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

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May 21st, 2026 TDP-43 summit, Madison, WI

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Disclosures

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

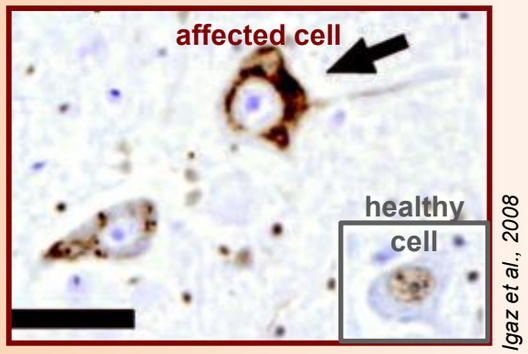
Funding

Grant from the Michael J Fox Foundation

Pathological TDP-43 is a promising therapeutic and diagnostic target

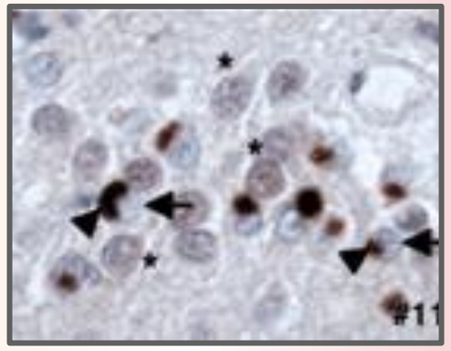
Pathological aggregation of TDP-43 is found in multiple neurodegenerative diseases

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



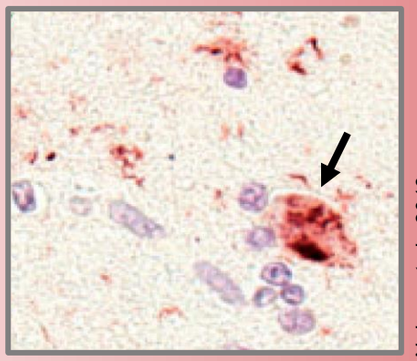
Sporadic ALS, spinal cord

Igaz et al., 2008



FTD, dentate gyrus

Neumann et al., 2006



LATE, hippocampus

Nelson et al., 2019

- TDP-43 aggregation is central to multiple neurodegenerative diseases as primary pathology or co-pathology
- TDP-43 therapeutics and biomarkers represent a major unmet medical need

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

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

Visualization of TDP-43 pathology in living patient brain

Target engagement and pharmacodynamic biomarker

For therapeutic programs targeting TDP-43 pathology directly or indirectly in ALS[2], FTD[3] and LATE[4]

Differential diagnostics

Distinguish FTLD[5]-TDP from FTLD-Tau opening new possibilities for FTD trials

Differentiate LATE and LATE-AD[6] 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) frontotemporal lobe degeneration; (6) Alzheimer's disease

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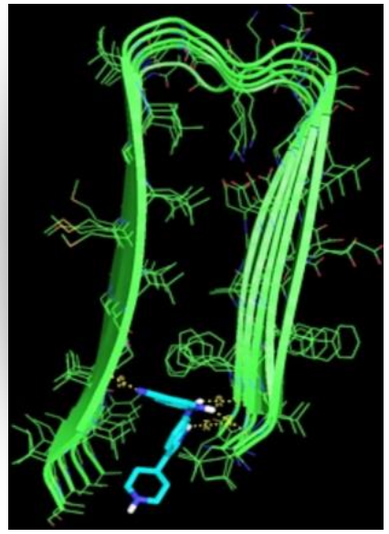
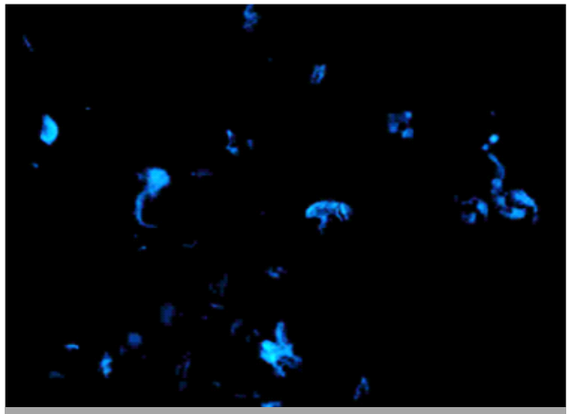
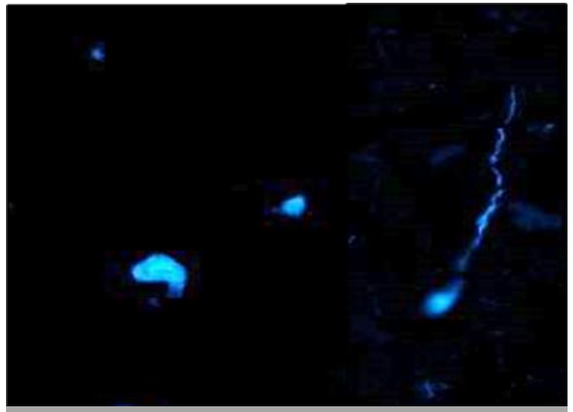
TDP-43 PET[1] tracers: improving the diagnosis and treatment of NDD[2]

