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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kehoe PG, Turner N, Howden B, et al. Safety and efficacy of losartan for the reduction of brain atrophy in clinically diagnosed Alzheimer's disease (the RADAR trial): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2021; **20**: 895–906.

Supplemental Tables

to

Safety and efficacy of losartan for the reduction of brain atrophy in clinically diagnosed Alzheimer's disease (the RADAR trial): a phase 2 double blind, randomised, placebo-controlled trial

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Supplemental Table 1 – Summary of Amendments to Protocol

Trial Amendment Type & Number	Protocol Version No.	Date Issued	Author(s) of changes	Summary of changes made
Substantial Amendment 1 (S/A1)	3.0	03/06/2013	Patrick Kehoe	Revisions made for clarity and to ensure consistency with the sponsor's SOPs and previous recommendations made by the ethics committee See S/A1 summary dated 03/06/2013
Substantial Amendment 2 (S/A2)	4.0	18/07/2013	Patrick Kehoe	Addition of information pertaining to pilot imaging procedures
Minor Amendment 2	4.1	23/07/2013	Patrick Kehoe	Minor clarifications added after review by TSC, DMEC and TMG
Substantial Amendment 3 (S/A3)	5.0	28/11/2013	Patrick Kehoe	Change to minimisation details and eligibility criteria. Clarification that an additional phonecall is required to provide the outcome of the screening blood test.
Minor Amendment 3	5.1	09/04/2014	Patrick Kehoe	Minor corrections to ensure consistency with other documentation/text e.g. timing of blood tests
Substantial amendment 6 (S/A 6) <u>NB</u> substantial amendments 4&5 were approved by the MHRA only due to	6.0	07/10/2014	Patrick Kehoe	Removal of exclusion criteria for severe hippocampal atrophy and inclusion of option to recruit via primary care.

change in brand of the IMP and shelf-life extension.				
Minor Amendment 4	6.0	07/10/2014	Patrick Kehoe	Submission for review of revised poster to be used in recruitment from primary care.
Minor Amendment 5	6.1	14/11/2014	Patrick Kehoe	Removal of residual references in protocol text and Appendix I of protocol to severe hippocampal atrophy as exclusion criteria that were missed in Substantial amendment 6 (S/A 6)
Minor Amendment 6	6.1	26.02.2015	Patrick Kehoe	Formatting changes to the open label diaries for BP and medication and change to the reply slip to include GP surgery.
Minor Amendment 7	6.1	12.05.2015	Patrick Kehoe	Inclusion of RADAR on 'Join Dementia Research' (JDR)
Substantial Amendment 7 (S/A7)	7.0	03/12/2015	Patrick Kehoe	Change of eligibility criteria for MMSE range from 18-28 to 15-28.
Substantial Amendment 8 (S/A8)	8.0	04.03.2016	Patrick Kehoe	Inclusion of an embedded qualitative component.
Substantial Amendment 9 (S/A9)	9.0	19.07.2017	Patrick Kehoe	Clarification of consent process. Inclusion of SPECT as a considered scan option for screening, and similarly use of ACE-R cognitive assessment scores as a reference point for screening of potentially eligible participants. Clarification of baseline Blood pressure exclusion criteria. Clarification of assessment timings. Replace 'informant' with 'companion'
Substantial Amendment 10 (S/A10)	10.0	11.10.2017	Patrick Kehoe	Correction to blood pressure exclusion criteria section 7.2.

Supplemental Table 2 – Comparisons of primary outcome according to Hippocampal and Lateral Ventricle volumes

