. Assessment and management of risk

This trial is categorised as 'Type B' according to the MHRA (testing authorised medicinal products according to treatment regimens outside the marketing authorisation). Rivastigmine is marketed and used in participants with Parkinson's Disease dementia. Its safety profile is well characterised.

Using Rivastigmine for falls represents a new indication in an essentially established patient group albeit without dementia. Up-titration to (now licensed) 13.3mg is routine in clinical practice.

It is not anticipated that application of placebo represents any risk above that of standard care.

8.3. Supply of the IMPs

The active and placebo transdermal patches will be supplied by:
Luye Pharma AG, Am Windfeld 35, 83714 Miesbach, Germany.

They will perform manufacturers QP release before shipping to Eramol for packaging and labelling. Eramol will perform the final QP release.

8.4. Packaging and labelling of IMP

The IMP and placebo will be packaged and labelled by:
Eramol, Unit 11 Gatwick Metro Centre, Balcombe Road, Horley, RH6 9GA. The core label texts for all packaging will comply with the requirements of Annex 13 of the Rules Governing Medicinal Products in the European Union and the national laws in force in the UK. Eramol will perform QP release prior to release to onward dispensing to patients.

8.5. Return and destruction of IMP

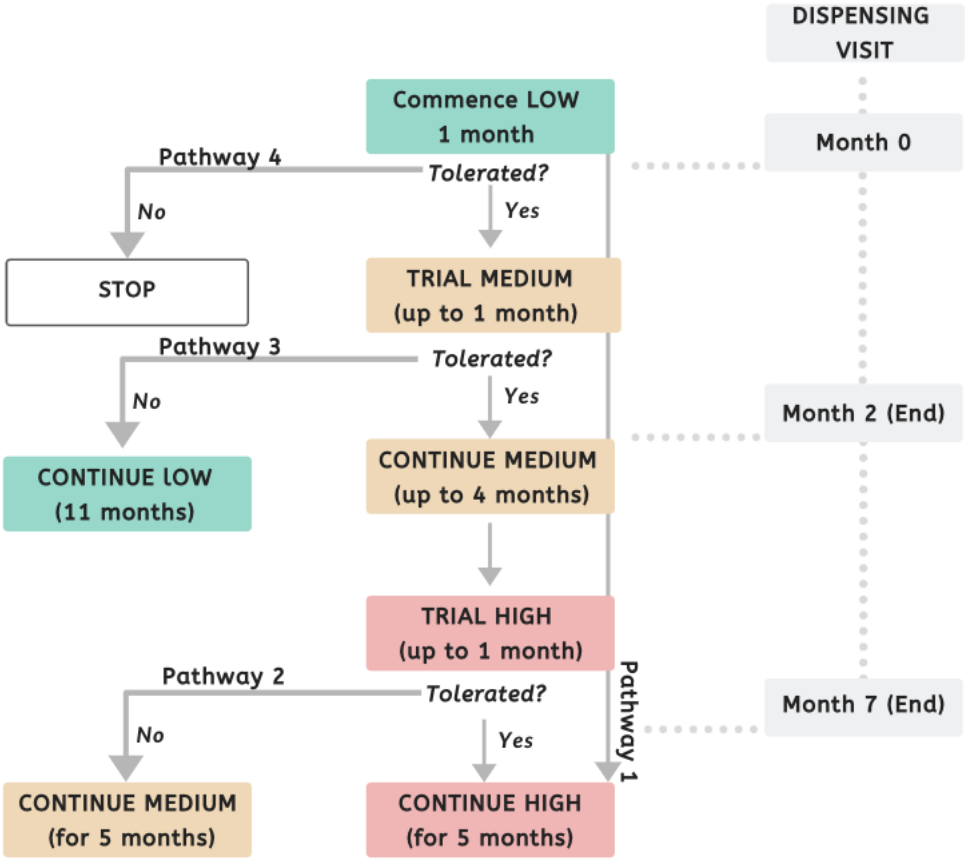
Any IMP that is returned by participants will be destroyed in line with the pharmacy trial specific instructions on the disposal of IMP.

8.6. Administration and routine titration

There are 3 strengths of patch. All patients will commence LOW dose (4.6mg / 24 hours) patches with the aim to escalate up through MEDIUM dose to HIGH dose (Figure 1).

After one month of LOW dose, participants will escalate to the MEDIUM (9.5mg/ 24 hours) patch. They will remain on this for 5 months. After 6 months (1 month LOW, 5 months MEDIUM) they will escalate to the HIGH (13.3mg dose), having followed pathway 1.
If they do not tolerate the LOW dose the IMP will be discontinued, having followed pathway 4.
If they do not tolerate the MEDIUM dose they will remain on LOW dose for the remaining 11 months of the trial having followed pathway 3.
If they do not tolerate the HIGH dose, they will remain on MEDIUM dose for the remaining 5 months of the trial having followed pathway 2.

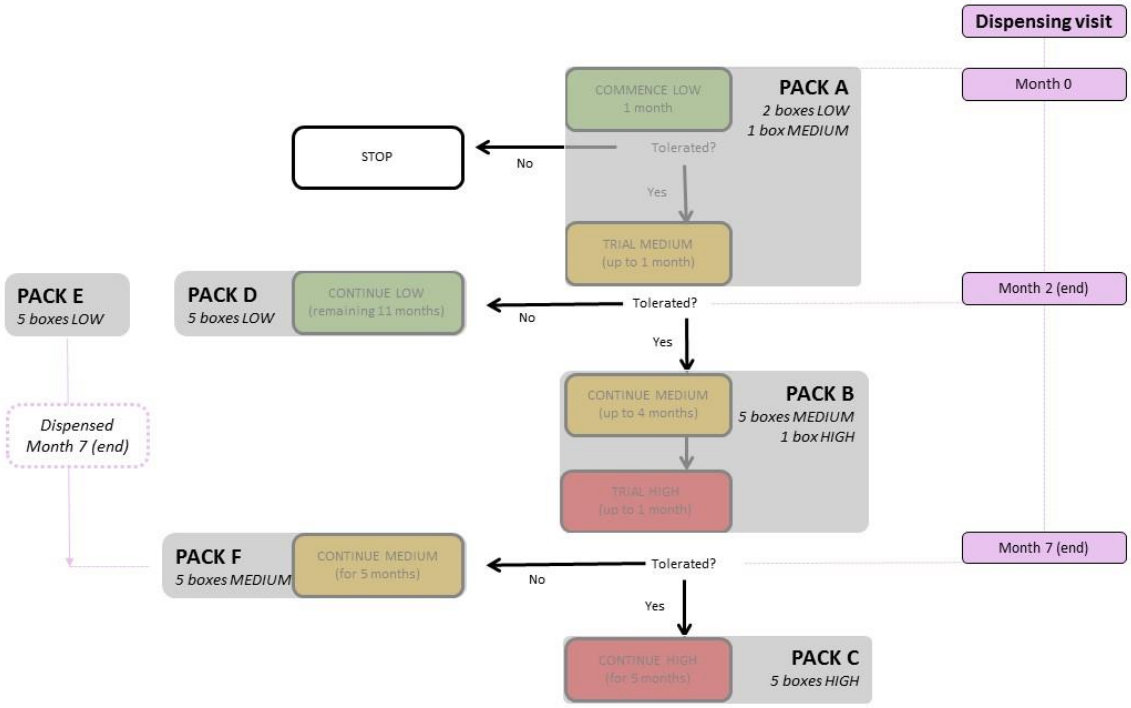
Figure 1 Titration of IMP according to tolerability



Key *Low: 4.6mg/day Medium: 9.5mg /day High: 13.3mg / day*

Medication packs will be dispensed at month 0 and end of months 2 and 7. Each pack allows for a one-month trial of up-titration to the next dose prior to the next pack being dispensed. This is shown diagrammatically overlaying the titration illustration in Figure 2.

Figure 2. Medication packs dispensed at months 0, 2 and 7 depending on tolerability.



Key *Low: 4.6mg/day Medium: 9.5mg /day High: 13.3mg / day*

8.7. Common side-effects

Application site skin reactions (usually mild to moderate application site erythema), are the most frequent adverse reactions observed with the use of rivastigmine transdermal patch. The next most common adverse reactions are gastrointestinal upset including nausea and vomiting.

8.8. Titration for side effects

In the event of a participant experiencing side effects the central and local research team will refer to the relevant trial specific instructions. This will determine whether down titration or ceasing the IMP is necessary. Reference will be made to the Summary of Product Characteristics for the management of adverse reactions. Recommendations will be made by the central team based on the tolerability,occurrence and severity of adverse events and agreed with the site PI (and where necessary the treating clinician e.g. Parkinson's specialist if clinically necessitated) . The recommendation will be communicated to the site team via (secure) email with the relevant prescription form attached to be signed by a medically qualified doctor (or appropriately qualified prescribing nurse) at site.
The same dosing schedule will be applied to participants in both groups with dummy dose titration being applied to the placebo group. Compliance will be monitored using the diary.

If the participant discontinues the medication because of unacceptable side effects or by choice, then they remain enrolled in the trial (unless they explicitly withdraw see section 7.10) and will complete the further assessments as per protocol.

8.9. Temporary Discontinuation, Restarting treatment and Bespoke Prescriptions

Where a participant has needed to temporarily suspend treatment for more than 3 days, the participant may be restarted on the IMP in line with the clinical decision made by the PI or a medical delegate. The participant should be restarted at 4.6mg/24h, but can be up-titrated using an accelerated schedule if tolerated and agreed by the clinician. It is recommended that the participant is restarted at 4.6mg/24h for at least 7 days before up-titrating. Up-titration from 9.5mg/24h to 13.3mg/24h should not occur in the immediate 7 days following up-titration.
In the eventuality that a participant, for clinical or safety reasons, have changed the treatment path or schedule, a bespoke prescription may be required signed by the PI or medical delegate.
Likewise, where the IMP may expire during the treatment period, a bespoke prescription may be used to replace the IMP for the same product with a longer expiration date.

8.10. Dispensing of IMP

Each trial pharmacy will be responsible for dispensing the IMP and will maintain the IMP dispensing log. The trial pharmacist who fulfils the trial prescription will be unblinded.
Trial pharmacies will be required to nominate a pharmacist and/or deputy who will be responsible for the IMP at site. Storage instructions, dispensing and alike will be detailed in a trial specific working instruction.
The trial pharmacies will be pharmacies with agreed capacity to undertake the dispensing procedures, preferably at more than one site. As the trial medication may be posted or couriered to participants, trial pharmacies may serve as 'hubs' for the dispensing activity for a range of sites and may include commercial pharmacy units following the clinical trials procedures.
Trial specific instructions will be issued to each site regarding the specific pharmacy arrangements. Note that the arrangement means that not all sites require a trial pharmacy.

8.11. Post-trial

Continuation of the treatment following the end of the intervention phase is the responsibility of the participant's normal PD clinician, an arrangement which is explicitly described in the PIB and site agreements.

