Supplementary Online Content

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

eAppendix. Supplemental Information

Selection and rationale for supplemental autopsy cases: Anticipating the possibility that enrollment of cognitively normal volunteers or non-AD dementia end-of-life patients (that is, truth-standard-negative subjects) might be challenging, a supplemental dataset of additional autopsy cases was developed as a protocol addendum at the suggestion of the FDA and in collaboration with external investigators who had independently collected flortaucipir PET scans and autopsy brain tissue from independent study protocols and funding sources. These historical autopsy samples and flortaucipir images were provided voluntarily, with the study sponsor (Avid Radiopharmaceuticals) providing requested preparation and shipping costs. The sponsor obtained flortaucipir images and autopsy tissue from all available cases (both truth-standard-positive and truth-standard-negative cases) that came to autopsy at cooperating institutions known to have collected at least 1 case that was reasonably likely to be truth-standard negative at autopsy and the autopsy tissue (n=16) was assessed for the truth standard during the third (last) autopsy consensus panel meeting. The protocol amendment specified that these cases would be included in the primary analysis cohort only if a minimum number of both autopsy positive and autopsy negative cases was not obtained in the main A16 study cohort. Ultimately, the minimum number of 14 truth-standard-negative and truth-standard-positive cases was met through A16 study enrollment without need for the supplemental cases in the primary efficacy analysis. Therefore, the primary efficacy analysis for Study A16 was based on the protocol-generated cases only, and, as specified by the protocol, an exploratory analysis was performed that included the primary efficacy cohort, the evaluable cases from the frontrunner autopsies, and the supplemental autopsy cases (referred to as the full autopsy dataset).

Selection of PET Scan readers for the A16 study: PET scan readers for the A16 study, including the supplemental autopsy cases addendum, and the FR01 confirmatory read study, were required to be board certified, practicing nuclear medicine physicians or radiologists. Readers had prior experience or training in reading amyloid PET scans, based on prior involvement in the florbetapir phase II or phase III studies with Avid Radiopharmaceuticals. It was also required that readers had no prior training on how to read flortaucipir PET scans, were not employed by the study sponsor (Avid Radiopharmaceuticals) or by any clinical research organization (CRO) contracted with Avid for study A16. Readers were not to be affiliated with any participating imaging center or clinical research site for study A16, or advisors/participants/reviewers for the data monitoring board for the study. Beyond these requirements, selection of readers was based on availability, interest in study participation, and agreement to the confidentiality and work requirement terms of a paid consultation agreement with Avid Radiopharmaceuticals. The list of readers meeting these criteria was provided to the imaging CRO, who then independently contacted the readers to schedule A16 study reads to meet sponsor-requested study timelines. Avid had no communication with the prospective readers throughout this process. The supplemental autopsy scans were read by the same five readers of the A16 primary efficacy cohort scans. Five novel readers were selected for the FR01 confirmatory read study.

Preparation of Images for Visual Interpretation:

1. Image Display and orientation

- Display images in all 3 standard planes
- Reorient to remove head tilt and rotation

2. Select and adjust the color scale

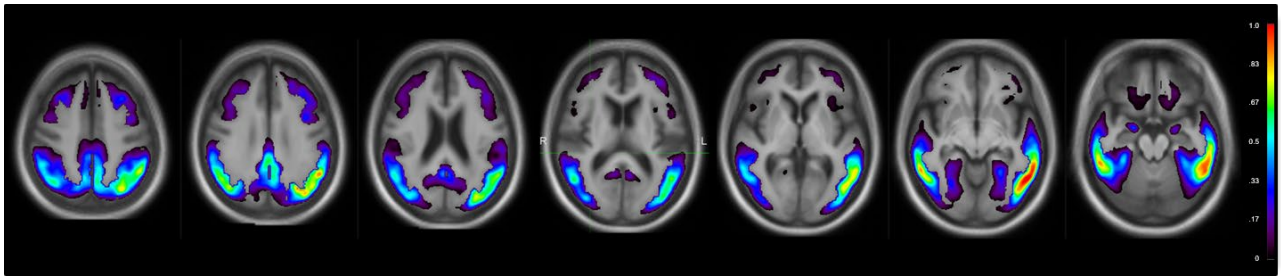
- Draw a region of interest around the whole cerebellum at the max cross sectional area of the cerebellum to obtain mean cerebellar counts (MCC)
- Choose a color scale that rapidly transitions between 2 distinct colors at 25-50% of max intensity
- Set the upper contrast (UC) of the color scale by multiplying the mean cerebellar counts: UC= (MCC x 1.65) x (100% / %level of color transition)

