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. SAEs, AEs leading to discontinuation, and AEs before and after dose reduction

	Randomized After Protocol Amendment for Dose Reduction, %		**Randomized Prior to Protocol Amendment for Dose Reduction, %**	
	Placebo (n=87)	**Avagacestat (n=86)**	**Placebo (n=44)**	**Avagacestat (n=46)**
Any SAE	27.6	34.9	15.9	41.3
Cardiac disorders	1.1	2.3	0	2.2
GI disorders	0	3.5	2.3	6.5
Neoplasms	12.6	14.0	2.3	23.9
Injury, poisoning, and procedural complications	3.4	8.1	2.3	0
Any AE leading to discontinuation	9.2	43.0	11.4	19.6
Any GI AE	1.1	18.6	4.5	6.5
Any skin AE	1.1	5.8	0	4.3
Any nervous system disorder	2.3	8.1	0	2.2
Any AE	89.7	97.7	72.7	91.3
Any GI AE	46.0	68.6	18.2	60.9
Diarrhea	24.1	36.1	6.8	21.7
Nausea	3.4	30.3	2.3	19.6
Vomiting	2.3	11.7	0	8.7
Any skin AE	39.1	60.5	36.4	43.5

Rash	5.7	26.7	6.8	8.7
Any neoplasms	19.5	16.3	6.8	23.9
BCC	5.7	5.8	0	6.5
SCC skin	1.1	4.7	0	8.7
SCC	0	4.7	0	8.6
Malignant melanoma	1.1	0	0	0
Other AEs				
Fatigue	8.0	22.1	4.5	10.9
Weight decreased	1.1	16.3	2.3	0
Appetite decreased	2.2	16.3	2.3	0
Dizziness	10.3	16.3	9.1	13.0
Depression	11.4	2.3	2.3	10.8
Anxiety	12.6	1.2	2.3	6.5
Cerebral Microbleed	1.1	3.5	2.3	2.2
Vasogenic edema	1.1	2.3	0	2.2

AE, adverse event; BCC, basal cell carcinoma; GI, gastrointestinal; SAE, serious AE; SCC, squamous cell carcinoma.

eTable 2. Percentage of Patients with Potentially Clinically Significant Glycosuria and Assessments of Renal Function

		Number of Patients/ Number Assessed (%)	
Variable	**Criteria**	**Placebo (n=131)**	**Avagacestat (n=132)**
Urinary glucose	Treatment-emergent glycosuria (defined as any glucose in the urine)	11/129 (8.5)	76/131 (58)
Glomerular filtration rate[a]	<30 mL/min/1.73m^2	1/130 (0.8)	2/131 (1.5)
	≤60 mL/min/1.73m^2	60/130 (46.2)	62/131 (47.3)
	Decrease from baseline ≥30 mL/min/1.73m^2	2/130 (1.5)	6/131 (4.6)
Urinary albumin to creatinine ratio	≥30 mg/g	39/127 (30.7)	43/128 (33.6)

[a]Glomerular filtration rate was assessed using the Cockroft-Gault method.

eTable 3. Laboratory Findings, Safety Sample

Variable, %	**Placebo (n=131)**	**Avagacestat (n=132)**
Glucose, fasting serum (≥126 mg/dL)	15.5	18.6
Cystatin C (>ULN)	34.4	49.2
Urinary alpha-1 microglobulin (>ULN)	45.1	42.2
Urinary n-acetyl-beta-D-glucosaminidase (>ULN)	9.9	12.2
Blood urea nitrogen/urea (≥30 mg/dL)	14.7	19.4
Creatinine (≥2 mg/dL)	0	0.8
Urine protein (category of 100 or higher)	3.9	4.6
Serum uric acid males/females (<LLN)	2.6/0	27.8/11.9
Inorganic phosphorous (<LLN)	8.8	43.1
TmP/GFR (≤2.0 mg/dL)	9.6	37.5
Low potassium (≤2.5 mEq/L)	0	0
Bicarbonate (<LLN)	1.6	9.5
Low phosphorus (<1.6 mg/dL)	0.8	3.4
Low calcium (≤LLN)	3.8	13.7
High PTH (>ULN)	24.5	33.7
CRP (≥25 mg/L)	5.4	13.0
Creatinine kinase (≥3x ULN)	3.8	9.2
TSH (≤0.3 uU/mL)	4.7	5.5
TSH (>4.3 uU/mL)	16.3	9.4
(T3 (>188 ng/dL)	0.8	1.6
Eosinophil (≥ 10%)	0.8	4.6
Low leukocytes (<2.8 x 10^3 c/uL)	4.6	3.1

CRP, C-reactive protein; GFR, glomerular filtration rate; LLN, lower limit of normal; MDRD, Modification of Diet in Renal Disease; PTH, parathyroid hormone; TmP, maximum rate of tubular phosphate reabsorption; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

eTable 4. Mean Changes From Baseline to Weeks 24 and 104 in Aβ40 and Aβ42

Variable	**Placebo (n=131)**		**Avagacestat[a] (n=132)**	
Week	**24**	**104**	**24**	**104**
Aβ-40				
No. of patients	102	42	91	27
Mean change (SE)[a]	–0.02 (0.023)	–0.03 (0.043)	–0.15 (0.032)	–0.11 (0.102)
LS mean (95% CI)	0.98 (0.94, 1.02)	0.97 (0.89, 1.05)	0.86 (0.80, 0.91)	0.90 (0.74, 1.11)
Difference vs placebo			0.87 (0.81, 0.93)	0.88 (0.74, 1.05)
P value			<0.001	0.162
Aβ-42				
No. of patients	102	42	91	27
Mean change (SE)[a]	–0.02 (0.028)	–0.06 (0.053)	–0.09 (0.036)	–0.05 (0.126)
LS mean (95% CI)	0.98 (0.93, 1.03)	0.94 (0.84, 1.05)	0.92 (0.86, 0.99)	0.95 (0.73, 1.23)
Difference vs placebo			0.93 (0.86, 1.01)	0.92 (0.74, 1.14)
P value			0.078	0.432

[a]Mean change is based on the log scale. Units are Log (pg/mL). For all statistical analyses, no adjustments were made for multiple comparisons. Nominal *P* values are provided for descriptive purposes and should be interpreted with caution.

