Initial clinical characterization of [^{18}F]ACI-19626: the first-in-class TDP-43 PET tracer

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Disclosures

Tamara Seredenina is an employee of AC Immune entitled to stock options

The value and potential applications of a TDP-43 PET[1] tracer

Visualization of TDP-43 pathology in living patient brain

	ALS[2]	FTD[3]	LATE[4]
Disease prevalence	4 per 100, 000[5]	15-22 per 100, 000[6]	1 in 5 clinical AD[7] diagnoses[8]
Brain regions primarily affected	Spinal cord & motor cortex	Frontal & temporal cortices	Amygdala, hippocampus, middle frontal gyrus
TDP-43 pathology	97%	45%	100%

Target engagement and pharmacodynamic biomarker

For therapeutic programs targeting TDP-43 pathology directly or indirectly in ALS, FTD and LATE

Differential diagnostics

Distinguish FTLD[9]-TDP from FTLD-Tau opening new possibilities for FTD trials

Differentiate LATE and LATE-AD enabling the treatment of co-pathologies

Patient stratification

Enrolling the right patients in clinical trials

Disease insight

Mapping the spatial distribution and spread of TDP-43 pathology in the living brain to understand disease mechanisms

(1) Positron emission tomography; (2) amyotrophic lateral sclerosis; (3) frontotemporal dementia; (4) limbic predominant age related TDP-43 encephalopathy; (5) Ling et al., 2013; (6) Onyike et al. 2014; (7) Alzheimer's disease; (8) Nelson et al., 2019; (9) frontotemporal lobe degeneration.

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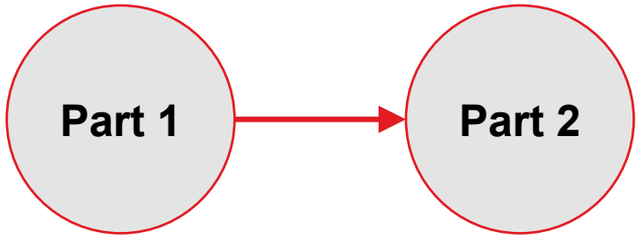
[^{18}F]ACI-19626 first in human PET study (ct.gov NCT06891716)

Study design and preliminary results



- Healthy volunteers
- Genetic FTD[1]

- Sporadic FTD
- Sporadic ALS[2]
- Suspected LATE[3]

Amsterdam UMC
University Medical Centers

[^{18}F]ACI-19626 is a first-in-class TDP-43 PET tracer specific to aggregated TDP-43 and selective over aggregated Aβ, Tau and α-synuclein (Vokali et al., 2025 Nature Comm)

Safety profile
- Good safety and tolerability; dosimetry profile within accepted limits

Brain pharmacokinetic profile
- Demonstrated fast brain uptake (SUV[4] >1) and fast washout
- Feasibility of kinetic modeling under exploration

Data from 4-5 HV[5], 4 C9orf72[6] FTD and 3 sporadic ALS patients
- 0-90 min dynamic scan
- Reference region: cerebellum grey matter[7]

- FIH[8] Part 1 focuses on C9orf72 FTD cases and Part 2 explores additional patient populations, including ALS

(1) Frontotemporal dementia; (2) Amyotrophic lateral sclerosis; (3) Limbic-predominant age-related TDP-43 encephalopathy; (4) standardized uptake values; (5) healthy volunteers; (6) chromosome 9 open reading frame 72; (7) Brettschneider et al., 2014; (8) first in human