8.12. Drug accountability

Activity	Responsibility
Supply of IMP, placebo and overtapes	Luye Pharma AG
Provision and QP of IMP, placebo and overtapes to Eramol	Luye Pharma AG

Activity	Responsibility
Package and labelling of IMP and placebo	Eramol
QP release IMP and placebo to trial pharmacies	Eramol
Receive IMP/placebo and overtapes and store appropriately	Trial pharmacy
Dispense IMP/placebo and overtapes in line with randomisation schedule to participant	Trial pharmacy
Maintain dispensing log	Trial pharmacy
Report stock levels	Trial pharmacy
Arrange additional deliveries of IMP/Placebo and overtapes at site	Eramol
Return of unused trial medicines	Participants will return unused medicine to recruiting site or central team via post
Destruction of unused trial medicines	Trial pharmacy
Unblinding	Central pharmacy

9. TRIAL DATA

Collection of sociodemographic information will facilitate defining the population studies including comorbidities, medication use and fall history. Neuropsychometric testing will be performed using MoCA which is one of the Movement Disorder Society recommenced scales for the Level 1 assessment of PD-MCI. The concurrence of depression can confound interpretation of cognitive function and will therefore be measured using the MDS recommended Geriatric Depression Scale (GDS). Apathy is one of the most common non-motor symptoms affecting people with PD (17). The Starkstein Apathy Scale will be used to measure apathy (18). Fear of falling will be measured using the Iconographical Falls Efficacy Scale (ICON-FES) and dysphagia using the Swallowing Disturbance Questionnaire which is validated in PD (7, 16).
The new Freezing of Gait Questionnaire (NFOGQ) is a validated tool that detects FOG and assesses impact and severity of FOG episodes. PD severity is quantified using the MDS-UPDRS scale which captures non-motor and motor symptoms and signs and is the recognized gold standard in clinical PD trials. Functional physical performance will be assessed using the Short Physical Performance Battery (SPPB). Questions from the SHARE-FI index and assessment of grip strength be used as part of the frailty status assessment. Functional performance will be assessed using the short physical performance battery (SPPB) as well as timed gait assessment with and without dual task and turning. This is designed to stress attentional resource between a physical and cognitive task to better elucidate underlying gait and cognitive dysfunction. Quality of life will be assessed using EQ-5D-5L to calculate QALYs. We will collect the EQ-5D-5L at the baseline and 12-month research clinic visits. We will also administer the EQ-5D-5L by paper questionnaire at 1, 3, 6- and 9-months post-randomisation to measure the quality of life trajectory during the trial. A well-being measure, ICECAP-O will be used at baseline and 12 months, to capture the broader impact of PD-falls on participants. ICECAP-O is a relatively new measure of capability in older people which has been previously used in patients with PD (8). In participants who have a primary carer who is also willing to take part in the trial and attend baseline and 12-month research clinics, we will use the Carer Experience Scale (CES) (9) to determine the impact of participant's care needs on carers. The CES focuses on 'care-related quality of life' rather than health-related quality of life, comprising attributes that are pertinent to family and friends who act as informal carers.

10. PHARMACOVIGILANCE

Please refer to the Safety Reporting section of the trial manual for additional information in this section.

10.1. Operational definitions

Pharmacovigilance will be carried out in accordance with the requirements set out by the European Commission Detailed Guidance CT-3 2011 including the terminology of adverse events and reactions and the assessment of seriousness, causality and expectedness of an event.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product "means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question
Suspected serious adverse reaction (SSAR)	A suspected serious adverse reaction (SSAR), is any serious adverse reaction that is suspected (possibly or probably) to be related to the investigational medicinal product/medical device/intervention.

10.2. Classification of Severity

Mild event:	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event:	An event that prevents normal everyday activities.

10.3. Classification of Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

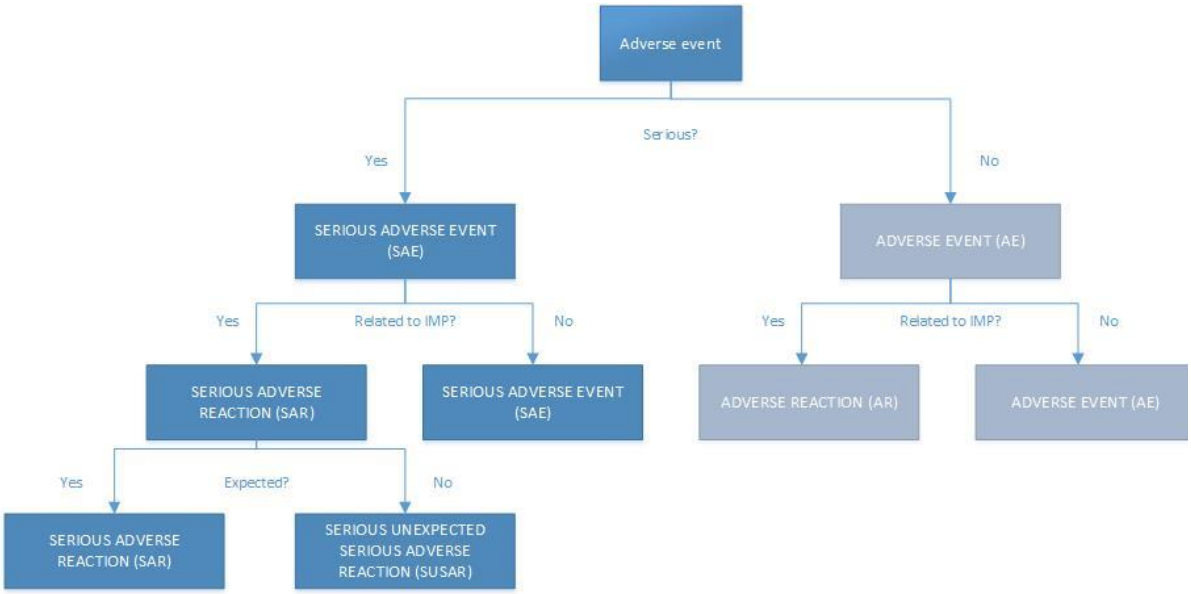
10.4. Classification of Expectedness

Expected	Reaction previously identified and described in the Summary of medicinal Product Characteristics (SmPC).
Unexpected	Reaction not previously described in the Summary of medicinal Product Characteristics (SmPC).

10.5. Adverse events classification flowchart

For each adverse event the seriousness, relatedness and expectedness will be determined (as per the definitions above) in order to appropriately classify the episode as per Figure 3.

Figure 3 Classification of adverse events flowchart



10.6. Adverse Events (AEs)

Only non-serious adverse events that are assessed as being possibly, probably or definitely related to the IMP (adverse reaction AR), will be reported from the time a signed and dated informed consent form is obtained until completion of the last trial-related procedure. Non-serious adverse events (with the exception of falls) that are **unrelated to the IMP** will not be reported.

AEs will be recorded by the research team at sites or centrally, in the CRF. It is anticipated that the majority of AE's will be detected via the monthly telephone calls. The central site team will communicate with the local PI and site team if additional information is required to e.g. determine causality. If a patient attends a routine (i.e. non-trial related appointment) and an AE is reported, the site research teams will assess and log this according to the same working instructions. AE's will be reviewed by the DMC at the next booked meeting.

10.7. Serious Adverse Events

All SAE/SAR/SUSARs will be recorded in an SAE log. The Sponsor will be notified in writing of all SAEs, SARs and SUSARs (see Figure 3) within 24hours of the investigator(s) becoming aware of the event. A full written report to the Sponsor of all SAR and SUSARs will be submitted within 7 days from the initial notification. SUSARS will be reported to the MHRA and REC within 7 days of the Sponsor being notified if fatal or life-threatening or 15 days otherwise (cf. flow chart in appendix 2). Hospitalisation for an elective procedure or for a pre-existing condition (prior to study entry) which has not worsened, does not constitute a serious adverse event. All SAEs will be followed until resolution.

The expectedness of a serious adverse reaction shall be determined according to the current approved Summary of medicinal Product Characteristics.

Reporting will be performed in accordance with the reporting framework (Appendix 2) for SAE's. All SAE's (SAR, SUSAR, SAE) will be reported to the DMC on a quarterly basis.

10.8. Suspected Unexpected Serious Adverse Reactions (SUSARS)

SUSAR's will be reported to the Sponsor, MHRA, REC and DMC within 15 days or, if life threatening or resultant in death, 7 days.

Occurrences meeting the definition of unexpected serious adverse event (SUSAR) will be reported using the Serious Adverse Event Form, including SAEs spontaneously reported to the Investigator within 30 days after the participant has completed the intervention phase of the trial. University Hospitals Bristol NHS Foundation Trust (UH Bristol), on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by the CI beyond the time frame specified in the protocol.

10.9. Urgent safety measures

Please refer to the trial specific instructions for Safety Reporting for further details. Reference is made to the SmPC for the management of Safety Reporting and Urgent Safety Measures.

10.10. Notification of deaths

All deaths occurring during the intervention phase of the trial or within 30 days after the last dose of trial medication will be reported immediately as soon as the central research team become aware.

10.11. Safety reporting period

The Sponsor Adverse Events Reporting Policy incorporates the requirements of the Medicine for Human Use (Clinical Trials) Regulations 2004. UH Bristol, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. For each participant the end of safety reporting will be 5 days after removal of the last transdermal patch. Any AE's within this period will follow normal reporting procedure.

10.12. Development Safety Update Reports (DSURs)

The sponsor will submit DSURs once a year throughout the clinical trial, or as necessary to the MHRA and where relevant the Research Ethics Committee. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

11. STATISTICS AND HEALTH ECONOMICS ANALYSIS

11.1. Sample size calculation

The mean falls per month on the log-transformed scale in the placebo group from the feasibility data was 0.3 (SD 1.2) and a 25% reduction in falls on the log-transformed scale is -0.2877, so the mean in the Rivastigmine group is 0.0123 on the log-transformed scale.
The correlation is 0.589 (lower bound of the 95% confidence interval for correlation found in feasibility trial) between baseline and follow-up measurements of log-transformed fall rate.
Using these values in the ANCOVA sample size calculation, we will have 480 (240 per group) participants to detect a 25% difference in mean fall rate with 90% power. We will recruit 600 people assuming a 20% drop out (n=120).

The sample size calculation is based on an Analysis of Covariance (ANCOVA) approach where any variance between individuals in post-treatment falls rate, which is correlated to the corresponding measure taken at baseline, is removed from the error variance resulting in increased statistical power. With one baseline assessment and one post-treatment assessment of outcome, the standard sample size target is reduced by a factor of (1 - r2), where r2 is the squared Pearson's correlation coefficient. This is a standard approach to sample size calculation for quantitative outcome measures, as detailed in Machin et al 1997 (10).

11.2. Statistical Analysis

Simple descriptive statistics will be used to describe all outcomes measures in both treatment groups. For continuous measures we will describe the mean (SD) for normally distributed variables and the median and interquartile range (IQR) if skewed.
The full analysis set will be all participants providing outcome data, in the treatment group to which they were randomly allocated, under the intention-to-treat (ITT) principle. The per protocol set will be all participants who took any dose of the drug for six months or longer, as randomised. These data will be used only in analyses aimed at estimating the treatment effect in those adhering to their allocation.
The primary outcome analysis is a linear regression model of log transformed fall rates, adjusted for participants' age, cognitive impairment, and fall histories at baseline. This will estimate the treatment effect as a percentage change in average fall rates.
Similar regression models to that used in the primary outcome analysis will be used for the analysis of secondary outcomes as statistically appropriate, including time to event models for outcomes such as mortality. These will be adjusted for participants' age, cognitive impairment, and fall histories at baseline (minimisation variables) and the baseline outcome, as appropriate. Sensitivity analyses will inform the interpretation of the primary outcome analysis only by imputing missing primary outcome data, if appropriate. Additional sensitivity analyses will be performed on primary and secondary outcomes by adjusting for any baseline variables which differ by chance between groups by more than 0.5 standard deviations (continuous variables) or 10% (binary variables).
A more detailed statistical analysis plan will be produced and published before the onset of the analyses.