Precision medicine approach enabled by the Morphomer® platform

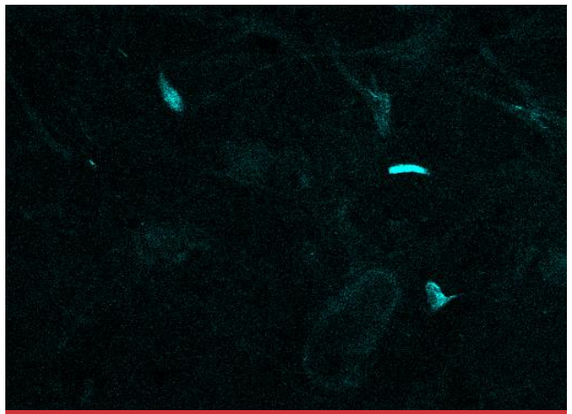




Tau NFTs[3]
PI-2620



α-synuclein inclusions
ACI-12589



TDP-43[4] inclusions

Leverage the Morphomer® small molecule platform:

- Non-peptidic, small molecules with CNS[5]-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, a-synuclein)
- Pharmacokinetics suitable for brain PET imaging

- AC Immune developed a first-in-class TDP-3 PET tracer ACI-19626 which displays an optimal profile for brain PET tracer development

(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) TAR DNA binding protein-43; (5) central nervous system

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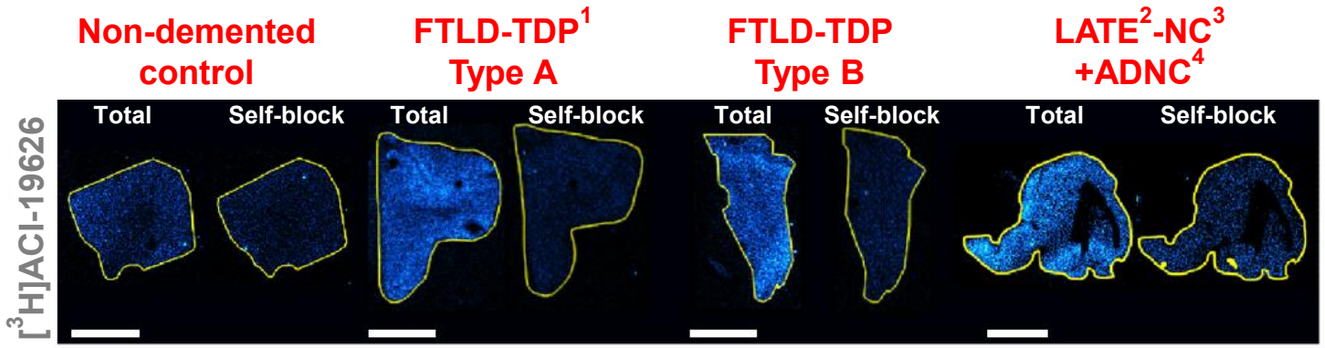
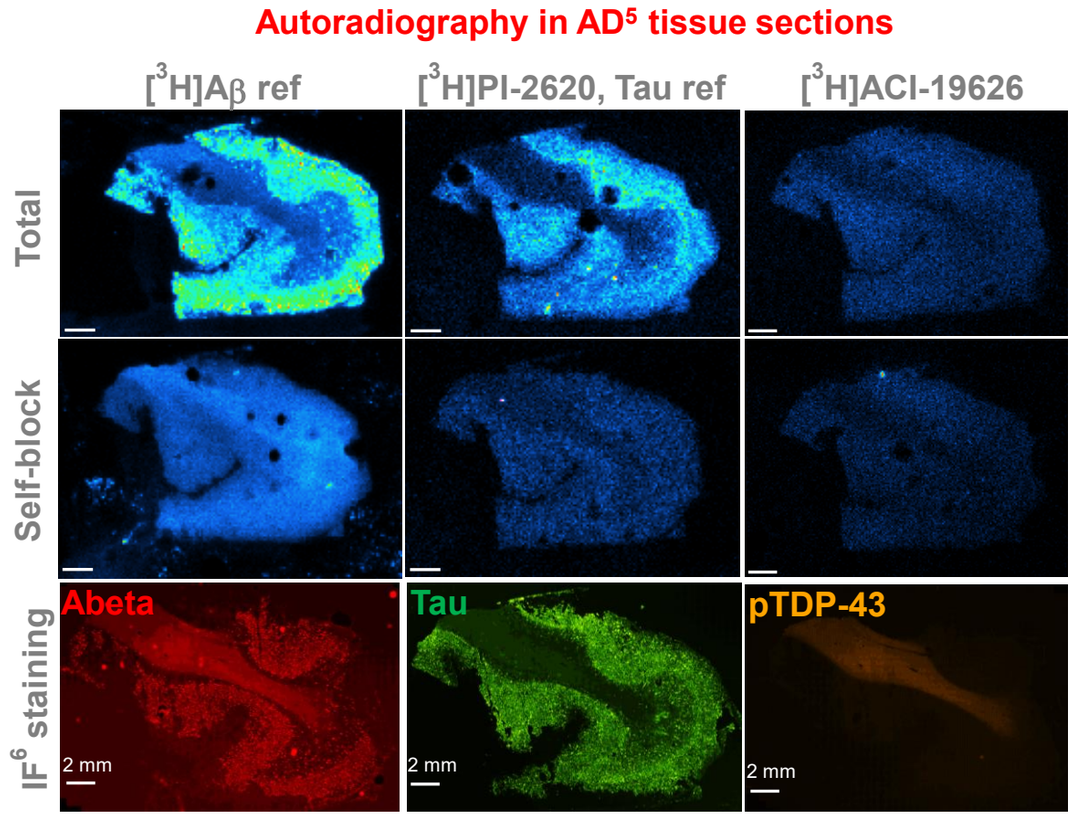
ACI-19626 binding profile, affinity and selectivity