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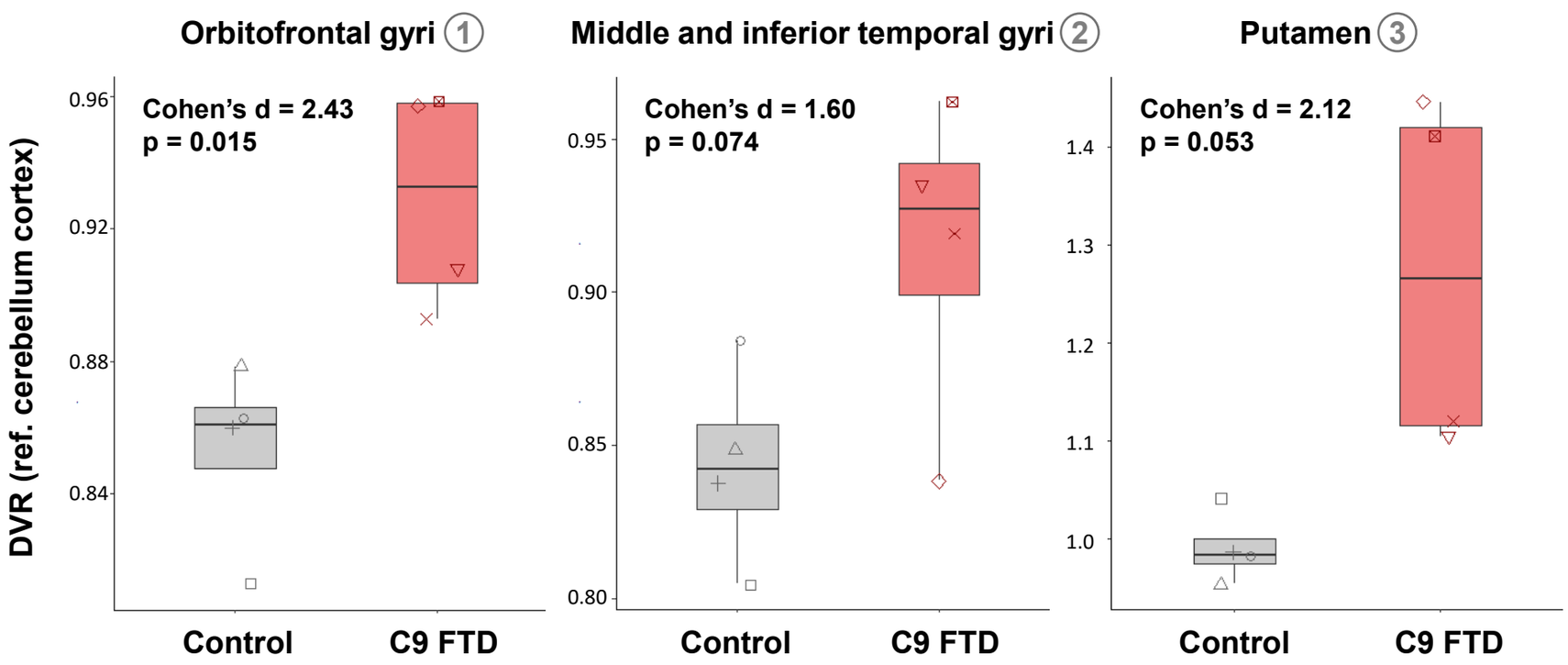
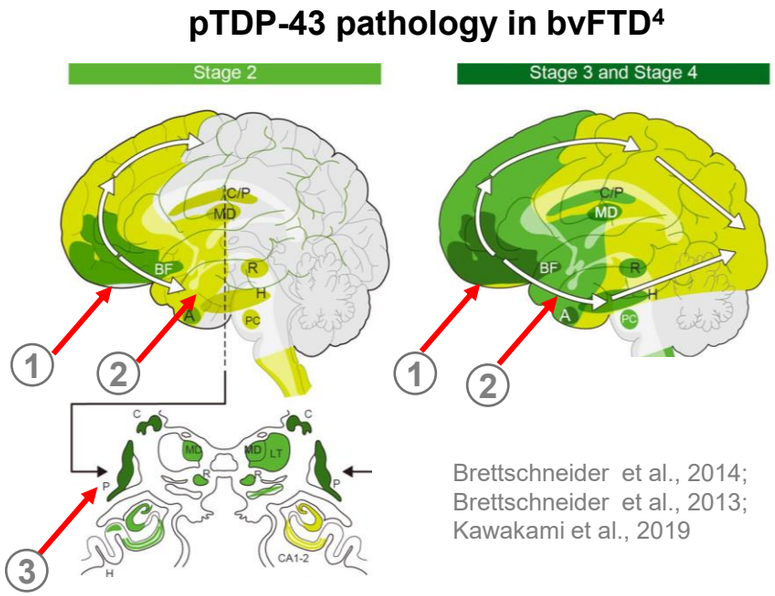
[18F]ACI-19626 FIH[1] study preliminary results: C9orf72 FTD