11.3. Analysis of safety endpoints

We will use descriptive statistics to describe adverse events for participants who took one or more dose(s) of the drug (safety set).

11.4. Economic evaluation

Participant consent will be sought to use data linkage (using e.g. NHS number (or CHI number in Scotland), date of birth) to access data on their hospital care and cost. We will purchase NHS Digital admitted patient (day case & inpatient), outpatient and A&E hospital episode statistics (HES) datasets covering the estimated 3 years from first participant randomised to 12 months after the last participant is randomised. HES datasets are typically available from NHS Digital 3 months after service use. Brief questions (based on the client service receipt inventory) (11) will be used to assess primary and community care use, medications and informal care via telephone interviews at 1, 3, 6, and 9 months and at the 12-month research clinic visit.

Use of hospital, primary and community care will be costed using national unit costs (12,13). Medication costs will be estimated from the British National Formulary. All unit costs will be taken from or inflated to the most recent available cost year. EQ5D-5L responses will be converted into utility scores using English value sets (14). Utility scores will be combined with ONS mortality data to estimate quality adjusted life years.

A secondary objective is to determine whether rivastigmine patches are cost-effective for use in the NHS. The economic analysis will take an ITT approach with imputation of missing data. In the primary economic analysis, we will estimate the cost per QALY gained of rivastigmine patches within the trial follow up period from the perspective of NHS and social services (to aid comparison with NICE appraisals). Based on the current NICE willingness to pay threshold for a QALY of £20,000 we will calculate the net benefit statistic for each participant and use net benefit regression, adjusting for baseline EQ5D-5L scores and other variables outlined above to estimate the incremental net benefit (and 95% confidence intervals) and determine whether rivastigmine is cost-effective at this threshold. Uncertainty will be explored using cost effectiveness acceptability curves to estimate the probability that rivastigmine is cost-effective at a range of plausible cost-effectiveness thresholds. In secondary analyses we will estimate the cost per fall prevented and expand the perspective of the analysis to include informal care costs, carer quality of life and participant wellbeing measures. If the intervention has a sustained effect in reducing falls and is potentially, but not definitively, cost-effective at 12 months, we will develop a simple extrapolation model to assess cost-effectiveness over a lifetime horizon.

12. DATA MANAGEMENT

12.1. Source Data and documents

When a participant consents to enter the trial, they will have a unique participant identification number allocated. Personal data entered directly onto the password protected database and maintained on a SQL Server database system within the University of Bristol will only be accessible to members of the research team. Any data stored on laptops will be encrypted. Any information that is analysed or transferred outside the EEA will be anonymised. Participants will be asked to consent to their name, email address and phone number being stored on the secure database with the central research team.
Data obtained by paper will also be entered onto the password protected database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to CHIEF-PD trial staff. Information capable of identifying participants will not be removed from University of Bristol or clinical centres or made available in any form to those outside the trial, for the exception of NHS digital for linkage.
Consent forms and clinical letters with personal identifiable data will be stored separately in a locked filing cabinet. Participant details will be anonymised in any publications that result from the trial.
Source data for this trial will consist of certified scanned copies and/or paper copies of the consent form, participant completed questionnaires, the patient reported falls diary and drawings from the MoCA assessment as well as the electronic case report forms designed specifically for the study.

12.2. Where video calls are recorded, the video recording will be stored until the end of the trial only. Data collection

Clinical outcomes will be assessed by participant-completed questionnaires at baseline and 12 months (completed at home prior to the face-to-face or video call visit or within clinic at their baseline appointment) as well as telephoning participants monthly to ask to corroborate information returned in the diary each month. Case report forms will be completed at the time of the baseline assessment and treatment phase over 12 months.
We are using standardised outcome instruments. The components and timing of follow-up measures are shown in Table 2.

12.3. Case Report Forms (CRFs)

Case report forms at study centres will be completed on paper and then uploaded or directly entered into the trial database. Questionnaires from participants will be identifiable only by participant trial number and will be returned by the participant by post or via electronic means to the central research team. Any paper copies will be stored in a secure locked cabinet in a locked room.

12.4. Data handling and record keeping

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR).

For this trial, research data will be kept for at least 15 years. Personal data (e.g. name and address, or any data from which a participant might be identified including video recordings) will not be kept for longer than is required for the purpose for which it has been acquired. Documents will be reviewed by the CI before being destroyed.

12.5. Access to data

For monitoring purposes, the PI will allow monitors from the sponsor (or delegate), persons responsible for the audit, representatives of the REC and other Regulatory Authorities to have direct access to source data/documents.
The Chief Investigator will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses (see section 15.9).

12.6. Archiving

This trial will be sponsored by the University of Bristol (UoB) who are also the data custodian. All research data will be retained in a secure location during the conduct of the trial and for 15 years after the end of the trial, when all paper records will be destroyed by confidential means. An archiving plan will be developed for all trial materials in accordance with the University of Bristol archiving policy.

13. TRIAL MANAGEMENT

13.1. Trial Management Group (TMG)

The TMG will have responsibility for the day-to-day management of the trial and will report to the TSC. The TMG will meet on a regular basis with a core working group of staff having frequent progress meetings. They will link to the network of site research teams to facilitate continuous feedback and early troubleshooting of local site issues that arise.

13.2. Trial Steering Committee (TSC)

Trial Steering Committee (TSC) will be established in conjunction with a Trial Management Group (TMG). Membership, responsibilities and reporting mechanisms of the TSC will be formalised in a TSC charter. The TSC will make recommendations/key decisions during the trial to the TMG and minutes will be sent to the funder. The TSC will comprise Prof C Clarke (University of Birmingham) as Chairperson, Miss N Ives as Independent Statistician and Dr R Campbell, Mr M Bond as patient representatives and Ms F Lindop (Derby NHS Trust) as the gait and falls expert. In addition, Prof Ben-Shlomo (Lead Epidemiologist) and Dr Henderson (CI) and Dr Metcalfe (Lead Statistician) will represent the TMG.

13.3. Data Monitoring Steering Committee (DMC)

The Data Monitoring Committee will meet once prior to recruitment of the first participant and convene prior to the TSC meeting to review the adverse event data and any other ethical aspects that arise and report to the TSC. The DMC will comprise Dr T Quinn (University of Glasgow) as Chairperson, Dr A McConnachie and Dr J Burns as independent members. In addition, Dr E Henderson (CI), Dr Metcalfe (Lead Statistician) (open session only) and Miss Grace Young (Trial Statistician) (attending both open and closed sessions).

13.4. Patient and Public Involvement (PPI)

People with PD will be involved in every phase of the research trial. This will involve group meetings, specific roles on the trial management group, review of the protocol, participant information, consent and data collection forms and informing dissemination of the research findings to participants.

14. MONITORING, AUDIT & INSPECTION

14.1. Monitoring

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All trial related documents will be made available on request for monitoring and audit by the sponsor, the relevant REC and for inspection by MHRA and other licensing bodies.
The University of Bristol holds a Service Level Agreement (SLA) with UH Bristol. Under the Agreement UH Bristol undertakes to monitor and carry out pharmacovigilance for certain UoB sponsored studies. These activities should be carried out in accordance with the SLA, the identified risks, subsequent proposed monitoring and the trial's specific Monitoring Plan.
A Trial Monitoring Plan will be developed by the Sponsor and agreed by the TMG and CI based on the trial risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the trial.
The sponsor usually delegates some of the monitoring to the central research team. The following checks would be typical:

- That written informed consent has been properly documented
- that data collected are consistent with adherence to the trial protocol
- that CRFs are only being completed by authorised persons
- that SAE recording and reporting procedures are being followed correctly
- that no key data are missing
- that data is valid
- review of recruitment rates, withdrawals and losses to follow up.

On a regular basis we will monitor the percentage of PD patients that meet the eligibility criteria and report the percentage of participants who consent. To assess the generalisability of the participants, the characteristics of consenting participants and non-consenting will be compared. We will also report to the DMC if requested, preliminary data on event rates observed in the trial population: SAE rates and dropout rates.

14.2. Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations will be documented and reported to the CI and Sponsor immediately. They will also be reported to the DMC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.
A serious protocol breach will be reported to the NHS R & I and Sponsor as soon as possible. The sponsor will determine the seriousness of the breach and whether onward reporting to the REC and MHRA is necessary.

14.3. Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:
a) the safety or physical or mental integrity of the subjects of the trial; or
b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate trial specific instructions.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Governance and legislation

This trial will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- General Data Protection Regulation

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC.
Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes along with other documentation required for the sponsor to grant sites with a greenlight letter.
For all amendments the CI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.
This research trial will be run in accordance with ICH GCP. ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible.

15.2. Research Ethics Committee (REC) review and reports

Ethics review of the protocol for the trial and other trial related Participant facing documents (e.g. PIB and consent form) will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.
All correspondence with the REC will be retained in the Trial Master File (TMF)/Investigator Site File (ISF). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the trial and if the trial is ended prematurely (including the reasons for the premature termination). Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.
ICH GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to ICH GCP guidelines.

15.3. MHRA review and reports

MHRA review of the protocol for the trial and other trial related documents relating to the IMP/placebo will be carried out by MHRA. Clinical Trial Authorisation (CTA) will be obtained.

After the initial CTA has been approved, any amendments (which effect the safety (physical or mental integrity) of the participants, the scientific value of the study, the conduct or management of the study or the quality or safety of any IMP) will constitute a substantial amendment and a request to the MHRA for approval will be submitted.

All correspondence with the MHRA will be retained in the Trial Master File (TMF)/Investigator Site File (ISF).

In addition to the expedited reporting required for Suspected Unexpected Serious Adverse Reactions (SUSARs), a Development Safety Update Report (DSUR) will be submitted to the MHRA, once a year throughout the clinical trial or on request until the end of the trial is declared. The annual safety report should take into account all new available safety information received during the reporting period and assess the safety of subjects included in the study.

The sponsor will submit an end of trial summary results to EudraCT as per the commission's guidelines on posting and publication of result-related information within one year of the end of study declaration being submitted

15.4. Amendments

HRA approval will be sought alongside the REC and MHRA approval process.
Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA (Clinical Trial Authorisation) or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) for consideration. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

15.5. Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

15.6. Regulatory compliance

The trial will comply with the necessary regulations (MHRA, CTA, etc.) and will gain sponsor and HRA approval. The trial will not commence until a CTA is obtained from the MHRA and Favourable REC opinion and HRA approval have been provided. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

15.7. Poor quality data, notification of serious breaches to GCP and/or the protocol

Poor quality data

The quality of the trial data will be monitored throughout the trial (see 14.1) and data completeness will be reported to the DMC and TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

15.8. Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

15.9. Indemnity

The necessary trial insurance is provided by the Sponsor. The PIB provides a statement regarding indemnity for negligent and non-negligent harm.

