Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Clinical Trial Outline and Flow

Table 1: Clinical Trial Flow Chart

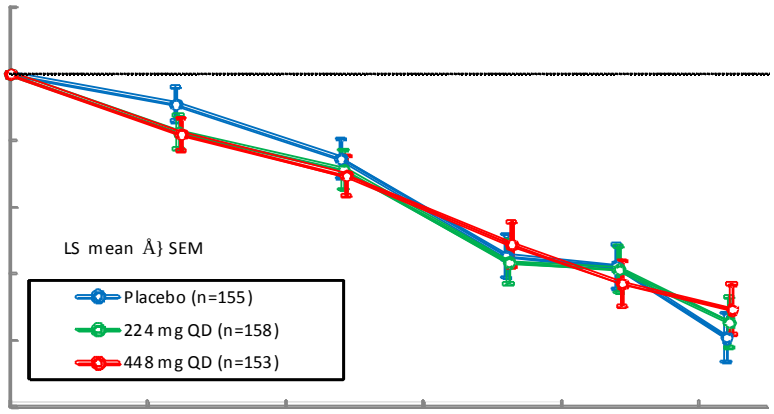
Visit Number	1	2	3	4	5	6	7	8	9	10	11 or Early Term	12
Stage of study	Screening (within 42 days prior to Randomization)	Baseline (Week 0)	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 18 (±7 days)	Week 24 (±7 days)	Week 30 (±7 days)	Week 36 (±7 days)	Week 44 (±7 days)	Week 52 (±7 days)	Follow-Up Week 56 (±7 days)
Informed consent	X											
Demographics, medical history, education	X											
Inclusion / Exclusion criteria	X	X										
Height & Weight	X	X			X		X		X		X	
Randomization		X										
Physical examination	X				X		X		X		X	X
Vital signs (Heart Rate and BP)	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, Serum chemistry[1]	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X
PPK blood draw[2]		X			X		X		X	X	X	
ApoE4 and CYP2D6		X										
Study drug dispense		X	X	X	X	X	X	X	X	X		
Study drug collection/compliance			X	X	X	X	X	X	X	X	X	
ADAS-cog	X	X			X		X		X	X	X	X
ADCS-CGIC		X			X		X		X	X	X	
ADCS-ADL		X			X		X		X		X	
MMSE	X	X			X		X		X	X	X	X
NPI		X			X		X		X		X	
FAQ		X			X		X		X		X	
C-SSRS Pediatric[3]		X			X		X		X		X	
vMRI or CT [4]	X										X	
CSF[5]		X									X	

[1] Height is done at baseline only
[2] B12 is done at Screening only
[3] PPK blood draws should be done before the first dose of study medication at Baseline, before dosing on the day of the Week 24 visit and 1-6 hours after patient's last dose of study medication at the other visits
[4] C-SSRS Ped Lifetime/Recent at Week 0 and C-SSRS Ped Since Last Visit at all others
[5] CT at Screening if MRI is contraindicated and the patient has not had a brain CT within past year
[6] Visit window for vMRI at Week 52 is 14 days before and up to 14 days after visit. If patient is terminating early at 36 week or after, obtain vMRI. Neither vMRI nor CT is necessary for patients who have a contraindication to MRI
[7] Only for the CSF substudy. Visit windows for CSF are up to 14 days prior to first dose of study medication and up to 14 days prior to Week 52 visit. If a patient in the CSF substudy is terminating early, they do not need to undergo lumbar puncture.
[8] Only applies to patients not going to the extension period.

eFigure. Protocol-Specified Secondary Analyses

Results for the ADAS-cog and ADCS-CGIC secondary outcomes at weeks 12, 24, 36, and 44; and the ADCS-ADL secondary outcome at week 52). The figure indicates the P values of the effects of each dose of edonerpic maleate compared to placebo at each time interval. None of the contrasts showed nominal statistical significance.