Kinetic modeling: DVR[2] estimates from 2TCM[3]





Brettschneider et al., 2014;
Brettschneider et al., 2013;
Kawakami et al., 2019

- Preliminary data indicates higher tracer uptake in C9orf72 FTD patients compared to healthy controls in relevant brain regions
- Refinement of the kinetic modelling is ongoing to assess to what degree uptake reflects specific binding and validate reference tissue approaches

(1) First in human; (2) distribution volume ratio; (3) two tissue compartment model; (4) behavioral variant frontotemporal dementia

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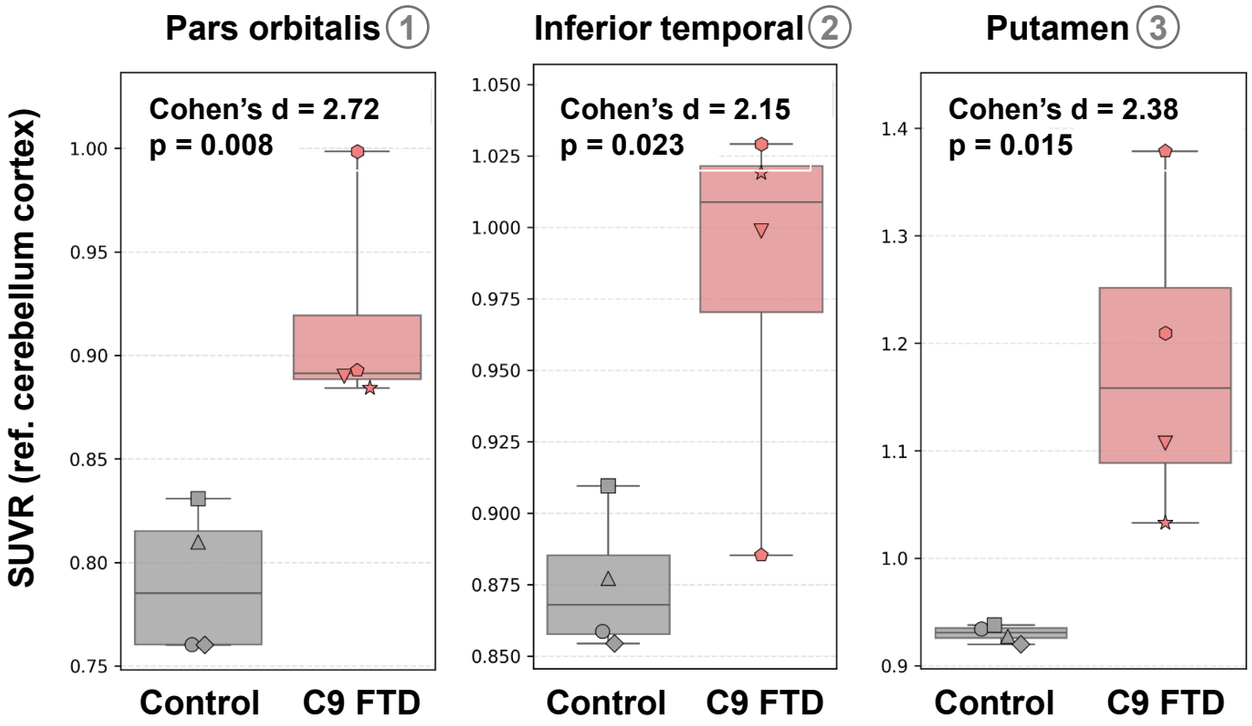
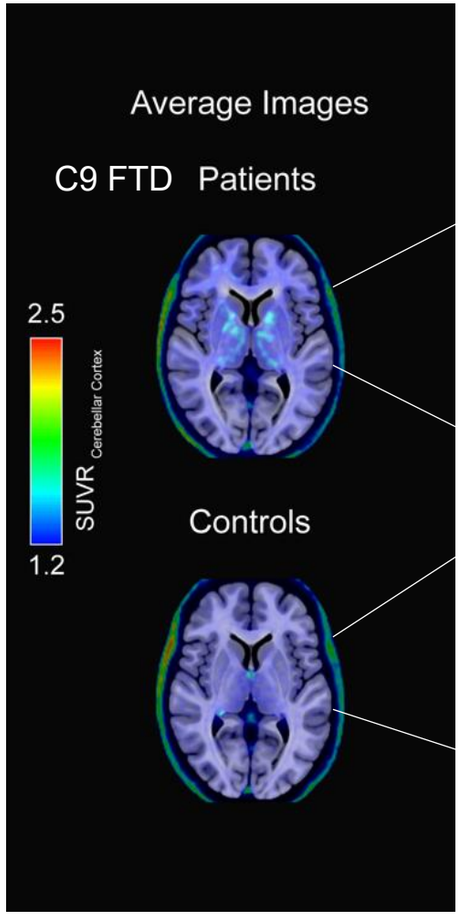
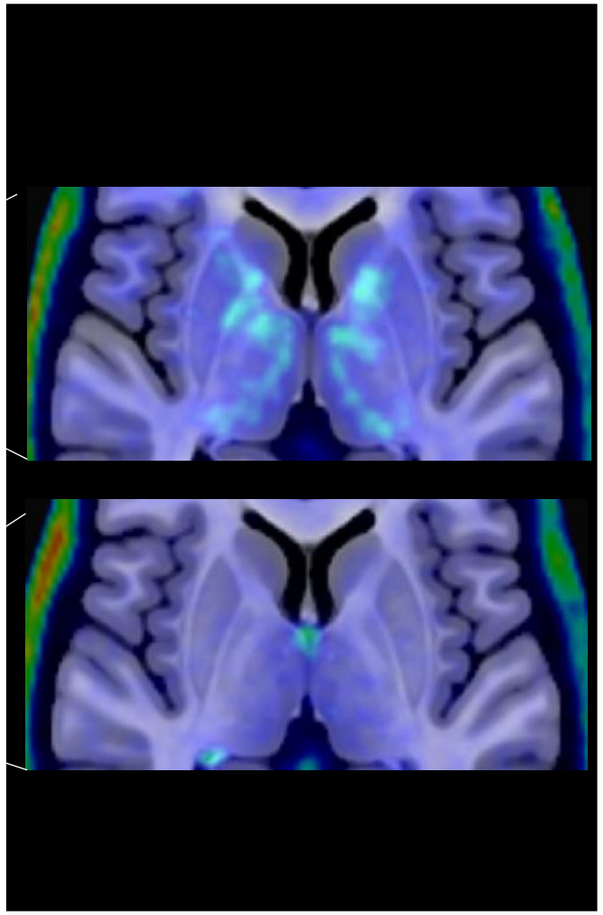
[18F]ACI-19626 FIH[1] study preliminary results: C9orf72 FTD

SUVR[2] analysis and parametric images, 15-50 min scan*







- Preliminary data indicates higher tracer uptake in C9orf72 FTD subjects compared to healthy controls in subcortical and cortical regions where TDP-43 pathology is expected based on *post-mortem* studies