3. Prepare for image interpretation

- Divide the temporal lobes into 4 quadrants by placing the horizontal cross hairs posterior to the brain stem nuclei and vertical crosshairs through the widest portion of the temporal lobe

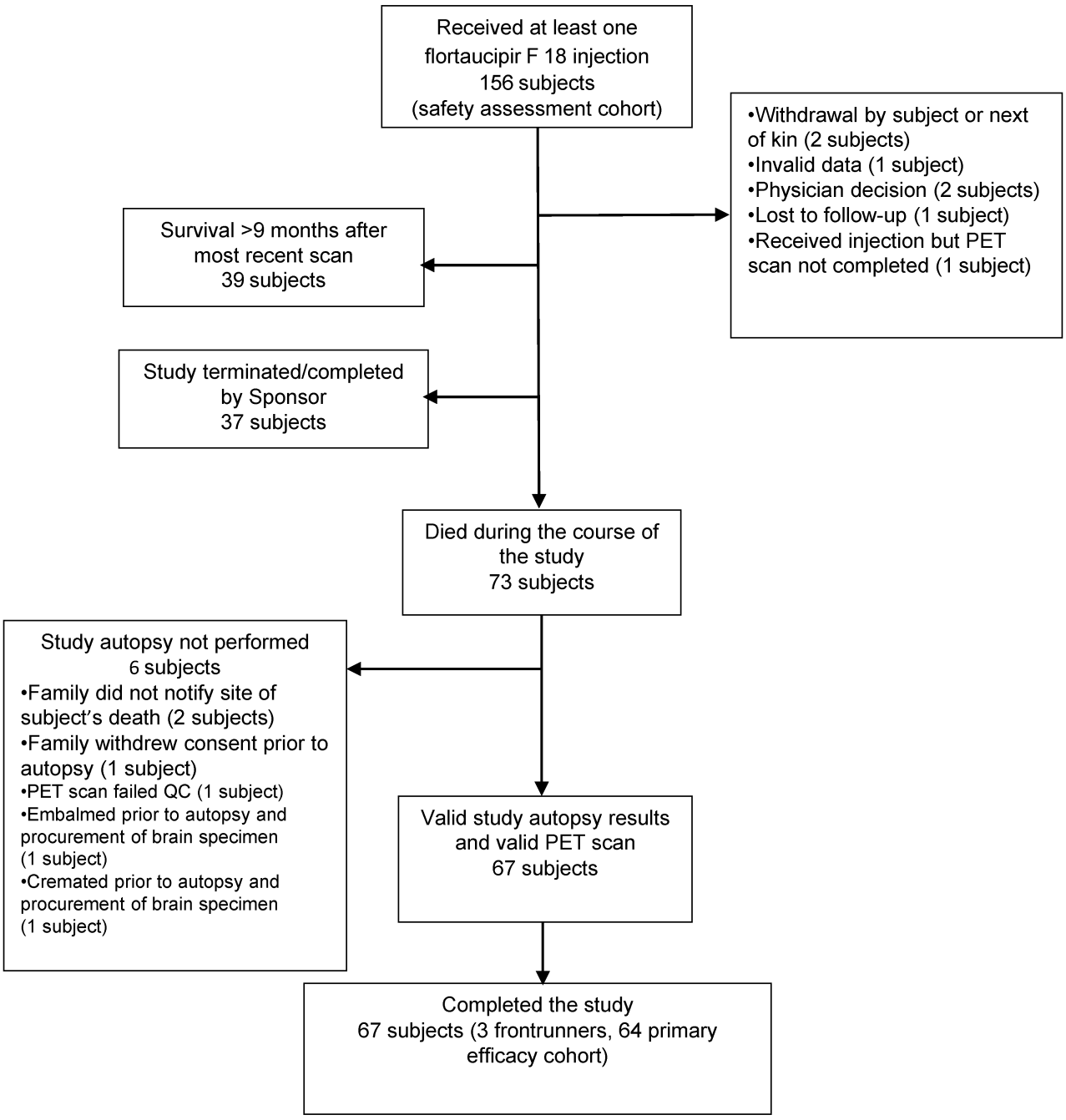
eFigure 1. Quantitative Analysis Cortical Regional of Interest