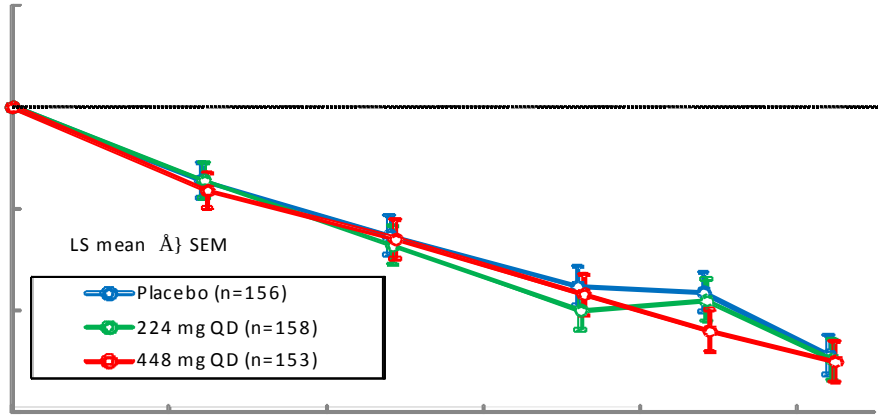
(a) Change from baseline ADAS-cog



Dose Group	Statistics	Baseline Score	Adjusted Change from Baseline*				
			Week 12	Week 24	Week 36	Week 44	Week 52
Placebo	No. of Raw Data	155	154	146	141	140	137
	Mean	27.94	0.92	2.55	5.47	5.78	7.91
224 mg QD	No. of Raw Data	158	156	142	130	122	115
	Mean	27.68	1.74	2.88	5.66	5.87	7.45
	Difference	-	0.83	0.33	0.19	0.09	-0.47
	P value	-	0.1614	0.6518	0.8143	0.9197	0.6302
448 mg QD	No. of Raw Data	153	151	130	121	117	117
	Mean	27.78	1.82	3.06	5.12	6.29	7.08
	Difference	-	0.90	0.51	-0.35	0.51	-0.84
	P value	-	0.1311	0.4989	0.6787	0.5600	0.3919

* Estimated by MMRM with covariates.

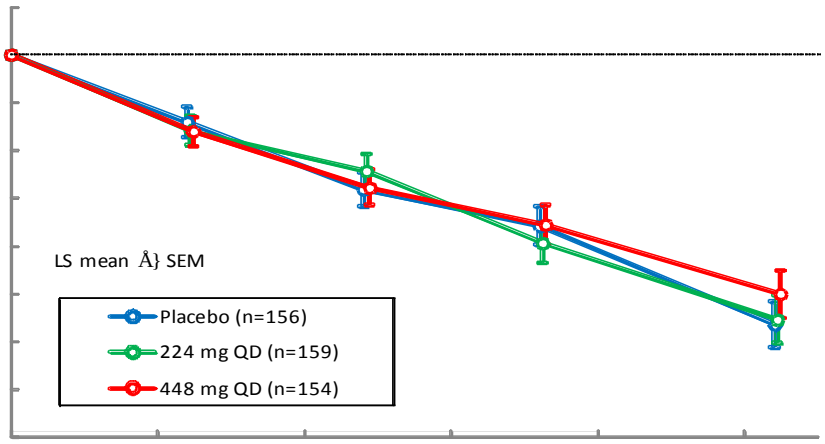
(b) Change from baseline ADCS-CGIC



Dose Group	Statistics	Adjusted Score*				
		Week 12	Week 24	Week 36	Week 44	Week 52
Placebo	No. of Raw Data	155	146	141	142	138
	Mean	4.36	4.63	4.88	4.91	5.22
224 mg QD	No. of Raw Data	156	141	130	121	116
	Mean	4.36	4.68	5.00	4.95	5.24
	Difference	0.01	0.05	0.12	0.03	0.03
	P value	0.9434	0.6359	0.2784	0.7697	0.8135
448 mg QD	No. of Raw Data	149	132	120	117	118
	Mean	4.41	4.65	4.92	5.10	5.25
	Difference	0.06	0.02	0.04	0.18	0.04
	P value	0.5466	0.8476	0.7290	0.1153	0.7588

* Estimated by MMRM with covariates.