15.10. Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymous on research data facility storage (RDSF). Requests for access to data must be via a written confidentiality and data sharing agreements (DSA) available from the RDSF website which will be confirmed by the CI (or appointed nominee).
The DSA should cover limitations of use, transfer to 3rd parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

16. DISSEMINATION POLICY

A plan for disseminating the trial results will be developed by the TMG.
The main results of the trial will be published in a high impact peer-reviewed journal. Initial findings will be submitted to relevant national and international meetings. Innovative methods of dissemination will be explored such as videos, YouTube clips and blogs to accompany scientific papers that are accessible to patients as well as providing a lay summary.
For participants of the trial, the dissemination routes which were utilised in the phase 2 trial will be mirrored by providing regular trial newsletters. PPI work has established that the demographics of the patients that participate are such that they tend to prefer paper updates as opposed to online material. However, updates will be provided through a variety of mediums including a live Twitter feed, a Facebook page, and regular updates on the web page. Research newsletters hosted by Parkinson's UK, such as 'Progress', will be utilised to reach people living with PD, as well as providing updates to newsletters that are distributed to those registered on the databases which will also be utilised during the recruitment phase (PRODeNDRoN (14) and Parkinson's Research Network).
On completion of the trial a final report will be prepared for the Funder (NHR HTA) and once approved, made publicly available on their website.

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1. APPENDIX 1: CARER STUDY

Assessment of the effect of cholinesterase inhibitor treatment versus placebo on those caring for a person with Parkinson's disease.

1.1. Trial Design

A nested sub-study within the multicentre, phase III, RCT of the ChEi rivastigmine versus placebo to prevent falls in PD.

1.2. Primary objective

To determine the effect of cholinesterase inhibitor or placebo treatment on those caring for people with Parkinson's disease who are enrolled in the phase III CHIEF-PD study.

1.3. Definition of a carer

For purposes of this trial a carer is defined as an individual who undertakes informal or formal care responsibility for the participant.

1.4. Outcome

Total CES score at 12 months. For carers enrolled during or after September 2022, follow-up will be *up to* 12 months.

1.5. Participants

Individuals who meets the definition of a carer who are caring for an individual(s) who are enrolled in CHIEF-PD.

1.6. Recruitment

Carers will be approached only with the agreement of the participant and be consented separately. If carers do not wish to, or is unable to consent to take part, the patient is still eligible to participate in the trial.

1.7. Trial population and size

Up to 600 carers recruited via their contact with people with Parkinson's Disease.

1.8. Number of study sites

Please see Section 4

1.9. Consent

Consent will be obtained by the site research team once the person with Parkinson's disease has been enrolled and randomised.

1.10. Intervention

The collection of sociodemographic data (name, gender, date of birth, address, ethnicity, GP details) and the Carer Experience Scale (CES) at time 0 and 12 months. It is anticipated that the questions will be mostly self-completed although the trained site researchers are positioned to facilitate this if required.

1.11. Enrolment duration

12 months

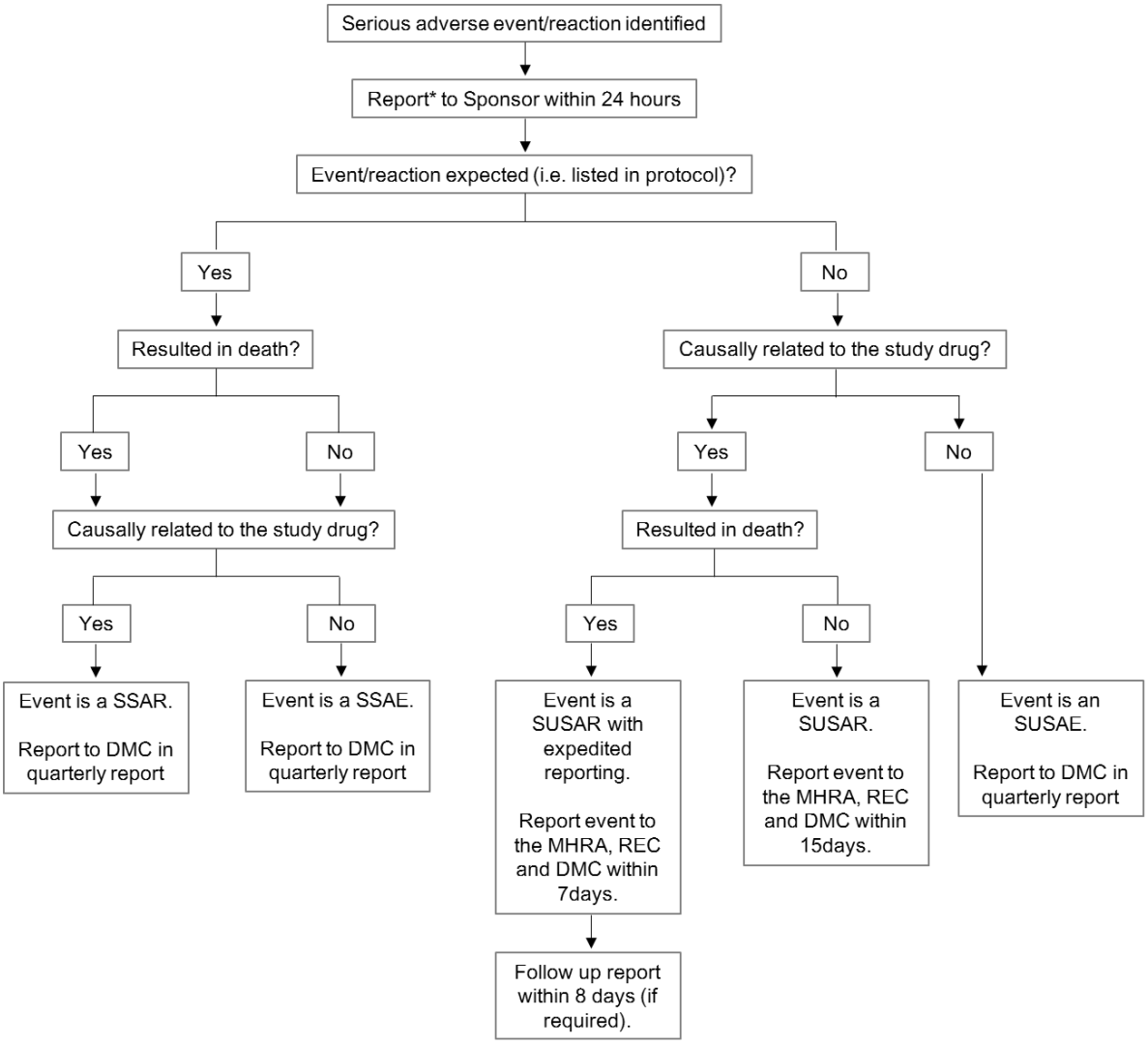
1.12. Study duration

Up to 12 months

1.13. Ethical considerations

As per Section 16

2. APPENDIX 2



*Reporting framework for Serious Adverse Events reporting flowchart. *refers to the initial notification of the Sponsor.*

3. APPENDIX 3

Supplemental Information on Rivastigmine transdermal patches up to 13.3 mg/24 hours

Summary of characteristics

Physical & chemical properties
Rivastigmine (3-[(1S)-1-(Dimethylamino)ethyl]phenyl ethyl(methyl)carbamate)
At room temperature, rivastigmine is a clear, colourless or yellow or very slightly brown, hygroscopic liquid. It is very soluble in ethanol, toluene, methanol, ethyl acetate, heptane and methylene chloride and slightly soluble in water. The chemical formula is $C_{14}H_{22}N_2O_2$ and the relative molecular mass is 250.34g/mol.

Pharmaceutical & pharmacological properties
Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones.
Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes.

Toxicological
Cholinergic toxicity has been reported with muscarinic symptoms that are observed with moderate poisonings due to overdose.
In preclinical trials, no target organ toxicity was observed. Rivastigmine was not found to be mutagenic, carcinogenic, phototoxic and showed no adverse effects on fertility or reproductive performance.
In some dermal toxicity studies, a mild irritant effect on the skin was observed. This may indicate a potential for rivastigmine transdermal patches to induce mild erythema in patients. A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study.

Pharmacokinetic & metabolic considerations
Absorption of rivastigmine from rivastigmine transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. C_{max} is reached after 10-16 hours. After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. With multiple dosing (such as at steady state), after the previous transdermal patch is replaced with a new one, plasma concentrations initially decrease slowly for about 40 minutes on average, until absorption from the newly applied transdermal patch becomes faster than elimination, and plasma levels begin to rise again to reach a new peak at approximately 8 hours.
There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease, except that plasma levels were higher on the second day of transdermal patch therapy than on the first.
Rivastigmine is weakly bound to plasma proteins (approximately 40%). It readily crosses the blood-brain barrier and has an apparent volume of distribution in the range of 1.8-2.7 l/kg.
Rivastigmine is rapidly and extensively metabolised with an apparent elimination half-life in plasma of approximately 3.4 hours after removal of the transdermal patch. Metabolism is primarily via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. Total plasma clearance of rivastigmine was approximately 130 litres/h after a 0.2 mg intravenous dose and

decreased to 70 litres/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, over-proportional pharmacokinetics of rivastigmine due to saturation of its elimination.
Unchanged rivastigmine is found in trace amounts in the urine; renal excretion of the metabolites is the major route of elimination after transdermal patch administration.
Following administration of oral ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours.
After oral administration, the C_{max} of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects. Following a single 3mg or 6mg oral dose, the mean oral clearance of rivastigmine was approximately 46-63% lower in patients with mild to moderate hepatic impairment (n=10, Child-Pugh score 5-12, biopsy proven) than in healthy subjects (n=10).
Clinical properties
Rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease. Rivastigmine transdermal patches are licensed for use in Alzheimer's disease in the UK. In the oral formulation, rivastigmine is also licensed in the UK for use in Parkinson's Dementia.

Introduction
This information is based on Rivastigmine TDS 13.3mg/24h transdermal patches. The active ingredient in the transdermal patch is Rivastigmine at a release concentration of 13.3mg/24h. The chemical name for Rivastigmine is 3-[(1S)-1-(Dimethylamino)ethyl]phenyl ethyl(methyl)carbamate. Rivastigmine belongs to the pharmacological class cholinesterase inhibitors (Pharmacotherapeutic group: psychoanaleptics, anticholinesterases, ATC code: N06DA03).
In patients with Parkinson's Disease (PD), the propensity to fall results from underlying loss of cholinergic function in cognitive (frontocortical) and gait (mesencephalic locomotor area) critical brain areas. Animal studies have established that the dual loss of dopaminergic and cholinergic networks precipitates gait instability, freezing of gait and falls in PD.
Amelioration of this underlying cholinergic deficient with cholinesterase inhibitors represents a promising strategy, targeting the aetiology of falls in PD.
The anticipated therapeutic indication is for the targeted therapy to prevent falls in patients with PD.
Rivastigmine TDS 13.3mg/24h will represent the highest dose to which patients can be up-titrated during the 12months treatment regime of the CHIEF-PD trial. The number of falls that patients incur will be followed up on a monthly basis throughout the 12 months. The primary outcome will be the difference in fall rate over 12 months between people with PD treated for 12 months with a rivastigmine and those treated with a placebo.
The lower dose interventions include Rivastigmine TDS 4.6 mg/24 h transdermal patch and Rivastigmine TDS 9.5 mg/24 h transdermal patch. Patches matching and identical to each dose of the patches differing only by the lack of the active ingredient will be used as placebo. All treatments will be double blind and randomised.