	Placebo				Intervention				Regression analysis	
	Baseline		12 months		Baseline		12 months		Adjusted* mean diff (95%CI)	p- value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
LHV	106	2.5 (0.5)	87	2.4 (0.5)	105	2.5 (0.5)	84	2.5 (0.5)	0.01 (-0.01, 0.03)	0.337
LHV BSI	-	-	87	0.11 (0.06)	-	-	84	0.11 (0.08)	-0.01 (-0.03, 0.01)	0.385
RHV	106	2.6 (0.5)	87	2.5 (0.5)	105	2.6 (0.5)	84	2.6 (0.5)	0.01 (-0.003, 0.03)	0.112
RHV BSI	-	-	87	0.12 (0.06)	-	-	84	0.11 (0.08)	-0.01 (-0.03, 0.01)	0.231
THV	106	5.0 (1.0)	87	4.9 (0.9)	105	5.2 (0.9)	84	5.0 (0.9)	0.02 (-0.01, 0.05)	0.144
LHV	106	47 [35, 64]	86	50 [40, 67]	105	48 [35, 69]	83	51 [40, 78]	0.99 ⁺ (0.98, 1.01)	0.443
LHV BSI	-	-	86	5 [3, 7]	-	-	83	5 [3, 8]	-0.45 (-1.45, 0.56)	0.380

Legend. LHV= left hippocampus volume; RHV= right hippocampus volume, THV= total hippocampal volume; BSI = Boundary Shift Integral; LVV = lateral ventricle volume,. *Adjusted for minimization variables (age and Scheltens score categories), baseline value of the outcome and centre. ⁺Ratio of geometric means.

Supplemental Table 3 - -Serious Adverse Events (SAE) according to Treatment Arm

SAE Number	Brief Summary	Arm
Cancer		
SAE002	Participant died pancreatic cancer	Placebo
Cardio-circulatory		
SAE003	Prolonged syncopal episode	Placebo
SAE018	Fainting and bradycardia	Placebo
Dermatological		
SAE030	Rash around armpits and right side of the abdomen	Intervention
Endocrine and metabolic		
SAE013	Development of Diabetes	Intervention
Gastrointestinal		
SAE016	Constipation and prolapse	Placebo
SAE033	Diverticulitis	Placebo
SAE027	Stomach pain and breathing difficulty	Placebo
SAE024	Urinary retention and diarrhoea and vomiting	Intervention
Haematological/thrombosis		
SAE040	Admission 3 days Right sided chest pain. Discharged with anticoagulant meds.	Placebo
Hepatic		
SAE017	Collapse Raised ALT 100 (0-55)	Intervention
SAE023	Grossly raised AST serum level	Placebo
SAE043	Safety bloods results outside of the safety range	Intervention
Infection		
SAE007	Hospital admission. Sepsis	Intervention
SAE019	Cellulitis left leg	Intervention
SAE020	Cellulitis left leg flare up	Intervention
SAE029	Recurrent bronchitis	Intervention
SAE039	Dizzy spell, tremor and cold hands. Discharged with antibiotics.	Intervention
SAE041	Chest infection	Placebo
SAE042	Lower respiratory tract infection	Intervention
Mechanical injury		
SAE006	Fall	Placebo
SAE008	Fainting	Placebo
SAE010	Participant died. Admitted with femur fracture, dehydration and anaemia. Unrelated to trial	Intervention
SAE011	Fall	Intervention
SAE014	Fainting	Intervention
SAE021	Falls	Intervention
SAE035	Fall	Placebo

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SAE Number	Brief Summary	Arm
Neuropsychiatric		
SAE012	Found slumped on sofa unable to sit up, visual hallucinations	Placebo
SAE004	Seizures	Intervention
SAE026	Seizure	Placebo
SAE032	Vivid delusions and aggressive outburst	Placebo
SAE034	Temp admission to Dementia Assessment Unit	Intervention
Other		
SAE031	Ankle swelling (oedema)	Placebo
SAE001	Brain pathology	Intervention
SAE005	Persistent nausea, dizziness and headache	Placebo
SAE009	Mobility problems and unable to get out of bath	Intervention
SAE015	Overdose of dementia medication	Intervention
SAE025	Food poisoning	Intervention
SAE028	Collapse	Intervention
SAE036	Elective surgery (throat biopsy)	Placebo
SAE037	Hospital admission knee pain. Arthritis	Placebo
SAE038	Collapse without loss of consciousness	Placebo
Renal		
SAE022	Increased creatinine	Open Label