(1) First in human; (2) standardized uptake volume ratio; (3) frontotemporal dementia; *Post-hoc analysis from a third-party external to the study, for informational purposes only and does not constitute official, finalized data

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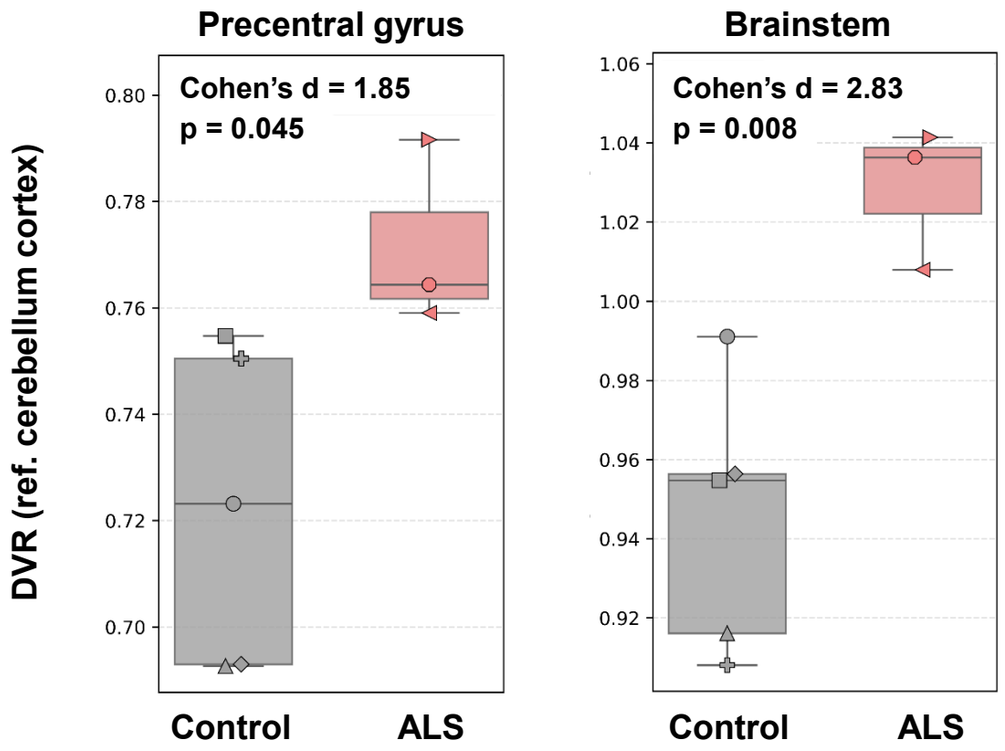
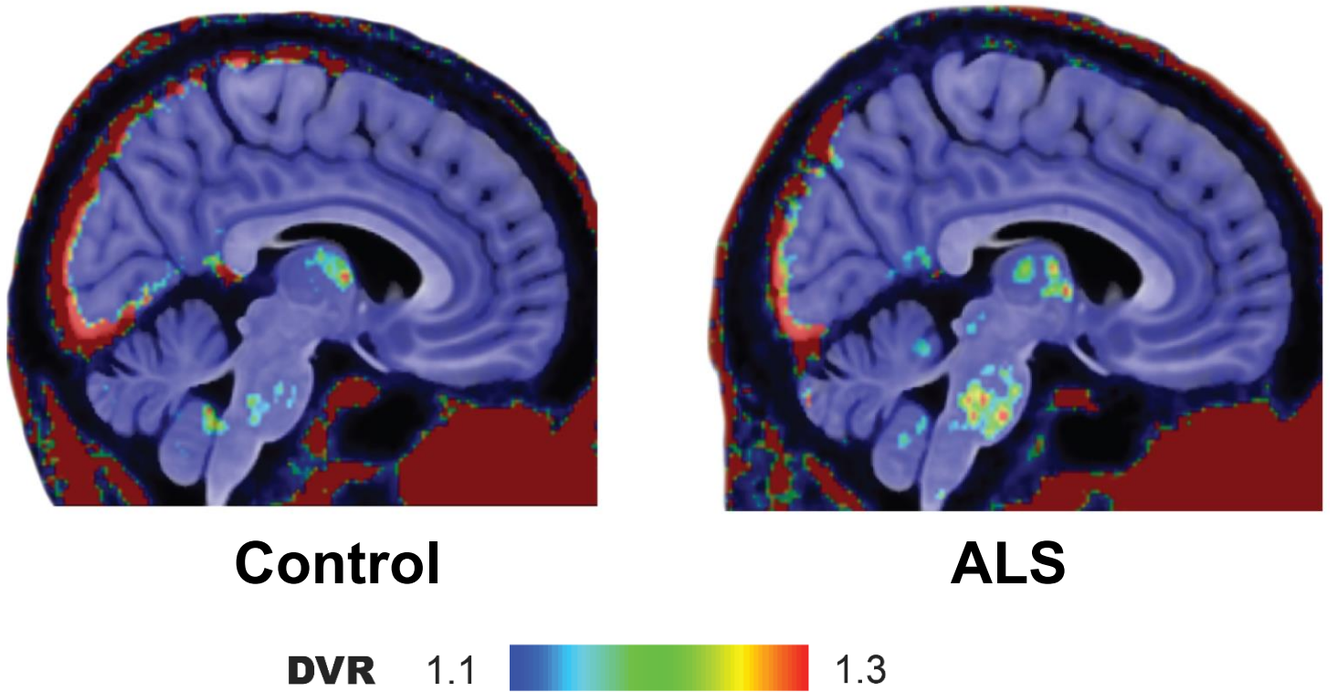
[18F]ACI-19626 FIH[1] study preliminary results: sporadic ALS[2]