Classical autoradiography on patient brain sections



Donor - pathology	K_d (nM)	Target occupancy*
Non-diseased control	No fit	
FTLD-TDP Type A #1	18	13
FTLD-TDP Type A #2	17	12
LATE-NC + ADNC	27	7



Vokali et al. Nature Comm 2025

- Broad potential to detect TDP-43 pathology in FTLD-TDP, LATE, AD, FTD[7]-MND[8] and ALS[9]
- Optimal *in vitro* binding potential (Bmax/Kd > 10) for further development as brain PET tracer[10]
- A promising selectivity profile for differential diagnostics in AD and FTD

(1) Frontotemporal lobar degeneration with TDP-43 pathology; (2) limbic-predominant age-related TDP-43 encephalopathy; (3) neuropathological change; (4) Alzheimer's disease neuropathological change; (5) Alzheimer's disease; (6) immunofluorescence; (7) frontotemporal dementia; (8) motor neuron disease; (9) amyotrophic lateral sclerosis; (10) Pike et al., 2016; * Bmax/Kd ratio

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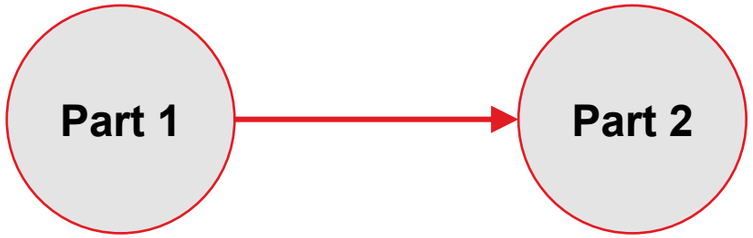
[^{18}F]ACI-19626 first in human PET study (ct.gov NCT06891716)

Study design and preliminary results



- Healthy volunteers
- Genetic FTD[1]

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

Safety profile
- Good safety and tolerability
- Dosimetry profile within accepted limits

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

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

Amsterdam UMC
University Medical Centers

- FIH[8] Part 1 is focused on C9orf72 FTD cases
- FIH Part 2 aims to explore additional patient populations, including ALS
- Confirmed safety and favorable pharmacokinetics

(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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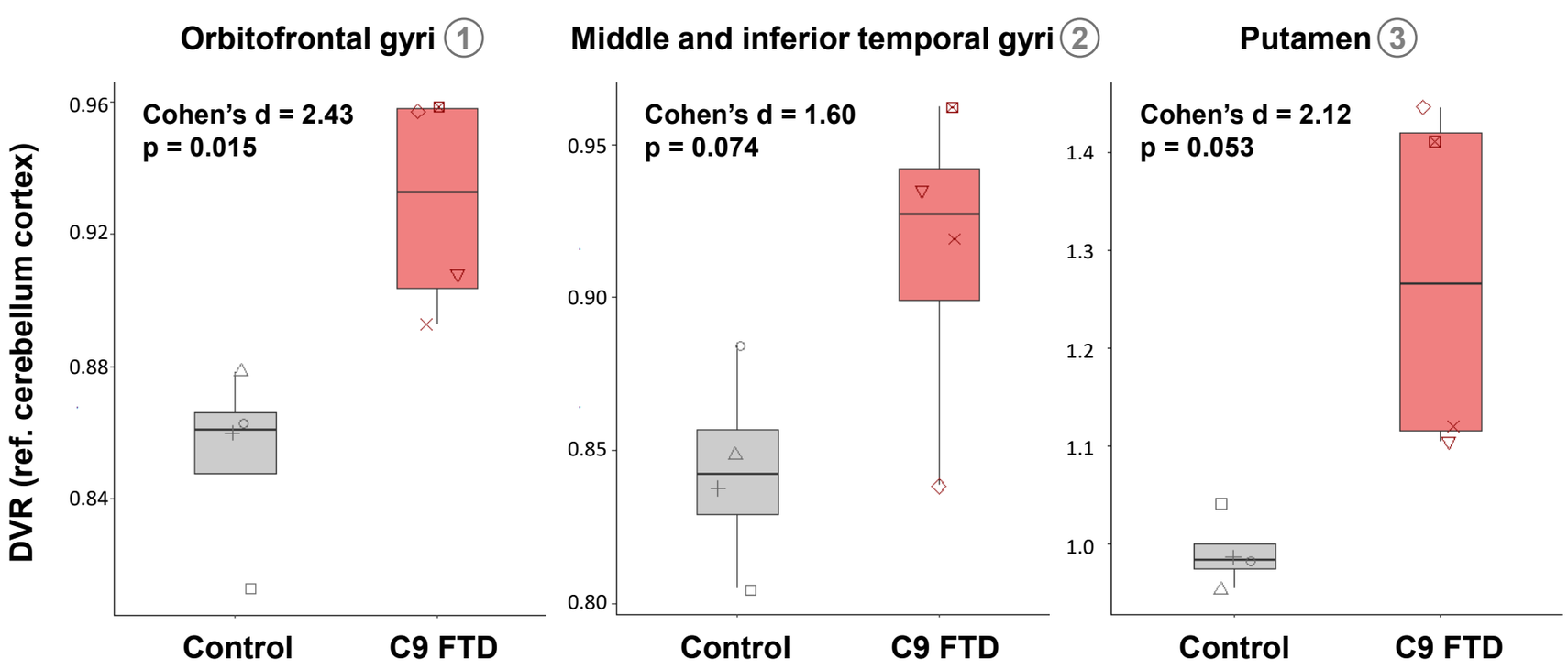
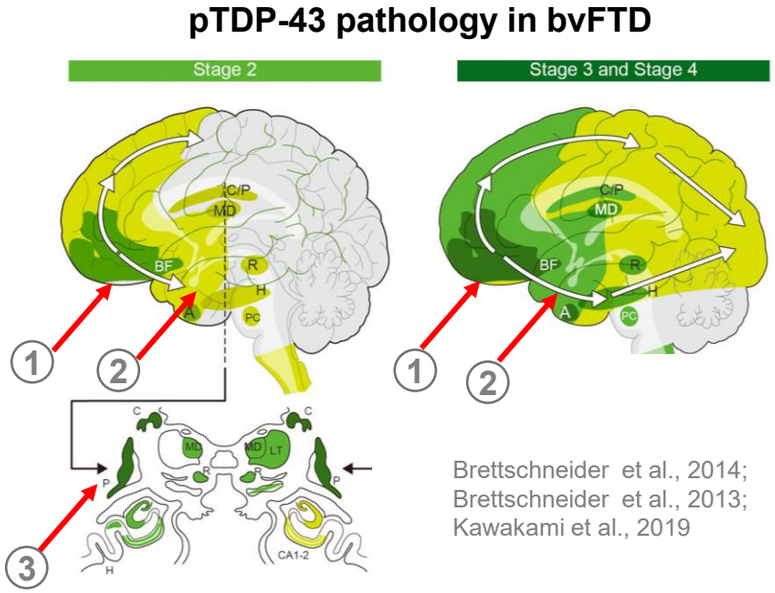
[18F]ACI-19626 FIH1 study preliminary results: kinetic modeling