(c) Change from baseline ADCS-ADLs



Dose Group	Statistics	Baseline Score	Adjusted Change from Baseline*			
			Week 12	Week 24	Week 36	Week 52
Placebo	No. of Raw Data	156	155	147	144	140
	Mean	58.7	-2.81	-5.63	-7.14	-11.29
224 mg QD	No. of Raw Data	159	158	144	132	118
	Mean	58.7	-3.17	-4.86	-7.87	-11.07
	Difference	-	-0.35	0.76	-0.73	0.23
	P value	-	0.6235	0.3921	0.4757	0.8604
448 mg QD	No. of Raw Data	154	152	133	123	118
	Mean	59.5	-3.21	-5.55	-7.11	-10.01
	Difference	-	-0.39	0.08	0.03	1.29
	P value	-	0.5877	0.9308	0.9772	0.3212

* Estimated by MMRM with covariates.

eAppendix 1. Protocol-Specified Responder Analyses

Methods

A clinical outcome responder analysis was specified in the statistical analysis plan to examine the relationship between clinical outcomes and treatment for the mITT and PP populations. Improvement was defined as a better score by the end of the study than at baseline. Stabilization was defined as an outcome that did not worsen or improved compared to baseline. For these analyses, the high and low doses of edonerpic were grouped together as the active treatment group. Active treatment and placebo were compared for improvement or stabilization on each of the primary and secondary outcomes at endpoint. One analysis included completers and non-completers with non-completers counted as non-responders regardless of their last efficacy result. A second analysis compared only participants with non-missing efficacy outcomes at 52 weeks. The relationships between individual clinical responses and treatment were analyzed. In addition, multiple clinical responses were correlated with treatment using the two variations described above [Not reported].

Those who experienced the following combined clinical responses were summarized in terms of counts and percent:

- Improvement or stabilization on none of the 6 primary/secondary endpoints;
- Improvement or stabilization on 1 of the 6 primary/secondary endpoints;
- Improvement or stabilization on at least 2 of the 6 primary/secondary endpoints;
- Improvement or stabilization on at least 3 of the 6 primary/secondary endpoints;
- Improvement or stabilization on at least 4 of the 6 primary/secondary endpoints;
- Improvement or stabilization on at least 5 of the 6 primary/secondary endpoints;
- Improvement or stabilization on all primary/secondary endpoints.

Treatment groups were compared in terms of percent of patients who experienced the combined clinical response or response on the individual primary and secondary efficacy outcomes. Fisher’s exact tests were performed to test if there was a significant difference in improving on individual and multiple clinical outcomes based on treatment group.

Results

Results are displayed in tables S3 and S4. None of the response definitions favored medication, either when analyzed individually or with the multiple clinical response definitions. The only nominally statistically significant responses were in favor of placebo over edonerpic.

Conclusion

Several responder analyses did not provide evidence for the clinical efficacy of edonerpic.

eTable 2. Individual Clinical Response Counting Non-completers as Non-responders, mITT Population

Efficacy Outcome Statistic	Placebo (N=156)	Active (N=313)
ADAS-Cog		
Experienced No Change or Improved (<=0)	25 (16.0%)	43 (13.7%)
Worsened (>0)	131 (84.0%)	270 (86.3%)
P-value vs. Placebo		0.5779
ADCS-CGIC		
Experienced No Change or Improved (<=4)	32 (20.5%)	47 (15.0%)
Worsened (>4)	124 (79.5%)	266 (85.0%)
P-value vs. Placebo		0.1501
ADCS-ADL		
Experienced No Change or Improved (>=0)	17 (10.9%)	37 (11.8%)
Worsened (<0)	139 (89.1%)	276 (88.2%)
P-value vs. Placebo		0.8782
MMSE		
Experienced No Change or Improved (>=0)	54 (34.6%)	70 (22.4%)
Worsened (<0)	102 (65.4%)	243 (77.6%)
P-value vs. Placebo		0.0055
FAQ		
Experienced No Change or Improved (<=0)	31 (19.9%)	57 (18.2%)
Worsened (>0)	125 (80.1%)	256 (81.8%)
P-value vs. Placebo		0.7069
NPI		
Experienced No Change or Improved (<=0)	79 (50.6%)	120 (38.3%)
Worsened (>0)	77 (49.4%)	193 (61.7%)
P-value vs. Placebo		0.0131

eTable 3. Multiple Clinical Response Definitions Counting Non-completers as Non-responders, mITT Population