DVR[3] estimates from Logan* and parametric images





- Preliminary data indicates higher tracer uptake in ALS patients compared to healthy controls in relevant brain regions
- Refinement of the kinetic modelling is ongoing to assess to what degree uptake reflects specific binding and validate reference tissue approaches

(1) First in human; (2) amyotrophic lateral sclerosis; (3) distribution volume ratio; *Post-hoc analysis from a third-party external to the study, for informational purposes only and does not constitute official, finalized data

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[18F]ACI-19626 holds promise as PET[1] tracer for multiple NDD[2]

1

Frontotemporal dementia

- Preliminary data suggests higher PET tracer uptake in genetic FTD[3] with C9orf72 mutation in some relevant cortical and subcortical brain regions compared to healthy subjects

2

Amyotrophic lateral sclerosis

- Preliminary data suggests higher PET tracer uptake in sporadic ALS[4] patients in disease relevant brain regions compared to healthy subjects

3

Clinical development status

- ACI-19626 uptake pattern closely mirrors the known distribution of TDP-43 pathology and is consistent with the main clinical symptoms in different diseases
- PET data analysis ongoing to validate reference tissue approaches
- ACI-19626 binding data to be confirmed in a larger number of subjects and in additional patient populations including sporadic FTD and LATE[5]/AD[6]

4

Future directions and tracer potential

- Longitudinal PET studies to explore the diagnostic and prognostic potential
- Include ACI-19626 in therapeutic trials to explore its potential as pharmacodynamic biomarker

(1) Positron Emission Tomography; (2) neurodegenerative diseases; (3) frontotemporal dementia; (4) amyotrophic lateral sclerosis; (5) limbic predominant age related TDP-43 encephalopathy; (6) Alzheimer's disease

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Brain banks

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- **Netherlands Brain Bank**, Netherlands Institute for Neuroscience, Amsterdam. All Material has been collected from donors from whom a written informed consent for brain autopsy and the use of the material and clinical information for research purposes had been obtained by the NBB.
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