DVR2 estimates from 2TCM3 for 4 HV4 and 4 C9orf72 FTD5 patients





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) healthy volunteers; (5) frontotemporal dementia

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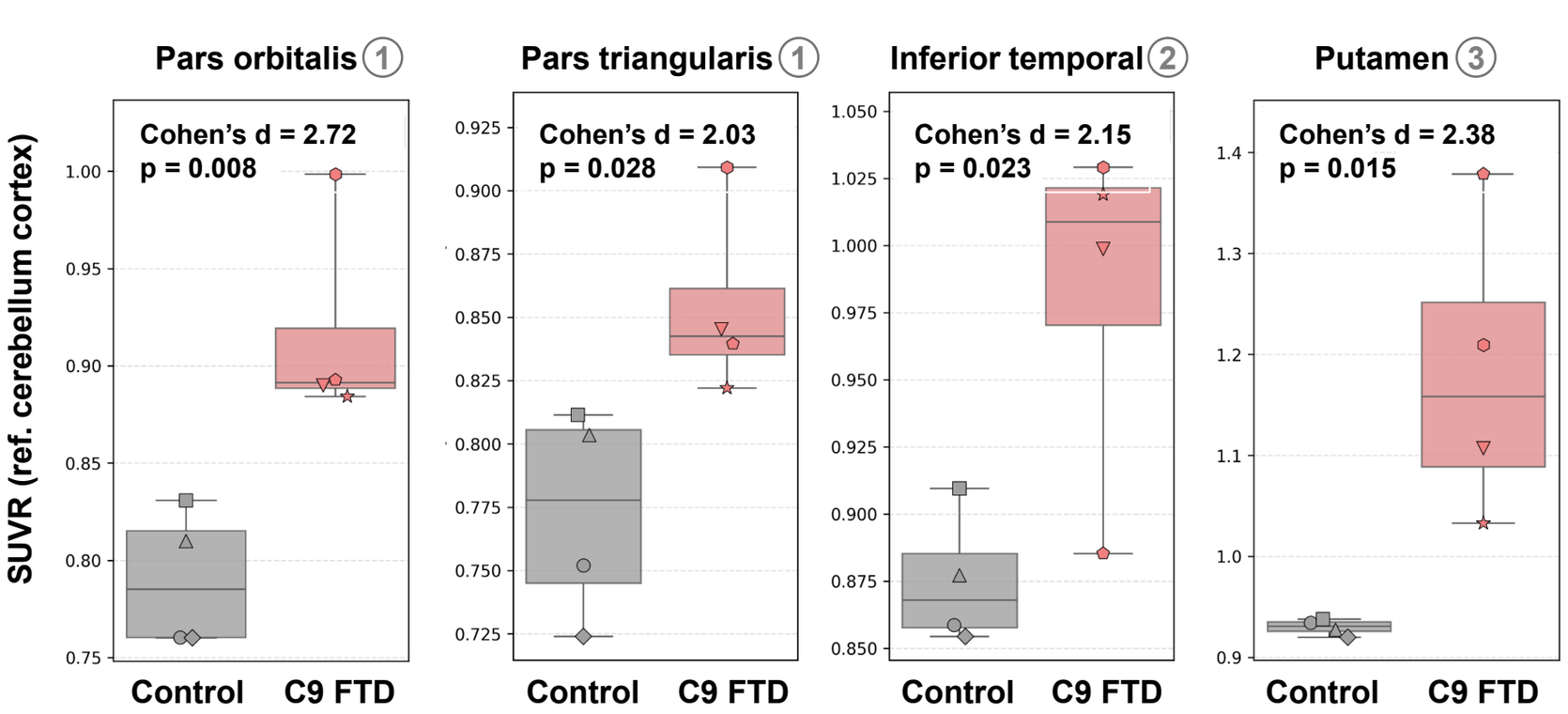
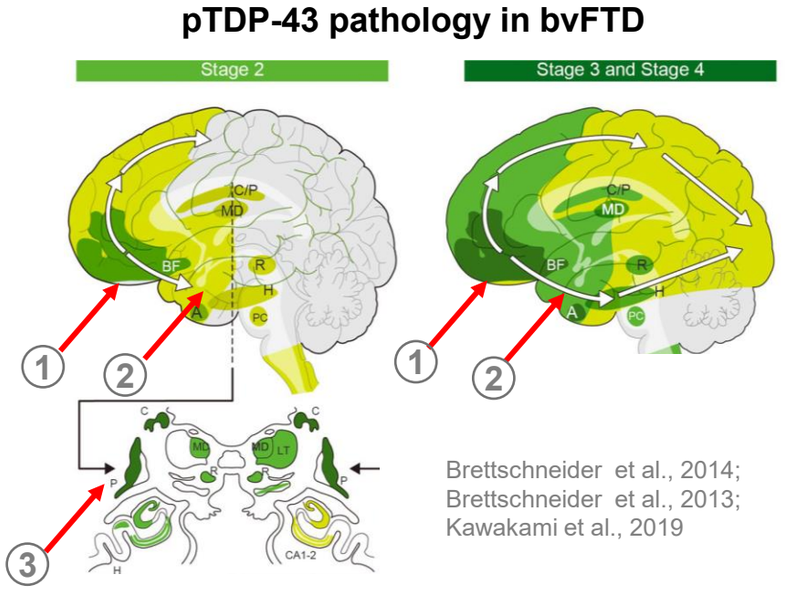
[18F]ACI-19626 FIH[1] study preliminary results: SUVR[2]