Aβ, amyloid-beta; CI, confidence interval; LS, least squares; SE, standard error.

eTable 5. Mean Volume Change from Baseline to Weeks 24, 56, and 104 in Whole-Brain, Ventricles, and Hippocampus normalized by number of days since Baseline.

Variable	**Placebo N = 131**				**Avagacestat N = 132**				**Observational N = 20**	
Week	**Baseline**	**24**	**56**	**104**	**Baseline**	**24**	**56**	**104**	**Baseline**	**104**
Whole-brain volume change, mL (MRI)										
No. of patients	106	99	81	53	94	89	61	32	20	20
Mean change (SE)[a]	1043.82 (102.95)	-3.20 (0.41)	-8.93 (0.91)	-19.72 (1.48)	1034.75 (121.29)	**-5.25** (0.57)	**-13.00** (0.91)	-23.79 (1.78)	1101.84 (111.59)	-11.33 (2.77)
P value						**0.004**	**0.002**	0.083		
Ventricular volume change, mL (MRI)										
No. of patients	106	102	83	58	94	93	64	34	20	20
Mean change (SE)[a]	37.40 (29.78)	0.87 (0.08)	2.63 (0.21)	5.82 (0.47)	35.52 (23.29)	**1.21** (0.15)	**3.39** (0.30)	5.98 (0.60)	33.57 (19.52)	3.18 (1.17)
P value						**0.041**	**0.042**	0.837		
Hippocampal volume change, mm^3 (MRI)										
No. of patients	106	104	86	59	94	93	65	35	20	20
Mean change (SE)[a]	6106.64 (1164.67)	-60 (8)	-183 (17)	-435 (32)	5955.64 (966.35)	**-87** (11)	**-259** (18)	-516 (42)	7365.84 (1136.27)	-187 (55)
P value						**0.050**	**0.002**	0.129		

[a]Mean (SD) volume is presented at baseline.

MRI, magnetic resonance imaging; SE, standard error.

Nominal *P* values are presented for comparisons of the avagacestat and placebo groups. Significant differences between avagacestat and placebo are highlighted in bold. Lack of statistical signficance at Week 104 may be related to low number of observations.

eTable 6. Baseline Amyloid-PET and CSF Biomarker Correlation Coefficients (Spearman's)

	PET SUVR Measurements				
CSF biomarkers	**Posterior Cingulate**	**Parietal**	**Lateral Temporal**	**Frontal**	**Mean**
Aβ42	–0.29*	–0.29*	–0.35*	–0.34*	–0.33*
T-tau	0.40†	0.49‡	0.51‡	0.50‡	0.48‡
T-tau:Aβ42	0.41†	0.47‡	0.53‡	0.52‡	0.49‡

*$P \leq 0.05$; †$P \leq 0.001$; ‡$P \leq 0.0001$.

Aβ, amyloid-beta; CSF, cerebrospinal fluid; PET, positron emission tomography; SUVR, standard uptake value ratio; T-tau, total tau.

eTable 7. Baseline Clinical Rating Scales and Amyloid-PET or CSF Biomarker Correlation Coefficients (Spearman's)

	PET SUVR Measurements					CSF Biomarkers		
	Posterior Cingulate	**Parietal**	**Lateral Temporal**	**Frontal**	**Mean**	**Aβ42**	**T-tau**	**T-tau:Aβ42**
ADAS-cog	0.24*	0.29*	0.32*	0.30*	0.30*	–0.26*	0.38†	0.39†
FCSRT	–0.46‡	–0.47‡	–0.48‡	–0.48‡	–0.49‡	0.43†	–0.35*	–0.44†
MMSE	-0.14NS	-0.18 NS	-0.24 NS	-0.22 NS	-0.20 NS	0.02 NS	-0.09 NS	-0.10 NS
CDR-SB	0.06 NS	0.13 NS	0.12 NS	0.13 NS	0.12 NS	-0.23 NS	0.03 NS	0.09 NS
ADCS -ADL-MCI	-0.14 NS	-0.21 NS	-0.19 NS	-0.21 NS	-0.20 NS	0.09 NS	-0.12 NS	-0.12 NS

*$P \leq 0.05$; †$P \leq 0.001$; ‡$P \leq 0.0001$; NSP=NS.

ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; CSF, cerebrospinal fluid; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; NS, not significant; PET, positron emission tomography; SUVR, standard uptake value ratio; T-tau, total tau.

eFigure. Concordance between Visual Amyloid-PET and CSF Biomarker Inclusion Criteria

		CSF Inclusion Criteria (Aβ42 <200 or T-tau:A42 ≥0.39)	
		+	–
Qualitative Amyloid-PET Read	+	68% (n=50) Mean CSF Aβ42 = 223 T-tau = 141	3% (n=2)
	–	10% (n=7)	19% (n=14) Mean CSF Aβ42 = 426 T-tau = 48

Of the 73 patients, randomized in this PET substudy, 9 discordant cases were observed at baseline:

7 cases (10%) were amyloid-PET negative but CSF-positive and 2 cases (3%) were amyloid-PET positive but CSF-negative.

CSF, cerebrospinal fluid; PET, positron emission tomography; T-tau, total tau.