Physical, chemical, and pharmaceutical properties and formulation

Physical, chemical and pharmaceutical properties
Rivastigmine (3-[(1S)-1-(Dimethylamino)ethyl]phenyl ethyl(methyl)carbamate)

At room temperature, rivastigmine is a clear, colourless or yellow or very slightly brown, hygroscopic liquid. It is very soluble in ethanol, toluene, methanol, ethyl acetate, heptane and methylene chloride and slightly soluble in water. The chemical formula is $C_{14}H_{22}N_2O_2$ and the relative molecular mass is 250.34g/mol. The structure of rivastigmine is shown in Figure 4.
Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes.

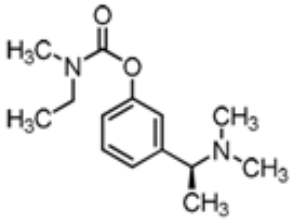


Figure 4: Structure Rivastigmine

Pharmaeutical formulation

Each transdermal patch is a thin, matrix-type transdermal patch of a circular shape. The outside of the backing layer is skin-coloured. Each transdermal patch releases 13.3 mg of rivastigmine per 24 hours. Each transdermal patch of 12.8 cm^2 contains 19.2 mg of rivastigmine. A list of excipients is provided in Table 3 below

Table 3: List of Excipients

Layer	Excipient(s)
Backing Layer	• polyethylene/thermoplastic resin/aluminium coated polyester film
Active Layer	• poly [(2-ethylhexyl)acrylate, vinylacetate (50:50)]
Adhesive Layer	• medium molecular weight polyisobutene • high molecular weight polyisobutene • silica, colloidal anhydrous • paraffin, light liquid
Release liner	• polyester film, fluoropolymer-coated

Incompatibilities

To prevent interference with the adhesive properties of the transdermal patch, no cream, lotion or powder should be applied to the skin area where the medicinal product is to be applied.

Shelf life

3 years
NB: placebo patches matched to strengths 4.6mg/24h and 9.5mg/24h have proven shelf life of 48 months.

Container/packaging

Each child-resistant sachet is made of a paper / polyethylene terephthalate / aluminium / polyacrylonitrile multilaminated material. One sachet contains one transdermal patch. Each transdermal patch is protected by a cover sheet made of siliconised polyethylene terephthalate film.

Available in study packs (boxes) for the CHIEF-PD trial contain 30 sachets.

Special precautions for disposal

Used transdermal patches should be folded in half, with the adhesive side inwards, placed in the original sachet and discarded safely. Any used or unused transdermal patches should be disposed of in accordance with local requirements.

Storage and handling instructions

The patches should be stored in the sachets until use and kept out of the reach of children. Each box of patches will be labelled with this instruction.
There is no specific temperature requirement for the storage of Rivastigmine TDS 13.3mg/24h. However, a recommendation based on other marketed product is to store the patches at temperatures between 15 and 25degrees Celcius.

Contact with the eyes should be avoided after handling Rivastigmine TDS transdermal patches. Hands should be washed with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Non-clinical Studies

a) Nonclinical pharmacology

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. Further information on the non-clinical pharmacology of Rivastigmine has been published (e.g. Polinsky *et al.* 1998)

The major metabolite is NAP226-90. Based on studies of marketed transdermal rivastigmine patches, NAP226-90 does no accumulate in the plasma. The metabolite, NAP226-90, shows minimal inhibition of acetylcholinesterase. Less NAP226-90 is formed with transdermal patches compared to oral administration of Rivastigmine.

The test patch formulation RIV-TDS consists of two matrix layers: an active layer containing rivastigmine and an adhesive layer to be adhered to the skin. The active layer comprises of the active ingredient and an acrylic pressure sensitive adhesive. The skin facing adhesive layer consists of a mixture of polyisobutylene polymers with different molecular weights, a gelling agent and a tackifier. These excipients have been chosen since they offer good adhesive properties. Both, acrylates and polyisobutylene-based adhesives are well known and

widely accepted for use in transdermal systems. The drug substance and all excipients are already contained in commercialized transdermal products.

RIV-TDS is a rivastigmine transdermal matrix system, which sufficiently delivers therapeutically relevant amounts of rivastigmine over 24 hours. *In vitro* skin permeation experiments with RIV-TDS and Exelon® transdermal patch have been performed using heat separated epidermis of human skin (Figure 5). As most relevant parameter the transdermal flux in steady state was defined. The steady state flux (J_{ss}) is determined as the slope of the linear part of the permeation profile and the respective values are depicted in Table 4. It can also be seen, that the RIV-TDS formulation tends to offer slightly higher permeated amounts of rivastigmine per unit area; with ratios of steady state fluxes (test/reference) of around 1.2, which is in good agreement with the results obtained for lower dosage strengths and formulations tested in previous clinical trials. RIV-TDS performed very consistently and well comparable, demonstrating a highly reproducible performance of the drug product.

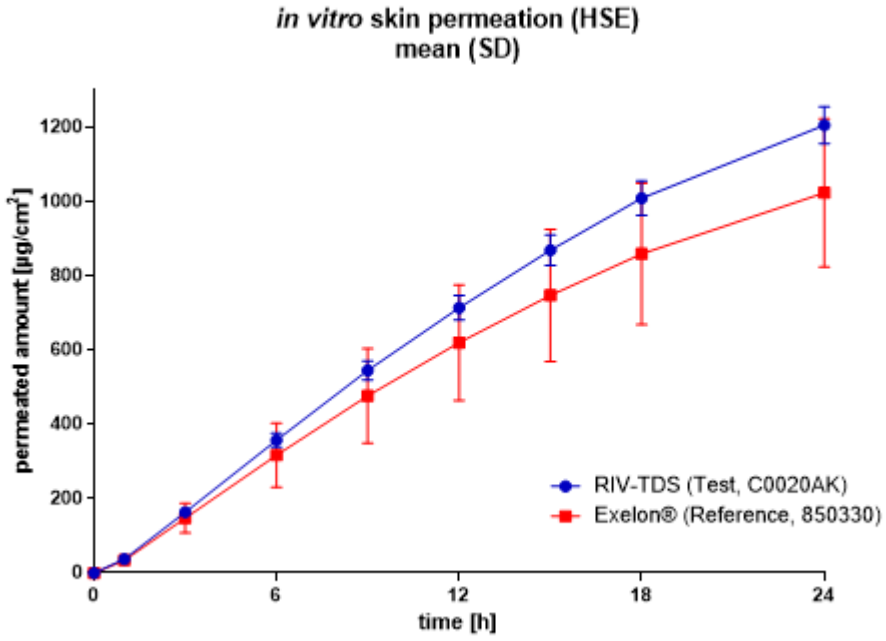


Figure 5: *In vitro* skin permeation profiles (heat separated epidermis) of RIV-TDS clinical batch C0020AK0BM compared to approved Exelon® patch

Table 4: Parameters of the permeation profiles of C0020AK0BM vs. Exelon®

Test formulation	N	J_{ss} Mean [µg/cm²/h]	SD [µg/cm²/h]
C0020AK0BM_HSE	5	57.7	2.6
Exelon_lot 850330_HSE	5	49.5	13.0

In order to provide evidence about comparability of the release profiles of RIV-TDS and Exelon® the drug release of the products was tested. The dissolution profiles for RIV-TDS batch C0020AK0BM and the reference batch of Exelon® (batch 850330) are shown in Figure 6. Both test and reference product release drug until the patch is nearly exhausted but there is

a clear difference between the two products at early time points. After 1 hour approximately 50 % of the drug is released from Exelon® whereas approximately 25 % are released from RIV-TDS.

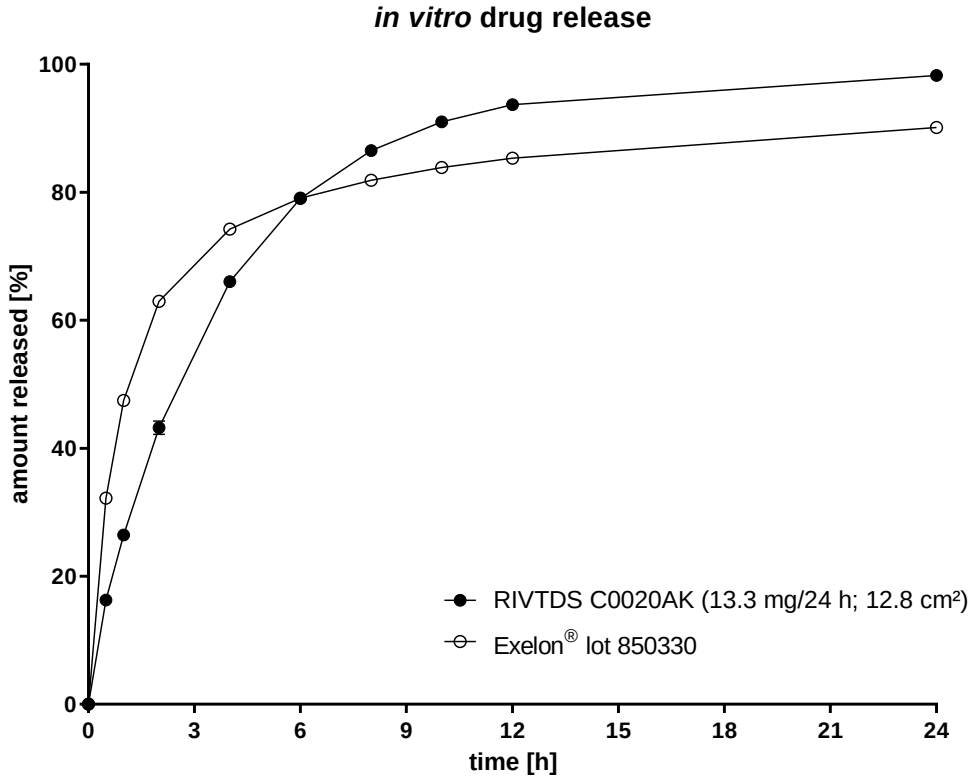


Figure 6: Dissolution profiles of RIV-TDS 13.3 mg/24h (C0020AK) and Exelon (Lot 850330) using rotating cylinder method (RC) (Mean and SD, N=6 each)

The drug release and the *in vitro* skin permeation profile of RIV-TDS show that the drug release is predominantly controlled by the drug delivery system itself and not by the skin. It is pointed out that the present formulation has been introduced into clinical trials with a patch size of 12.8 cm^2 (C_30170_P1_14 (single dose), C_30170_P1_16 (multiple dose)), which met the pharmacokinetic and adhesion endpoint. The formulation was also well tolerated locally by the subjects in all studies. In the meantime, an application for marketing authorization has been filed at German authority (BfArM).
For general nonclinical pharmacology and toxicology data of transdermal rivastigmine reference is made to the Summary of Product Characteristics (SmPC) of the originator Exelon® transdermal patch (Prescribing information).

b) Pharmacokinetics and product metabolism in animals

Not relevant as human data available. Please see section 'Effects in Humans' below

c) Preclinical safety data

The results of the pre-clinical safety data are summarised in Table 5.