15-50 min scan, cerebellum cortex as reference region*, 4 HV[3] and 4 C9orf72 FTD[4] patients





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

- Preliminary data indicates higher tracer uptake in C9orf72 FTD[3] 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) healthy volunteers; (4) 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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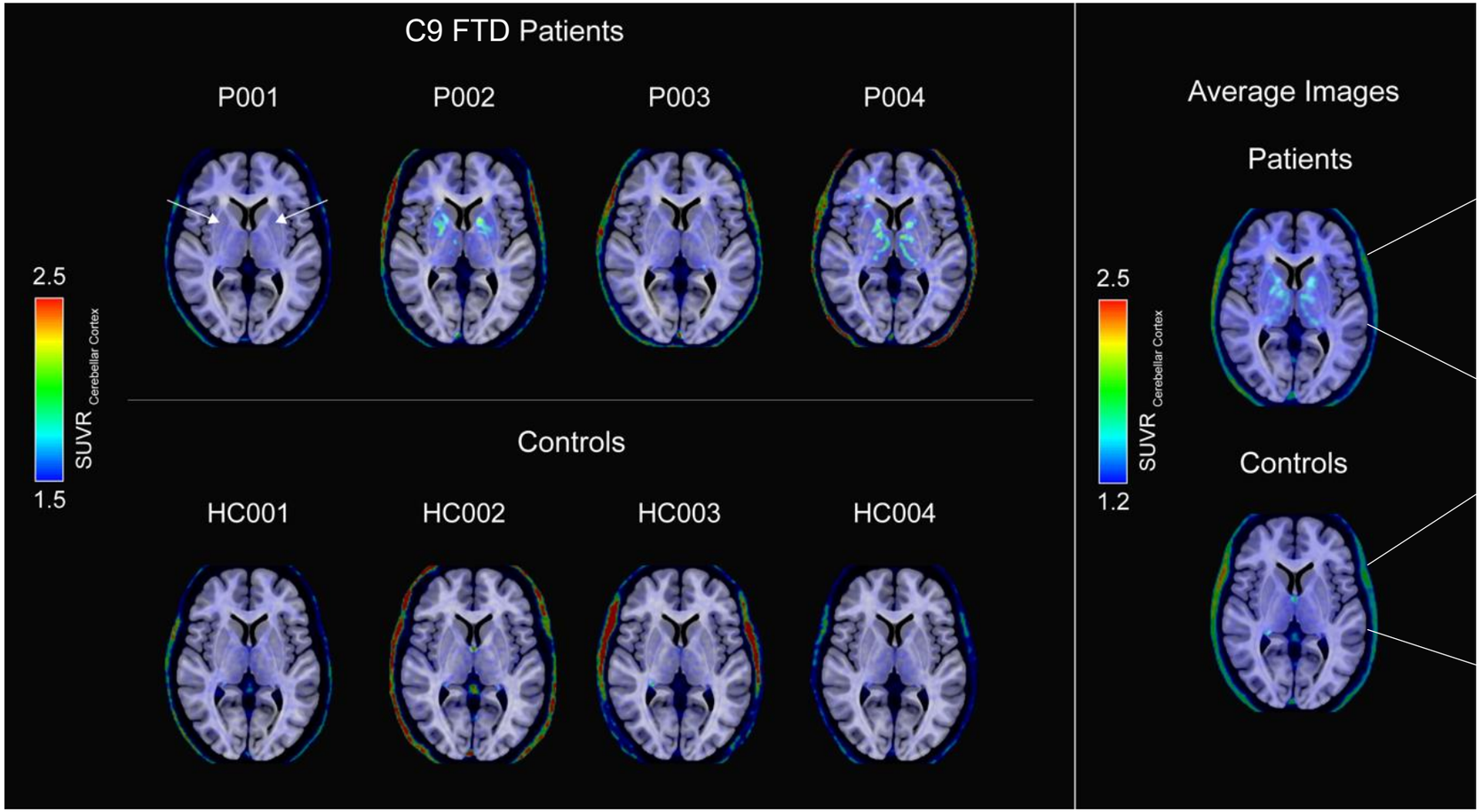
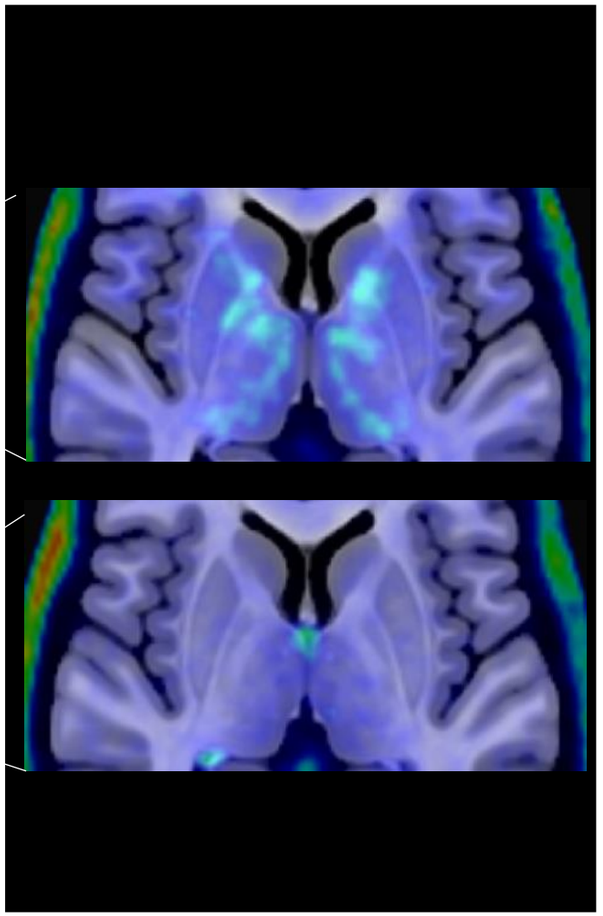
[18F]ACI-19626 FIH[1] study preliminary results: parametric images