MUBADA (Multi-block Barycentric Discriminant Analysis) weighted template:

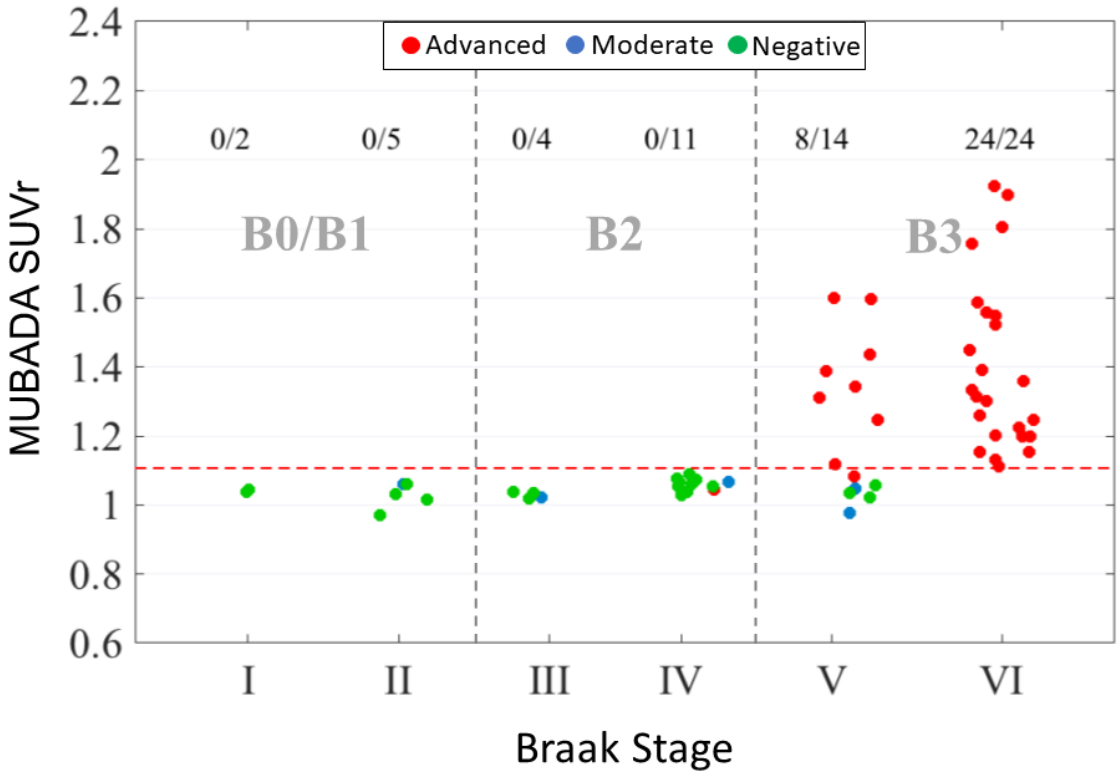


Multi-block barycentric discriminant analysis (MUBADA) is an extension of mean-centered partial least squares correlation often used in neuroimaging research.[1,2] It was developed as a statistical method to predict group membership from large data sets that are structured into coherent blocks of variables, when the data have far more variables than participants (as is typically the case with neuroimaging data). The MUBADA volume of interest (VOI) utilized here was derived by using this voxel-wise discriminant analysis to maximally separate diagnostic groups of amyloid PET (florbetapir) negative older normal controls from amyloid PET positive symptomatic (MCI or dementia) Alzheimer's disease patients in a dataset of N=202 flortaucipir images. This model explained 95% of the variance.[2] The analysis provides weights for each voxel according to the degree they contributed to the VOI (weights are displayed as a color scale in figure). Thus, the MUBADA VOI represents the spatial distribution of the voxels that best discriminated between these diagnostic groups, retaining the individual voxel variance weights as they contributed to the model. Each voxel in the VOI is multiplied by its relative variance weight between 0 to 1.0. The resulting spatial map (figure) represents the weighted image template resulting from this analysis that was applied to extract the standardized uptake values for quantitative analysis.