Statistic	Placebo (N=156)	Active (N=313)
1-Improvement or Stabilization on 6 Primary/Secondary Outcomes	1 (0.6%)	0 (0.0%)
2-Improvement or Stabilization on 0, 1, 2, 3, 4 or 5 Primary/Secondary Outcomes	155 (99.4%)	313 (100.0%)
P-value vs. Placebo		0.3326
1-Improvement or Stabilization on 5 or 6 Primary/Secondary Outcomes	5 (3.2%)	11 (3.5%)
2-Improvement or Stabilization on 0, 1, 2, 3 or 4 Primary/Secondary Outcomes	151 (96.8%)	302 (96.5%)
P-value vs. Placebo		1.0000
1-Improvement or Stabilization on 4, 5 or 6 Primary/Secondary Outcomes	19 (12.2%)	28 (8.9%)
2-Improvement or Stabilization on 0, 1, 2 or 3 Primary/Secondary Outcomes	137 (87.8%)	285 (91.1%)
P-value vs. Placebo		0.3273
1-Improvement or Stabilization on 3, 4, 5 or 6 Primary/Secondary Outcomes	37 (23.7%)	52 (16.6%)
2-Improvement or Stabilization on 0, 1 or 2 Primary/Secondary Outcomes	119 (76.3%)	261 (83.4%)
P-value vs. Placebo		0.0797
1-Improvement or Stabilization on 2, 3, 4, 5 or 6 Primary/Secondary Outcomes	68 (43.6%)	103 (32.9%)
2-Improvement or Stabilization on 0 or 1 Primary/Secondary Outcomes	88 (56.4%)	210 (67.1%)
P-value vs. Placebo		0.0254
1-Improvement or Stabilization on 1, 2, 3, 4, 5 or 6 Primary/Secondary Outcomes	108 (69.2%)	180 (57.5%)
2-Improvement or Stabilization on 0 Primary/Secondary Outcomes	48 (30.8%)	133 (42.5%)
P-value vs. Placebo		0.0157

eTable 4. Cerebrospinal Fluid Amyloid and Tau Analyses

CSF Biomarkers at Week 52

	Placebo		Edonerpic maleate, 224 mg				Edonerpic maleate, 448 mg			
	Baseline (SD)	Change from baseline, mean (SE)	Baseline (SD)	Change from baseline, mean (SE)	Difference vs. placebo, mean (95% CI)	P Value	Baseline (SD)	Change from baseline, mean (SE)	Difference vs. placebo, mean (95% CI)	P Value
CSF biomarker outcomes[(b)]										
N	N = 18		N = 17				N = 24			
Aβ 40, pg/mL	6766 (2001)	-916.0 (546.1)	7275 (2477)	-840.3 (559.5)	75.7 (-1507.6, 1659.0)	.92	8272 (2513)	290.8 (467.0)	1206.9 (-236.4, 2650.2)	.10
Aβ 42, pg/mL	407.0 (102.1)	-21.35 (29.6)	417.8 (144.9)	-9.70 (30.4)	11.65 (-73.4, 96.7)	.78	439.1 (121.3)	11.55 (25.6)	32.90 (-45.6, 111.41)	.40
PhosphoTau181, pg/mL	102.8 (38.4)	0.29 (2.64)	102.6 (33.4)	-3.94 (2.72)	-4.23 (-11.83, 3.37)	.27	95.0 (29.8)	-7.30 (2.28)	-7.59 (-14.57, -0.60)	.03
Tau, pg/mL	1147.7 (483.8)	28.2 (37.7)	1162.3 (421.6)	-7.88 (38.6)	-36.10 (-144.3, 72.1)	.51	1085.0 (327.3)	-101.4 (32.6)	-129.57 (-229.5, -29.6)	.01