SUVR[2] analysis, 15-40 min scan, using cerebellum cortex as reference region*





- Preliminary data indicates higher tracer uptake in C9orf72 FTD[3] cases compared to healthy controls in subcortical 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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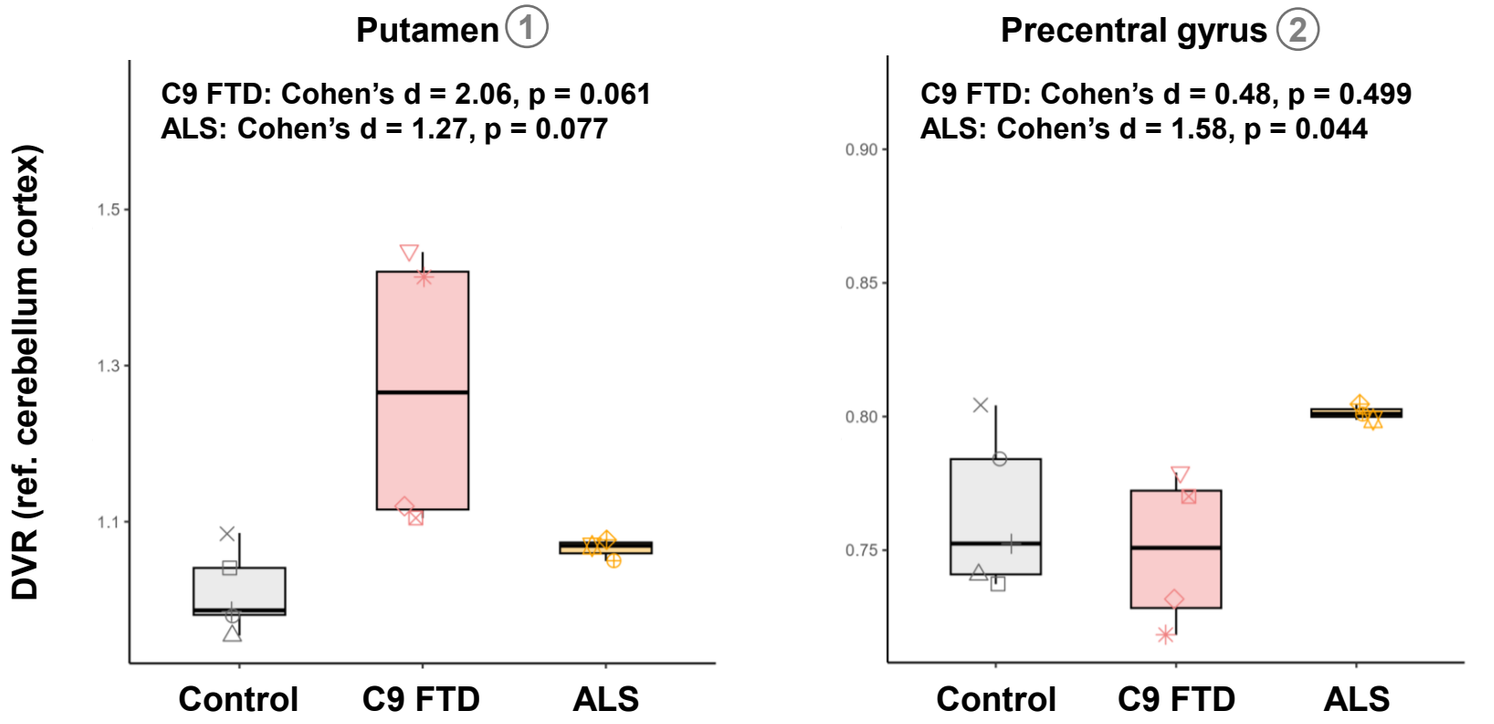
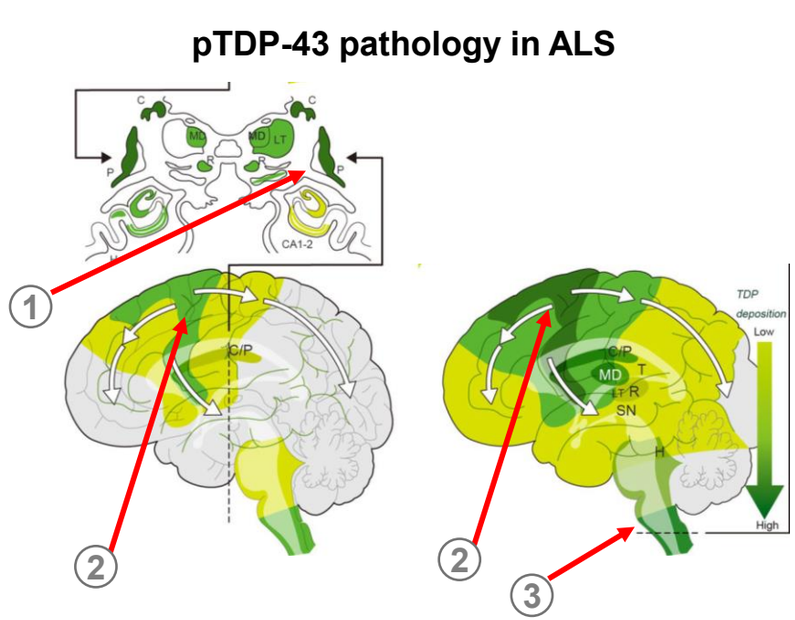
[18F]ACI-19626 FIH1 study preliminary results: kinetic modeling

DVR2 estimates from 2TCM3 for 5 HV4, 4 C9orf72 FTD5 and 3 sporadic ALS6 patients





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

- 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) distribution volume ratio; (3) two tissue compartment model; (4) healthy volunteers; (5) frontotemporal dementia ; (6) amyotrophic lateral sclerosis