Oral and topical repeated-dose toxicity studies in mice, rats, rabbits, dogs and minipigs revealed only effects associated with an exaggerated pharmacological action. No target organ toxicity was observed. Oral and topical dosing in animal studies was limited due to the sensitivity of the animal models used.

Rivastigmine was not mutagenic in a standard battery of *in vitro* and *in vivo* tests, except in a chromosomal aberration test in human peripheral lymphocytes at a dose exceeding 10^4 times the foreseen clinical exposure. The *in vivo* micronucleus test was negative. The major metabolite NAP226-90 also did not show a genotoxic potential.

No evidence of carcinogenicity was found in oral and topical studies in mice and in an oral study in rats at the maximum tolerated dose. The exposure to rivastigmine and its metabolites was approximately equivalent to human exposure with highest doses of rivastigmine capsules and transdermal patches.

In animals, rivastigmine crosses the placenta and is excreted into milk of lactating animals. Oral studies in pregnant rats and rabbits gave no indication of teratogenic potential on the part of rivastigmine. In oral studies with male and female rats, no adverse effects of rivastigmine were observed on fertility or reproductive performance of either the parent generation or the offspring of the parents. Specific dermal studies in pregnant animals have not been conducted.

Rivastigmine transdermal patches were not phototoxic and considered to be a non-sensitiser. In some other dermal toxicity studies, a mild irritant effect on the skin of laboratory animals, including controls, was observed. This may indicate a potential for rivastigmine transdermal patches to induce mild erythema in patients.
A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study. Therefore, the patient/caregiver should avoid contact with the eyes after handling of the patch

The absorption spectrum of rivastigmine does not overlap with the emission spectrum of natural sunlight in the range of 290 nm to about 350 nm (Figure 7). Moreover, since rivastigmine is a known chemical entity that has already been approved for transdermal administration it is justified not to conduct a photosafety study with the investigational medicinal product at this stage of development.

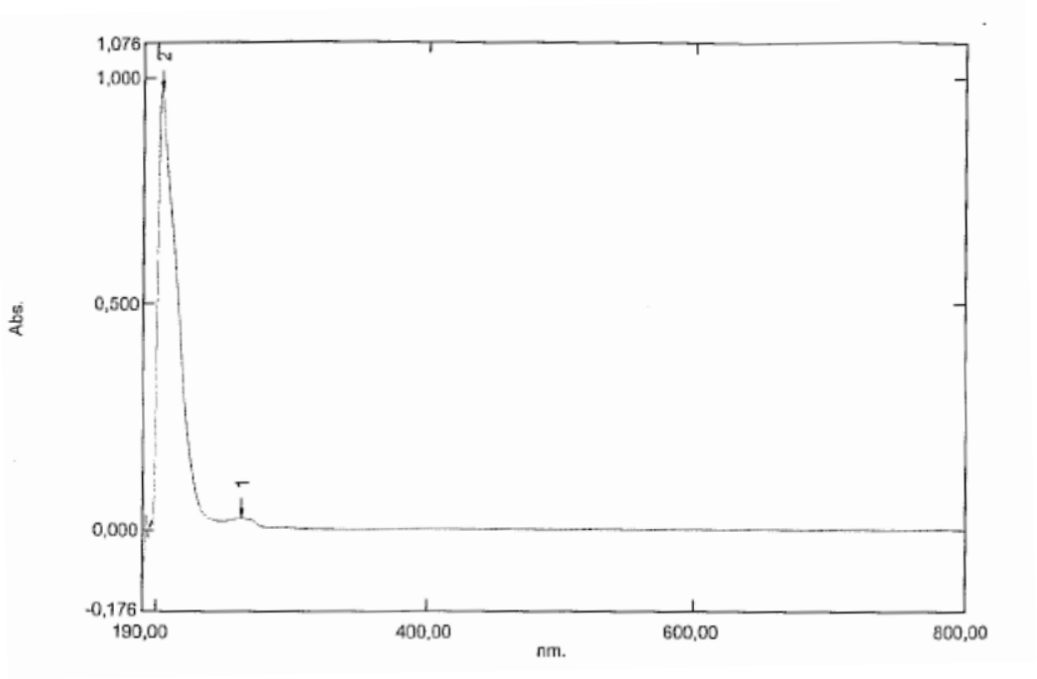


Figure 7: **Absorption spectrum of rivastigmine in methanol (0.1 mmol/l)**

Table 5: Outcome of pre-clinical toxicology screens

Toxicology	**Test results**
Target Organ Toxicity	× Absent
Mutagenesis *in vivo*	× Absent
Mutagenesis *in vitro*	✓ Present at doses 10^4 x expected human exposure
Carcinogenesis	× Absent
Teratogenesis	× Absent
Crosses placental barrier	✓ Present
Excreted in milk	✓ Present
Effect on fertility	× Absent
Effect on reproductive performance 1st generation	× Absent
Effect on reproductive performance 2nd generation	× Absent
Phototoxicity	× Absent
Dermal toxicity	✓ Mild irritant effect
Mucosal toxicity	✓ Mild irritant effect

Effects in humans

Pharmacokinetics and product metabolism in humans

Absorption

Absorption of rivastigmine from rivastigmine transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. C_{max} is reached after 10-16 hours. After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. With multiple dosing (such as at steady state), after the previous transdermal patch is replaced with a new one, plasma concentrations initially decrease slowly for about 40 minutes on average, until absorption from the newly applied transdermal patch becomes faster than elimination, and plasma levels begin to rise again to reach a new peak at approximately 8 hours. At steady state, trough levels are approximately 50% of peak levels, in contrast to oral administration, with which concentrations fall off to virtually zero between doses. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally by a factor of 2.6 and 4.9 when escalating from 4.6 mg/24 h to 9.5 mg/24 h and to 13.3 mg/24 h, respectively. The fluctuation index (FI), a measure of the relative difference between peak and trough concentrations ((Cmax-Cmin)/Cavg), was 0.58 for rivastigmine 4.6 mg/24 h transdermal patches, 0.77 for rivastigmine 9.5 mg/24 h transdermal patches and 0.72 for rivastigmine 13.3 mg/24 h transdermal patches, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 (6 mg/day) and 4.15 (12 mg/day)).

The dose of rivastigmine released from the transdermal patch over 24 hours (mg/24 h) cannot be directly equated to the amount (mg) of rivastigmine contained in a capsule with respect to plasma concentration produced over 24 hours.

The single-dose inter-subject variability in rivastigmine pharmacokinetic parameters (normalised to dose/kg bodyweight) was 43% (C_{max}) and 49% (AUC_{0-24h}) after transdermal administration versus 74% and 103%, respectively, after the oral form. The inter-patient variability in a steady-state study in Alzheimer's dementia was at most 45% (C_{max}) and 43% (AUC_{0-24h}) after use of the transdermal patch, and 71% and 73%, respectively, after administration of the oral form.

A relationship between active substance exposure at steady state (rivastigmine and metabolite NAP226-90) and bodyweight was observed in Alzheimer's dementia patients. Compared to a patient with a body weight of 65 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved. The effect of bodyweight on active substance exposure suggests special attention to patients with very low body weight during up-titration.

Exposure (AUC_{∞}) to rivastigmine (and metabolite NAP266-90) was highest when the transdermal patch was applied to the upper back, chest, or upper arm and approximately 20–30% lower when applied to the abdomen or thigh.

There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease, except that plasma levels were higher on the second day of transdermal patch therapy than on the first.

Distribution
Rivastigmine is weakly bound to plasma proteins (approximately 40%). It readily crosses the blood-brain barrier and has an apparent volume of distribution in the range of 1.8-2.7 l/kg.

Biotransformation
Rivastigmine is rapidly and extensively metabolised with an apparent elimination half-life in plasma of approximately 3.4 hours after removal of the transdermal patch. Elimination was absorption rate limited (flip-flop kinetics), which explains the longer t½ after transdermal patch (3.4 h) versus oral or intravenous administrations (1.4 to 1.7 h). Metabolism is primarily via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (<10%).
Based on *in vitro* studies, no pharmacokinetic interaction is expected with medicinal products metabolised by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 litres/h after a 0.2 mg intravenous dose and decreased to 70 litres/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, over-proportional pharmacokinetics of rivastigmine due to saturation of its elimination.

The metabolite-to-parent AUC_{∞} ratio was around 0.7 after transdermal patch administration versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal compared to oral treatment. Less NAP226-90 is formed following application of the transdermal patch, presumably because of the lack of pre-systemic (hepatic first pass) metabolism, in contrast to oral administration.

Elimination
Unchanged rivastigmine is found in trace amounts in the urine; renal excretion of the metabolites is the major route of elimination after transdermal patch administration. Following administration of oral ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

A population pharmacokinetic analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% in patients with Alzheimer's disease (n=75 smokers and 549 non-smokers) following rivastigmine oral capsule doses for up to 12 mg/day.

Pharmacokinetics in Population subgroups

Older people
Age had no impact on the exposure to rivastigmine in Alzheimer's disease patients treated with rivastigmine transdermal patches.

Hepatic impairment
No study was conducted with rivastigmine transdermal patches in subjects with hepatic impairment. After oral administration, the C_{max} of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

Following a single 3 mg or 6 mg oral dose, the mean oral clearance of rivastigmine was approximately 46-63% lower in patients with mild to moderate hepatic impairment (n=10, Child-Pugh score 5-12, biopsy proven) than in healthy subjects (n=10).

Renal impairment

No study was conducted with rivastigmine transdermal patches in subjects with renal impairment. Based on population analysis, creatinine clearance did not show any clear effect on steady state concentrations of rivastigmine or its metabolite. No dose adjustment is necessary in patients with renal impairment.

Interactions

No specific interaction studies have been performed with rivastigmine transdermal patches.

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed.

In view of its pharmacodynamic effects and possible additive effects, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products (e.g. oxybutynin, tolterodine).

Additive effects leading to bradycardia (which may result in syncope) have been reported with the combined use of various beta-blockers (including atenolol) and rivastigmine. Cardiovascular betablockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers. Therefore, caution should be exercised when rivastigmine is combined with beta-blockers and also other bradycardia agents (e.g.class III antiarrhythmic agents, calcium channel antagonists, digitalis glycoside, pilocarpin).

Since bradycardia constitutes a risk factor in the occurrence of torsades de pointes, the combination of rivastigmine with torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacine should be observed with caution and clinical monitoring (ECG) may also be required.

No pharmacokinetic interaction was observed between oral rivastigmine and digoxin, warfarin, diazepam or fluoxetine in studies in healthy volunteers. The increase in prothrombin time induced by warfarin is not affected by administration of oral rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and oral rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medicinal products, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, calcium channel blockers, inotropic agents, antianginals, non-steroidal anti-inflammatory agents, oestrogens, analgesics, benzodiazepines and antihistamines, was not associated with an

alteration in the kinetics of rivastigmine or an increased risk of clinically relevant untoward effects.

According to its metabolism, metabolic interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances.