CSF Biomarker Outcomes Estimated by ANCOVA with Covariates

eTable 5. Pharmacokinetic Parameters of Edonerpic

Parameters	Statistics	224 mg QD	448 mg QD
$C_{ss,max}$	n	144	138
(ng/mL)	Mean	271.30	618.68
	SD	99.67	222.28
	CV (%)	36.7	35.9
	Geo. Mean	256.22	583.17
	Median	253.57	563.96
	Min	107.55	254.71
	Max	878.30	1636.00
$C_{ss,min}$	n	144	138
(ng/mL)	Mean	65.57	125.64
	SD	57.56	118.17
	CV (%)	87.8	94.1
	Geo. Mean	49.95	95.05
	Median	44.05	82.45
	Min	15.32	10.11
	Max	315.70	783.80
$AUC_{ss,tau}$	n	144	138
(ng*hr/mL)	Mean	3409.90	7345.74
	SD	1521.07	3390.85
	CV (%)	44.6	46.2
	Geo. Mean	3140.93	6740.31
	Median	3040.32	6371.42
	Min	1475.46	2640.38
	Max	9321.73	24005.99

eTable 6. Penetration of Edonerpic and the M5 Metabolite Into CSF

	Statistics	CSF Concentration (ng/mL)	Plasma Concentration (ng/mL)	Ratio
edonerpic	N	31	30	30
	Mean	41.07	437.36	0.107
	SD	31.22	279.23	0.055
	Median	34.00	373.50	0.107
	Min	3.22	83.7	0.008
	Max	119	1090	0.201
M5	n	31	30	30
	Mean	9.57	390.48	0.034
	SD	10.71	305.93	0.034
	Median	5.28	306.00	0.024
	Min	0	40.9	0
	Max	50.1	1310	0.163

eTable 7. Exploratory MRI Outcomes Performed Using NeuroQuant Volumes

	Placebo (N=120)	Edonerpic maleate, 224 mg (N=99)	Edonerpic maleate, 448 mg (N=99)
Brain volume[2]			
Baseline, mL, mean (SD)	841.3 (91.47)	841.8 (101.30)	859.1 (99.02)
N	118	99	98
Adjusted change from baseline, mean (SE)	-23.32 (2.670)	-19.92 (2.698)	-20.09 (2.842)
Treatment vs. Placebo			
Difference vs. placebo, mean (95% CI)		3.40 (-2.35, 9.14)	3.23 (-2.52, 8.99)
P-value		0.25	0.27
Effect size, Cohen's d		0.16	0.15
Lateral ventricle volume, right and left[2]			
Baseline, mL, mean (SD)	56.8 (22.22)	56.0 (22.68)	57.6 (26.22)
N	118	99	98
Adjusted change from baseline, mean (SE)	6.54 (0.622)	6.09 (0.632)	7.25 (0.668)
Treatment vs. Placebo			
Difference vs. placebo, mean (95% CI)		-0.45 (-1.63, 0.74)	0.71 (-0.47, 1.89)
P-value		0.46	0.24
Effect size, Cohen's d		-0.11	0.17

Hippocampal volume, right and left[2]			
Baseline, mL mean (SD)	5.3 (1.03)	5.2 (0.99)	5.1 (1.13)
N	118	99	98
Adjusted change from baseline, mean (SE)	-0.38 (0.039)	-0.28 (0.039)	-0.31 (0.042)
Treatment vs. Placebo			
Difference vs. placebo, mean (95% CI)		0.10 (0.02, 0.17)	0.06 (-0.02, 0.14)
P-value		0.016	0.12
Effect size, Cohen's d		0.34	0.22

eAppendix 2. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial*

Section/Topic	Item No	Checklist item	Reported, page No.
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	9, 18
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5-6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5-6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5-6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how	5-6
	11b	If relevant, description of the similarity of interventions	6

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9-10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10 Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9-11 Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10 Figure 2 Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N.A.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Suppl. Table S3 to S7
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12, Table 3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-15
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Supplement
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

*see www.consort-statement.org.