eFigure 2. Flow Diagram for Subject Enrollment and Disposition



eFigure 3. Quantitative Analysis—Scatter Plot of SUVR vs NFT Braak stage



A16 (Primary Cohort plus test cases) Individual MUBADA ROI quantitative SUVR's for each individual within each Braak stage. Receiver-Operating-Curve-derived SUVR threshold for positivity of >1.113 is used here. Case count ratios represent numbers of positive MUBADA cases over total cases Abbreviations: Advanced, consistent with an advanced flortaucipir AD tau pattern; Moderate, consistent with a moderate flortaucipir AD tau pattern; and Negative, not consistent with a flortaucipir AD tau pattern

eTable 1. Cases with Non-AD Clinical Diagnoses

Listing of all non-AD clinical diagnosis cases with corresponding binary visual read category (Negative flortaucipir AD Pattern vs Moderate/Advanced (Mod/Adv) flortaucipir AD pattern), Braak stage from autopsy (highest hemisphere), and NIA-AA criteria Alzheimer's Disease Neuropathologic Change category

Clinical diagnosis	Visual PET majority reads	Braak stage	ADNC stage
Corticobasilar Syndrome[1,2]	Moderate/Advanced	V	INTERMEDIATE ADNC
Dementia with Gate disorder[1]	Negative	I	NOT AD
Frontotemporal dementia	Negative	V	LOW ADNC
Frontotemporal dementia[1]	Negative	II	LOW ADNC
Frontotemporal dementia[1]	Negative	II	LOW ADNC
Frontotemporal dementia	Moderate/Advanced	VI	HIGH ADNC
Frontotemporal dementia[1]	Moderate/Advanced	V	INTERMEDIATE ADNC
Lewy body dementia[1]	Negative	IV	INTERMEDIATE ADNC
Lewy body dementia	Negative	II	LOW ADNC
Lewy body dementia	Negative	IV	INTERMEDIATE ADNC
Lewy body dementia	Negative	IV	INTERMEDIATE ADNC
Lewy body dementia	Moderate/Advanced	V	HIGH ADNC
Lewy body dementia	Moderate/Advanced	V	HIGH ADNC
Mixed dementia	Negative	V	HIGH ADNC
Mixed dementia	Negative	IV	INTERMEDIATE ADNC
Mixed dementia	Moderate/Advanced	II	LOW ADNC
Other – delirium	Negative	IV	LOW ADNC
Other - organic mental syndrome	Moderate/Advanced	V	HIGH ADNC
Other - Parkinson's disease	Negative	IV	INTERMEDIATE ADNC
Other – Parkinson's disease dementia	Negative	IV	INTERMEDIATE ADNC
Progressive supranuclear palsy[1,2]	Negative	V	NOT AD
Progressive supranuclear palsy[1]	Negative	IV	LOW ADNC
Progressive supranuclear palsy[1]	Negative	V	LOW ADNC
Vascular dementia[1,2]	Negative	IV	LOW ADNC
Vascular dementia	Moderate/Advanced	VI	HIGH ADNC
Vascular dementia	Moderate/Advanced	VI	HIGH ADNC

Abbreviations: Negative = Negative flortaucipir Alzheimer's disease tau pattern; Moderate = moderate flortaucipir AD tau pattern; Advanced = advanced flortaucipir AD tau pattern; ADNC = Alzheimer's Disease Neuropathologic Change; AD = Alzheimer's Disease

[1] From Supplemental Autopsy Cases

[2] Clinical diagnosis of mild cognitive impairment at enrollment, and dementia at time of death

eTable 2. Incidence of Treatment-Emergent Adverse Events by Preferred Term (Safety Assessment of Original Eligible A16 Study Cohort)