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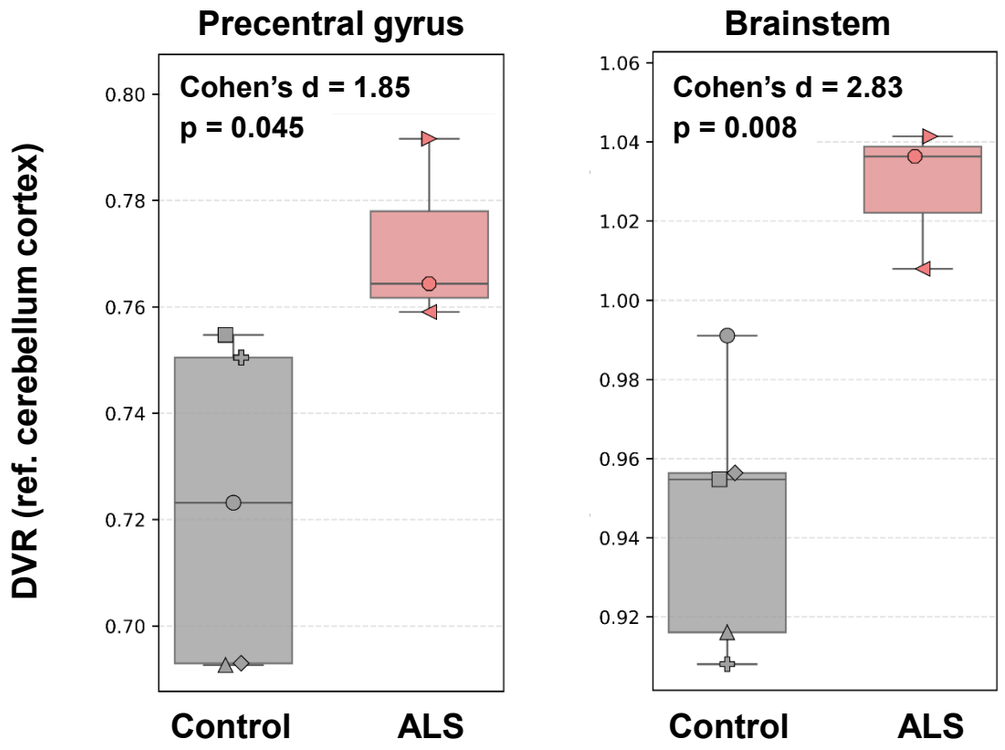
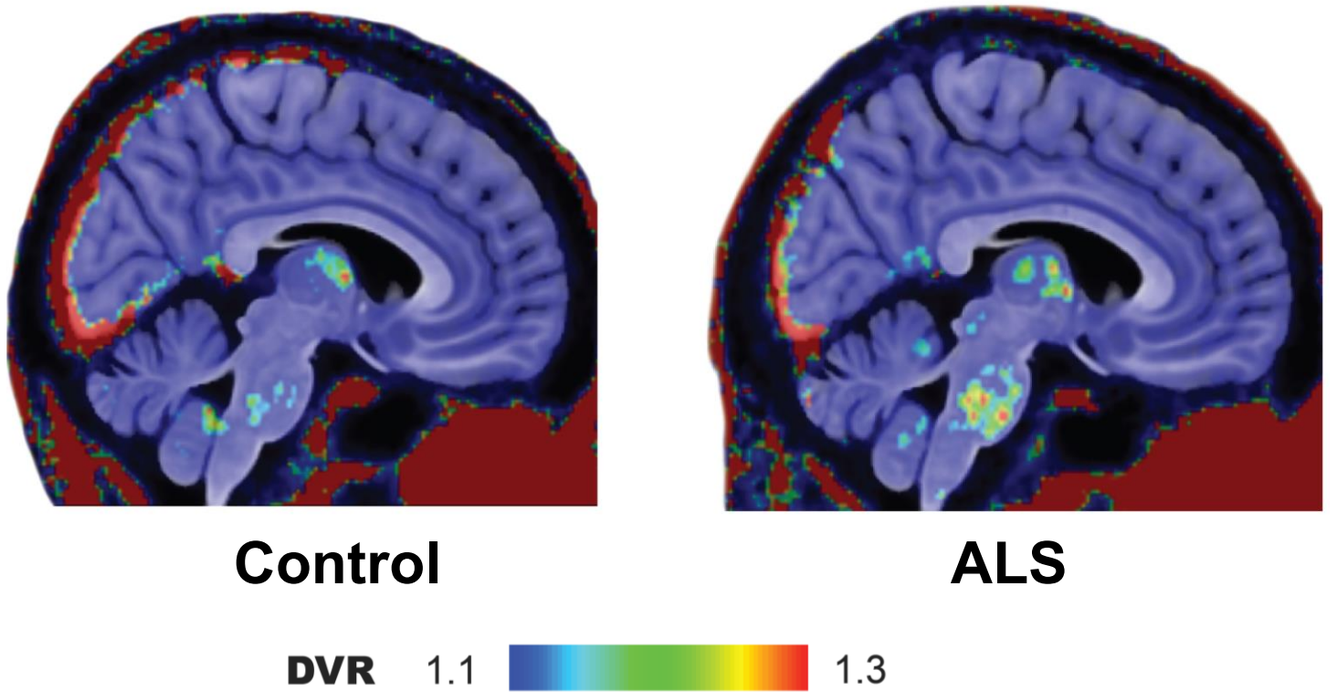
[18F]ACI-19626 FIH1 study preliminary results: parametric images

DVR2 estimates from Logan* for 5 HV3 and 3 sporadic ALS4 patients





- Preliminary data indicates higher tracer uptake in ALS patients compared to healthy controls in relevant brain regions
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[^{18}F]ACI-19626 as first-in-class TDP-43 PET[1] tracer

Conclusions

Promising preliminary clinical data

- Preliminary data suggests higher PET tracer uptake in genetic FTD and sporadic ALS patients in some relevant brain regions compared to healthy controls
- PET data analysis ongoing to validate reference tissue approaches

Clinical development status

- ACI-19626 binding data to be confirmed in a larger number of subjects and in additional patient populations
- FIH Part 2 ongoing

(1) Positron emission tomography; (2) frontotemporal dementia; (3) amyotrophic lateral sclerosis

Acknowledgements

We sincerely thank the study participants and their families for their invaluable contribution to this study

Brain banks

- **Neurodegenerative Disease Brain Bank UCSF, Prof. William Seeley** (funding support from NIH grants P01AG019724 and P50AG023501, the Consortium for Frontotemporal Dementia Research, and the Tau Consortium).
- **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.
- **Queen Square Brain Bank for Neurological Disorders, UCL, Prof. Tammaryn Lashley**
- **Target ALS, Prof. Robert Bowser**
- **University of Kentucky, Prof. Peter Nelson**

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Grant ID: MJFF-022232

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Julien Mermoud
Valerie Hliva
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David Ribas
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UMC Utrecht

Leonard van den Berg
Henk-Jan Westeneng

ZRO New Gen Neuroimaging

Antoine Leuzy
Alexis Moscoso
Alejandro Costoya-Sánchez

JPND ImageTDP43 research
EU Joint Programme – Neurodegenerative Disease Research

Magda Polymenidou
Emanuele Buratti
Harro Seelaar

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