Safety and Efficacy

Clinical pharmacokinetics

The test formulation has been used in clinical trials at patch sizes of 13.8 cm^2 (single dose C_30170_P1_10 and multiple dose C_30170-P1_12) and 12.8 cm^2 (single dose C_30170_P1_13 and C_30170_P1_14 as well as multiple dose C_30170_P1_16). These trials were designed as randomized, cross-over trials (reference: Exelon®) in healthy subjects with the objective to assess the bioavailability of rivastigmine from the developed test patch formulation. Details are given in the investigational medicinal product dossier. Additionally, reference is made to the rivastigmine pharmacokinetics described in the Summary of Product Characteristics of the approved originator product Exelon® transdermal patch.

Clinical studies in Alzheimer's dementia

The efficacy of rivastigmine transdermal patches in patients with Alzheimer's dementia has been demonstrated in a 24-week double-blind, placebo-controlled core study and its open-label extension phase and in a 48-week double blind comparator study.

24-week placebo-controlled study

Patients involved in the placebo-controlled study had an MMSE (Mini-Mental State Examination) score of 10–20. Efficacy was established by the use of independent, domain-specific assessment tools which were applied at regular intervals during the 24-week treatment period. These include the ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-CGIC (Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change, a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the ADCS-ADL (Alzheimer's Disease Cooperative Study – Activities of Daily Living, a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as shopping, retention of ability to orient oneself to surroundings as well as involvement in activities related to finances). The 24-week results for the three assessment tools are summarised in Table 6.

Table 6: Results of 24 week study in Alzheimer's Disease

ITT-LOCF population	**Rivastigmine transdermal patches 9.5 mg/24 h N = 251**	**Rivastigmine capsules 12 mg/day N = 256**	**Placebo N = 282**
ADAS-Cog	(n=248)	(n=253)	(n=281)
Mean baseline ± SD	27.0 ± 10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005*[1]	0.003*[1]	
ADCS-CGIC	(n=248)	(n=253)	(n=278)
Mean score ± SD	3.9 ± 1.20	3.9 ±± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*[2]	0.009*[2]	
ADCS-ADL	(n=247)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013*[1]	0.039*1	

* p≤0.05 versus placebo
ITT: Intent-To-Treat; LOCF: Last Observation Carried Forward
[1] Based on ANCOVA with treatment and country as factors and baseline value as a covariate. Negative ADAS-Cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement.
[2] Based on CMH test (van Elteren test) blocking for country. ADCS-CGIC scores <4 indicate improvement.

The results for clinically relevant responders from the 24-week placebo-controlled study are provided in Table 7. Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADASCog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.

Table 7: Results of 24 week study in Alzheimer's Disease

	Patients with clinically significant response (%)		
ITT-LOCF population	**Rivastigmine transdermal patches 9.5 mg/24 h N = 251**	**Rivastigmine capsules 12 mg/day N = 256**	**Placebo N = 282**
At least 4 points improvement on ADAS-Cog with no worsening on ADCSCGIC and ADCS-ADL	17.4	19.0	10.5
p-value versus placebo	0.037*	0.004*	

* p≤0.05 versus placebo

As suggested by compartmental modelling, 9.5 mg/24 h transdermal patches exhibited exposure similar to that provided by an oral dose of 12 mg/day.

48-week active comparator controlled study

Patients involved in the active comparator controlled study had an initial baseline MMSE score of 10-24. The study was designed to compare the efficacy of the 13.3 mg/24 h transdermal patch against the 9.5 mg/24 h transdermal patch during a 48-week double-blind treatment phase in Alzheimer's disease patients who demonstrated functional and cognitive decline after an initial 24-48 week open-label treatment phase while on a maintenance dose of 9.5 mg/24 h transdermal patch. Functional decline was assessed by the investigator and cognitive decline was defined as a decrease in the MMSE score of >2 points from the previous visit or a decrease of >3 points from baseline. Efficacy was established by the use of ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-IADL (Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living) assessing instrumental activities which include maintaining finances, meal preparation, shopping, ability to orient oneself to surroundings, ability to be left unattended. The 48-week results for the two assessment tools are summarised in Table 8.

Table 8: Results of 48 week comparator study in Alzheimer's

Population/Visit			Rivastigmine patch 15 cm^2 N = 265		Rivastigmine patch 10 cm^2 N = 271		Rivastigmine patch 15 cm^2		Riva-stigmine patch 10 cm^2
			n	Mean	n	Mean	DLSM	95% Cl	p-value
ADAS-Cog									
LOCF		Baseline	264	34.4	268	34.9			
	DB-week 48	Value	264	38.5	268	39.7			
		Change	264	4.1	268	4.9	-0.8	(-2.1, 0.5)	0.227
ADCS-IADL									
LOCF		Baseline	265	27.5	271	25.8			
	Week 48	Value	265	23.1	271	19.6			
		Change	265	-4.4	271	-6.2	2.2	(0.8, 3.6)	0.002*

CI – confidence interval.
DLSM – difference in least square means.
LOCF – Last Observation Carried Forward.
ADAS-cog scores: A negative difference in DLSM indicates greater improvement in rivastigmine 15 cm^2 as compared to rivastigmine 10 cm^2.
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in rivastigmine 15 cm^2 as compared to rivastigmine 10 cm^2.
N is the number of patients with an assessment at baseline (last assessment in the initial open-label phase) and with at least 1 post-baseline assessment (for the LOCF).
The DLSM, 95% CI, and p-value are based on an ANCOVA (analysis of covariance) model adjusted for country and baseline ADAS-cog score.
* $p<0.05$
Source: Study D2340-Table 11-6 and Table 11-7

Clinical studies in Parkinson's dementia

76-week prospective phase 3

A 76-week prospective phase 3, open-label, multi-center study trial with the purpose to provide long-term safety data for rivastigmine capsule and transdermal patch treatments, in particular the effect of rivastigmine on worsening of the underlying motor symptoms of Parkinson's Disease (PD), in patients with mild to moderately severe dementia associated with PD have been performed.
The study used transdermal patches of 4.6mg/24h and 9.5mg/24hours with one patch a day applied in the morning, worn for 24 hours, starting at 4.6 mg for 4 weeks then titrated up to 9.5 mg rivastigmine. The patches were compared to rivastigmine capsules starting at a total dose of 3 mg/day (1.5 mg twice daily orally) titrated up in 3 mg/day increments every 4

weeks to a final dose of 12 mg/day (6 mg twice daily orally). The 12 mg/day dose or the highest dose tolerated was maintained until week 76.

The adverse events (AEs) were summarized by presenting the number and percentage of patients having any of the 4 predefined events, *i.e.* i) tremor, ii) muscle rigidity, iii) bradykinesia, and iv) fall, or discontinued due to any of the 4 predefined AEs in each treatment group.

Table 9 below shows a summary of the results for the primary outcome.

Table 9: Result of primary outcome for Study in Parkinson's Dementia

	Rivastigmine Capsule	Rivastigmine Patch
Patients analysed (n)	294	288
Tremor (%)	24.5	9.7
Muscle Rigidity	4.1	5.2
Bradykinesia	5.1	6.3
Fall	17.0	20.1

Clinical studies in Parkinson's Disease without Dementia

The 32 week phase II trial for preventing falls in Parkinson's Disease (ReSPonD trial) showed a potential of rivastigmine administered orally to reduce the number of falls in people with Parkinson's disease by ~50%. This trial was a randomized placebo-controlled, double-blind, parallel arm trial in Parkinson's patients without dementia (Hoehn & Yahr stage 2-3). Rivastigmine (or equivalent as placebo) dose was started at 3 mg per day (1·5 mg tablet taken twice a day) and was up-titrated in 3 mg per day (or placebo) increments every 4 weeks to a maximum of 12 mg per day at week 13 onwards. Identical titration was performed for those taking placebo to maintain masking. The highest tolerated dose was maintained for the following 16 week period, yielding a total treatment period of 32 weeks. The results pertaining to the primary outcome are summarised in Table 10 whilst the results of the secondary outcomes are summarised in Table 11.

Table 10: Primary outcome of the 32 week phase II trial for preventing falls in Parkinson's Disease

	Rivastigmine Capsule	**Placebo**	**p-value**	**% reduction**
Patients analysed (n)	55	59		
Normal Walk† (s)	0.043	0.064	0.002	28%
Simple cognitive task plus walk (s)	0.111	0.122	0.045	21%
Complex cognitive task plus walk (s)	0.145	0.161	0.17	19%

† n=58 for placebo group.

Table 11: Secondary outcomes of the 32 week phase II trial for preventing falls in Parkinson's Disease

	Rivastigmine Capsule	Placebo	p-value
Falls per month	1.4, (65)	2.4, (65)	0.002
PPA falls risk score	2.2, (57)	2.2 (63)	0.85
Fear of falling	23.8, (58)	24.9 (63)	0.78
Gait speed, normal walking (m/s)	1.08 (55)	0.99 (58)	0.003
Walk + simple cognitive task (m/s)	0.79, (55)	0.74 (58)	0.037
Walk + complex cognitive task (m/s)	0.71, (55)	0.66 (59)	0.048
Controlled leaning balance score, medium	12, (50)	17, (58)	0.008
Controlled leaning balance score, high	8, (50)	19, (58)	0.009
Controlled leaning balance score, very high	12, (50)	15, (58)	0.085
FOG (freezing) episode(s) in past month	36, (57)	48, (63)	0.22

Data are reported as mean, (n)

Possible risks and adverse drug reactions

Summary of the safety profile

Application site skin reactions (usually mild to moderate application site erythema), are the most frequent adverse reactions observed with the use of rivastigmine transdermal patch. The next most common adverse reactions are gastrointestinal in nature including nausea and vomiting.

In double-blind controlled clinical trials, application site reactions were mostly mild to moderate in severity. The incidence of application site skin reactions leading to discontinuation was ≤2.3% in patients treated with rivastigmine transdermal patches. The incidence of application site skin reactions leading to discontinuation was higher in the Asian population with 4.9% and 8.4% in the Chinese and Japanese population respectively.
In a 24-week double-blind, placebo-controlled clinical trial, skin reactions were measured at each visit using a skin irritation rating scale. When observed in patients treated with rivastigmine transdermal patches, skin irritation was mostly slight or mild in severity. It was rated as severe in ≤2.2% of patients in these studies and in ≤3.7% of patients treated with rivastigmine transdermal patches in a Japanese study.

The following reactions are defined as ‘common’ meaning that 1 to 10% of people taking rivastigmine may experience them.

- Urinary tract infection
- Anorexia, decreased appetite
- Anxiety, depression, delirium, agitation
- Headache, fainting, dizziness
- Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
- Rash
- Urinary incontinence

The following reactions are defined as 'uncommon' meaning that between 0.1% and 1% of people taking rivastigmine may experience them.

- Dehydration
- Aggression
- Hyperactivity
- Bradycardia (slow pulse)
- Gastric ulcer

The following reactions are defined as 'very rare' meaning that less than 0.01 % of people taking rivastigmine may experience them.

- Extrapyramidal symptoms (Parkinson's symptoms)

The last side effects listed below have been noted to occur in people taking the rivastigmine but there is insufficient evidence to determine the frequency.