Preferred Term	Most Recent Neurological Disease Diagnosis[a]			Total (N=156) n (%)
	Normal (N=50) n (%)	Mild Cognitive Impairment (N=3) n (%)	Dementia (N=103) n (%)	
Number of patients with at least 1 TEAE	5 (10.0)	0	9 (8.7)	14 (9.0)
Agitation	1 (2.0)	0	2 (1.9)	3 (1.9)
Headache	0	0	2 (1.9)	2 (1.3)
Acute kidney injury	0	0	1 (1.0)	1 (0.6)
Cardiac failure congestive	1 (2.0)	0	0	1 (0.6)
Diarrhea	1 (2.0)	0	0	1 (0.6)
Dizziness postural	0	0	1 (1.0)	1 (0.6)
Fall	0	0	1 (1.0)	1 (0.6)
Hypomagnesaemia	1 (2.0)	0	0	1 (0.6)
Hypoxic-ischaemic encephalopathy	1 (2.0)	0	0	1 (0.6)
Injection site bruising	1 (2.0)	0	0	1 (0.6)
Mental disorder	1 (2.0)	0	0	1 (0.6)
Myocardial infarction	1 (2.0)	0	0	1 (0.6)
Myopathy	1 (2.0)	0	0	1 (0.6)
Nausea	1 (2.0)	0	0	1 (0.6)
Neoplasm malignant	1 (2.0)	0	0	1 (0.6)
Procedural vomiting	0	0	1 (1.0)	1 (0.6)
Restlessness	1 (2.0)	0	0	1 (0.6)
Tremor	0	0	1 (1.0)	1 (0.6)
Vertigo	1 (2.0)	0	0	1 (0.6)

[a] Most recent neurological diagnosis collected prior to subject's most recent flortaucipir F 18 PET scan.

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1.

Note: A TEAE is defined as an AE that started or worsened in intensity or frequency on or after each injection of flortaucipir F 18 and up to 48 hours after each flortaucipir F 18 injection.

Note: Subjects are counted only once within each preferred term.

Note: Preferred terms are presented in descending order of total frequency.

Note: Percentages are based on the number of subjects in the Safety Analysis Set reported in each column.

eTable 3. Diagnostic Performance of 5 Independent Reader Interpretations of the Flortaucipir F18 images in the **FR01 Validation study** Primary Cohort and the Full Autopsy Data Set Cohort[a]