- Hallucinations, restlessness, nightmares
- Worsening of Parkinson's disease, seizure, tremor, somnolence
- Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome
- Hypertension
- Pancreatitis,
- Hepatitis, elevated liver function tests
- Pruritus, erythema, urticaria, vesicles, allergic dermatitis

The following adverse reactions have only been observed with rivastigmine capsules and oral solution and **not in clinical studies with rivastigmine transdermal patches**:

- malaise,
- confusion,
- sweating increased (common);
- duodenal ulcers,
- angina pectoris (rare);
- gastrointestinal haemorrhage (very rare);
- severe vomiting associated with oesophageal rupture (not known).

Tabulated list of adverse reactions

Table 12 displays the adverse reactions reported in 1670 patients with Alzheimer's dementia treated in randomised, double-blind, placebo and active-controlled clinical studies with rivastigmine transdermal patches for a duration of 24-48 weeks and from post-marketing data. Adverse reactions in Table 12 are listed according to MedDRA system organ class and frequency category.
Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 12: Adverse reactions by MedDRA system organ class and frequency category

Infections and infestations		
	Common	Urinary tract infection
Metabolism and nutrition disorders		
	Common	Anorexia, decreased appetite
	Uncommon	Dehydration
Psychiatric disorders		

Common	Anxiety, depression, delirium, agitation
Uncommon	Aggression
Not known	Hallucinations, restlessness, nightmares
Nervous system disorders	
Common	Headache, syncope, dizziness
Uncommon	Psychomotor hyperactivity
Very rare	Extrapyramidal symptoms
Not known	Worsening of Parkinson's disease, seizure, tremor, somnolence
Cardiac disorders	
Uncommon	Bradycardia
Not known	Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome
Vascular disorders	
Not known	Hypertension
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
Uncommon	Gastric ulcer
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis, elevated liver function tests
Skin and subcutaneous tissue disorders	
Common	Rash
Not known	Pruritus, erythema, urticaria, vesicles, allergic dermatitis (disseminated)
Renal and urinary disorders	
Common	Urinary incontinence
General disorders and administration site conditions	
Common	Application site skin reactions (e.g. application site erythema*, application site pruritus*, application site oedema*, application site dermatitis, application site irritation), asthenic conditions (e.g. fatigue, asthenia), pyrexia, weight decreased
Rare	Fall

*In a 24-week controlled study in Japanese patients, application site erythema, application site oedema and application site pruritus were reported as "very common".

Further information on the adverse reaction profile

Gastrointestinal disorders

Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose-related, and may occur when initiating treatment and/or increasing the dose. These adverse reactions occur more commonly in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with intravenous fluids and dose reduction or discontinuation if recognised and treated promptly. Dehydration is uncommon but can be associated with serious outcomes.

Weight loss

Patients with Alzheimer's disease have shown that weight loss may occur whilst taking cholinesterase inhibitors, including rivastigmine. The patient's weight should be monitored during therapy with rivastigmine transdermal patches.

Bradycardia
Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with identified risk factors. All patients in the CHIEF-PD will have pulse check at baseline. Where appropriate, the patient will receive an ECG prior to enrolment in the trial.

Skin application site reactions
Skin application site reactions may occur with rivastigmine patches and are usually mild or moderate in intensity. These reactions are not in themselves an indication of sensitisation. However, use of rivastigmine patch may lead to allergic contact dermatitis.

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued.

Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

There have been rare post-marketing reports of patients experiencing allergic dermatitis (disseminated) when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued.

Worsening of Parkinson's Symptoms
Rivastigmine may exacerbate or induce extrapyramidal symptoms.

Dose-dependency
The incidence and severity of adverse reactions generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24 h. When doses higher than 13.3 mg/24 h were used in placebo-controlled study, insomnia and cardiac failure were observed more frequently than with 13.3 mg/24 h or placebo, suggesting a dose effect relationship. However, these events did not occur at a higher frequency with rivastigmine 13.3 mg/24 h transdermal patches than with placebo.

Overdose and dose dependency of symptoms
The most commonly reported safety incidence with the use of rivastigmine transdermal patches is the application of multiple patches. Multiple patch application bears particular risk where patients are reliant on healthcare staff or caregivers to remove and apply patches. In these incidents, the patches often did not have the date/day of application written on them. As such, the CHIEF-PD require all site staff to provide enough information to both the patient and carers about the possible side effects and risks associated with multiple patches. The advice may be given to write on the patch with a fine marker pen the day or date that the patch was applied; this is in accordance with the marketed prescribing advice for Rivastigmine TDS.
All patches will be clearly marked with the dose as well as colour coded for the ease of identifying the right strength of the patch. Furthermore, the CHIEF-PD requires the

participants to keep a diary of when they have applied a patch of a certain strength which should aid in minimising the risk of overdose.

Symptoms of overdose

Most cases of accidental overdose of oral rivastigmine have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment 24 hours after the overdose.

Cholinergic toxicity has been reported with muscarinic symptoms that are observed with moderate poisonings such as miosis, flushing, digestive disorders including abdominal pain, nausea, vomiting and diarrhoea, bradycardia, bronchospasm and increased bronchial secretions, hyperhidrosis, involuntary urination and/or defecation, lacrimation, hypotension and salivary hypersecretion. In more severe cases nicotinic effects might develop such as muscular weakness, fasciculations, seizures and respiratory arrest with possible fatal outcome.

Additionally, there have been post-marketing cases of dizziness, tremor, headache, somnolence, confusional state, hypertension, hallucinations and malaise. Overdose with rivastigmine transdermal patch resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting but rarely in clinical trials.

Management of overdose

As rivastigmine has a plasma half-life of about 3.4 hours and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose all Rivastigmine TDS patches should be removed immediately and no further transdermal patch should be applied for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse reactions should be given as necessary.

In severe overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

Contraindications

The use rivastigmine is contraindicated in patients with known hypersensitivity to the active substance rivastigmine, to other carbamate derivatives or to any of the excipients listed in Table 3.

Special warnings and precautions for use

If treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24 h.

Special populations

Patients with body weight below 50 kg:

These patients may experience more adverse reactions and may be more likely to discontinue due to adverse reactions. Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the maintenance dose to the 4.6 mg/24 h transdermal patch if such adverse reactions develop.

Patient with hepatic impairment:

Patients with clinically significant hepatic impairment may experience more adverse reactions. Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. Particular caution must be exercised in titrating these patients.

Pregnancy:
Rivastigmine should not be used during pregnancy unless clearly necessary.
In pregnant animals, rivastigmine and /or metabolites crossed the placenta. It is not known if this occurs in humans. No clinical data on exposed pregnancies are available. In peri/postnatal studies in rats, an increased gestation time was observed.

Breast feeding:
Women on rivastigmine should not breast-feed. For the CHIEF-PD trial, rivastigmine should not be prescribed to women who are breast feeding.
In animals, rivastigmine is excreted in milk. It is not known if rivastigmine is excreted into human milk.

Patient at risk of bradycardia:
Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, brady-arrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes.

Care must be taken when prescribing Rivastigmine TDS transdermal patches:
- to patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block),
- to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions,
- to patients predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases;
- to patients with a history of asthma or obstructive pulmonary disease.

Paediatric population:
There is no relevant use of rivastigmine in the paediatric population in the CHIEF-PD trial.

Effects on ability to drive and use machines

Rivastigmine may induce syncope or delirium. As a consequence, rivastigmine has minor or moderate influence on the ability to drive and use machines. Therefore, it is recommended that in patients with dementia treated with rivastigmine, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

Marketing Experience

Rivastigmine TDS has received marketing authorization for the transdermal patches at 4.6mg/24h (MA number: 2200565) and 9.5mg/24h (MA number: 2200566). Marketing authorization for Rivastigmine TDS 13.3mg/24h is expected in 2019.

In the UK, the following preparations are available:

Brand	Strength	Marketing Authorisation Number	Frequency
Almuriva	4.6mg	PL 04416/1369	24 hours transdermal patch
	9.5mg	PL 04416/1370	
Alzest	4.6mg	PL 08553/0506	
	9.5mg	PL 08553/0507	
Erastig	4.6mg	PL 00289/1815	
	9.5mg	PL 00289/1814	
	13.3mg	PL 00289/1886	
Exelon	4.6mg	EU/1/98/066/031-032	
	9.5mg	EU/1/98/066/033-034	
	13.3mg	EU/1/98/066/027-030	
Prometax	4.6mg	EU/1/98/092/019-022	
	9.5mg	EU/1/98/092/023-026	
	13.3mg	EU/1/98/092/027-030	
Voleze	4.6mg	PL20046/0101	
	9.5mg	PL20046/0102	
	13.3mg	PL20046/0278	

Summary of data and guidance for the investigator

Rivastigmine transdermal patches are currently authorised for the use in Alzheimer's Dementia in the UK. The active substance, rivastigmine, is in use for the Parkinson's patient group but with indication for dementia.

Side effects are generally mild to moderate with the most common adverse reactions being skin site reactions and gastrointestinal upset.

Given that side effects are dose dependent, and due to the risk of overdose, it is important that the patient is up-titrated according to the protocol (see also appendix 3.1). Patients must be advised to remove the previous patch before applying a new patch.
Strictly only one patch must be worn at any time; the use of 2 patches of a lower strength to achieve a higher dose is not permitted. The patches must not be cut into pieces and should be worn with the overtapes as per the CHIEF-PD protocol instructions.

If the patient experience moderate-to-severe side effects, and/or in the case of a suspected overdose, please remove the patch and do not apply a new patch for 24hours.
Patches should not be applied to the same skin area twice within 14 days. This reduces the risk of adverse skin reactions.
Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.

If the patient falls within any category of the 'special populations', please monitor patient carefully in accordance with standard care.

Patients and caregivers should be instructed on important administration instructions:

- The previous day's patch must be removed before applying a new one every day
- The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time
- The patch should be pressed down firmly for at least 30 seconds using the palm of the hand until the edges stick well.
- If the patch falls off, a new one should be applied for the rest of the day, then it should be replaced at the same time as usual the next day.
- The patch can be used in everyday situations, including bathing and during hot weather.
- The patch should not be exposed to any external heat sources (e.g. excessive sunlight, saunas, solarium) for long periods of time.
- The patch should not be cut into pieces.

Appendix 3.1: Posology and method of administration

Initial dose
Treatment is started with 4.6 mg/24 h.

Maintenance dose
After a minimum of four weeks of treatment and if well tolerated according to the treating physician, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, the daily recommended effective dose, which should be continued for as long as the patient continues to demonstrate therapeutic benefit.

Dose escalation
9.5 mg/24 h is the recommended daily effective dose which should be continued for as long as the patient continues to demonstrate therapeutic benefit. If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 h, the treating physician may consider increasing the dose to 13.3 mg/24 h.

The clinical benefit of rivastigmine should be reassessed on a regular basis. Discontinuation should also be considered when evidence of a therapeutic effect at the optimal dose is no longer present.

Treatment should be temporarily interrupted if gastrointestinal adverse reactions are observed until these adverse reactions resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise treatment should be re-initiated with 4.6 mg/24 h.

Method of administration
Rivastigmine TDS is for transdermal use.
Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.

The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation.

References

Polinsky RJ (1998) Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease *Clin Ther* 20(4): 634-647

EMA (2016) Guidelines for good clinical practice E6(R2), Step 5