Reader		TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	NPV (95% CI)	PPV (95% CI)
Flortaucipir PET Read compared with B3 NFT score										
1	PC (n=64)	37	2	7	18	94.9 (83.1, 98.6)	72.0 (52.4, 85.7)	85.9 (75.4, 92.4)	90.0 (69.9, 97.2)	84.1 (70.6, 92.1)
	FAS (n=82)	43	4	8	27	91.5 (80.1, 96.6)	77.1 (61.0, 87.9)	85.4 (76.1, 91.4)	87.1 (71.2, 94.9)	84.3 (72.0, 91.8)
2	PC (n=64)	37	2	3	22	94.9 (83.1, 98.6)	88.0 (70.0, 95.8)	92.2 (83.0, 96.6)	91.7 (74.2, 97.7)	92.5 (80.1, 97.4)
	FAS (n=82)	42	5	3	32	89.4 (77.4, 95.4)	91.4 (77.6, 97.0)	90.2 (81.9, 95.0)	86.5 (72.0, 94.1)	93.3 (82.1, 97.7)
3	PC (n=64)	36	3	4	21	92.3 (79.7, 97.4)	84.0 (65.4, 93.6)	89.1 (79.1, 94.6)	87.5 (69.0, 95.7)	90 (77.0, 96.0)
	FAS (n=82)	41	6	5	30	87.2 (74.8, 94.0)	85.7 (70.6, 93.7)	86.6 (77.6, 92.3)	83.3 (68.1, 92.1)	89.1 (77.0, 95.3)
4	PC (n=64)	38	1	12	13	97.4 (86.8, 99.6)	52.0 (33.5, 70.0)	79.7 (68.3, 87.7)	92.9 (68.5, 98.7)	76.0 (62.6, 85.7)
	FAS (n=82)	44	3	13	22	93.6 (82.8, 97.8)	62.9 (46.3, 76.8)	80.5 (70.6, 87.6)	88.0 (70.0, 95.8)	77.2 (64.8, 86.2)
5	PC (n=64)	36	3	7	18	92.3 (79.7, 97.4)	72.0 (52.4, 85.7)	84.4 (73.6, 91.3)	85.7 (65.4, 95.0)	83.7 (70.3, 91.9)
	FAS (n=82)	42	5	8	27	89.4 (77.4, 95.4)	77.1 (61.0, 87.9)	84.1 (74.7, 90.5)	84.4 (68.3, 93.1)	84.0 (71.5, 91.7)
Majority reads	PC (n=64)	36	3	6	19	92.3 (79.7, 97.3)	76.0 (56.6, 88.5)	85.9 (75.4, 92.4)	86.4 (66.7, 95.3)	85.7 (72.2, 93.3)
	FAS (n=82)	42	5	7	28	89.4 (77.4, 95.4)	80 (64.1, 90.0)	85.4 (76.1, 91.4)	84.8 (69.1, 93.4)	85.7 (73.3, 92.9)
Flortaucipir PET Read compared with high ADNC score										
1	PC (n=64)	36	2	8	18	94.7 (82.7, 98.5)	69.2 (50.0, 83.5)	84.4 (73.6, 91.3)	90.0 (69.9, 97.2)	81.8 (68.0, 90.5)
	FAS (n=82)	39	2	12	29	95.1 (83.9, 98.7)	70.7 (55.5, 82.4)	82.9 (73.4, 89.6)	93.5 (79.3, 98.2)	76.5 (63.2, 86.0)
2	PC (n=64)	37	1	3	23	97.4 (86.5, 99.5)	88.5 (71.0, 96.0)	93.8 (85.0, 97.5)	95.8 (79.8, 99.3)	92.5 (80.1, 97.4)
	FAS (n=82)	39	2	6	35	95.1 (83.9, 98.7)	85.4 (71.6, 93.1)	90.2 (81.9, 95.0)	94.6 (82.3, 98.5)	86.7 (73.8, 93.7)
3	PC (n=64)	36	2	4	22	94.7 (82.7, 98.5)	84.6 (66.5, 93.9)	90.6 (81.0, 95.6)	91.7 (74.2, 97.7)	90.0 (77.0, 96.0)
	FAS (n=82)	39	2	7	34	95.1 (83.9, 98.7)	82.9 (68.7, 91.5)	89.0 (80.4, 94.1)	94.4 (81.9, 98.5)	84.8 (71.8, 92.4)
4	PC (n=64)	37	1	13	13	97.4 (86.5, 99.5)	50.0 (32.1, 67.9)	78.1 (66.6, 86.5)	92.9 (68.5, 98.7)	74.0 (60.5, 84.1)
	FAS (n=82)	40	1	17	24	97.6 (87.4, 99.6)	58.5 (43.4, 72.2)	78.0 (68.0, 85.6)	96.0 (80.5, 99.3)	70.2 (57.4, 80.5)
5	PC (n=64)	36	2	7	19	94.7 (82.7, 98.5)	73.1 (53.9, 86.3)	85.9 (75.4, 92.4)	90.5 (71.1, 97.4)	83.7 (70.0, 91.9))
	FAS (n=82)	39	2	11	30	95.1 (83.9, 98.7)	73.2 (58.1, 84.3)	84.1 (74.7, 90.5)	93.8 (79.9, 98.3)	78.0 (64.8, 87.3)
Majority reads	PC (n=64)	36	2	6	20	94.7 (82.7, 98.5)	76.9 (58.0, 89.0)	87.5 (77.2, 93.5)	90.9 (72.2,97.5)	85.7 (72.2, 93.3)
	FAS (n=82)	39	2	10	31	95.1 (83.9, 98.7)	75.6 (60.7, 86.2)	85.4 (76.1, 91.4)	93.9 (80.4, 98.3)	79.6 (66.4, 88.5)

Abbreviations: TP = True Positive, FN = False Negative, FP = False Positive, TN = True Negative, NPV = Negative Predictive Value, PPV = Positive Predictive Value, PC = Primary Cohort, FAS = Full Autopsy Data Set

[a]Sample size and accuracy statistics comparing flortaucipir PET visual reads for all 5 individual readers, compared with pathology findings for identifying standards of B3 NFT scores and high ADNC scores.

eReferences

1. Abdi H, Williams LJ, Beaton D, et al. Analysis of regional cerebral blood flow data to discriminate among Alzheimer's disease, frontotemporal dementia, and elderly controls: a multi-block barycentric discriminant analysis (MUBADA) methodology. *J Alzheimers Dis.* 2012;31 Suppl 3:S189-201.
2. Devous MD, Sr., Joshi AD, Navitsky M, et al. Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F 18. *J Nucl Med.* 2018;59(6):937-943.