



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

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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%



- 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

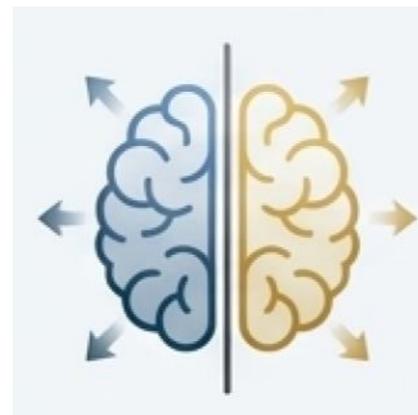
The value and potential applications of a TDP-43 PET¹ tracer

Vizualization of TDP-43 pathology in living patient brain



Target engagement and pharmacodynamic biomarker

For therapeutic programs targeting TDP-43 pathology directly or indirectly in ALS², FTD³ and LATE⁴



Differential diagnostics

Distinguish FTLD⁵-TDP from FTLD-Tau opening new possibilities for FTD trials
Differentiate LATE and LATE-AD⁶ enabling the treatment of co-pathologies



Patient stratification

Enrolling the right patients in clinical trials



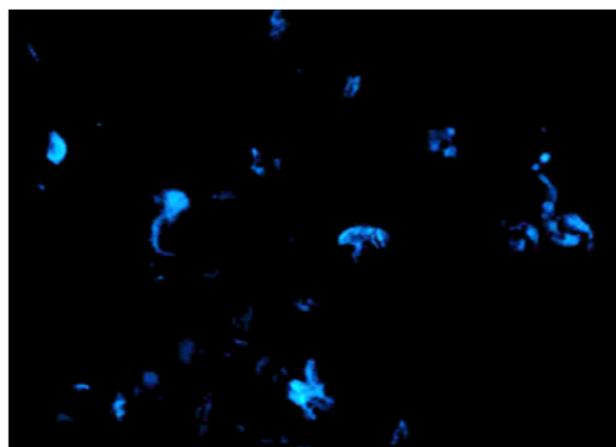
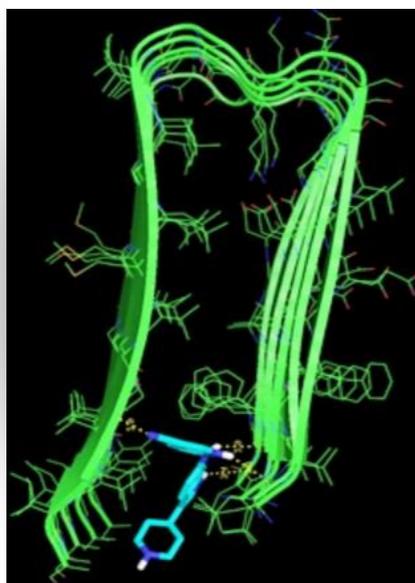
Disease insight

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

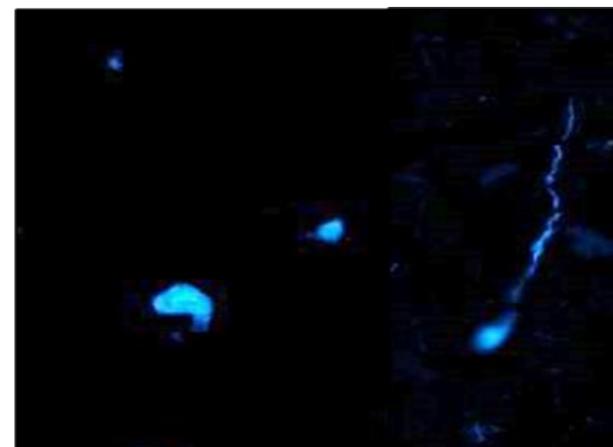
(1) Positron emission tomography; (2) amyotrophic lateral sclerosis; (3) frontotemporal dementia; (4) limbic predominant age related TDP-43 encephalopathy; (5) frontotemporal lobe degeneration; (6) Alzheimer's disease

TDP-43 PET¹ tracers: improving the diagnosis and treatment of NDD²

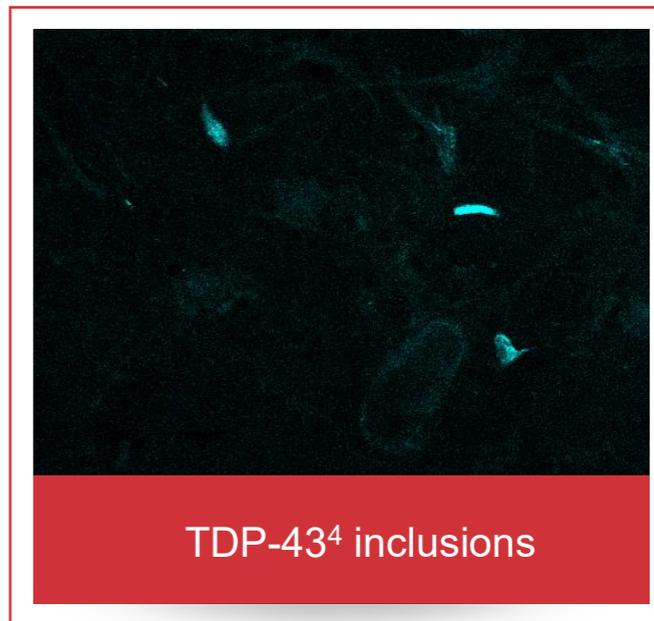
Precision medicine approach enabled by the Morphomer® platform



Tau NFTs³
PI-2620



α-synuclein inclusions
ACI-12589



TDP-43⁴ inclusions

Leverage the Morphomer® small molecule platform:

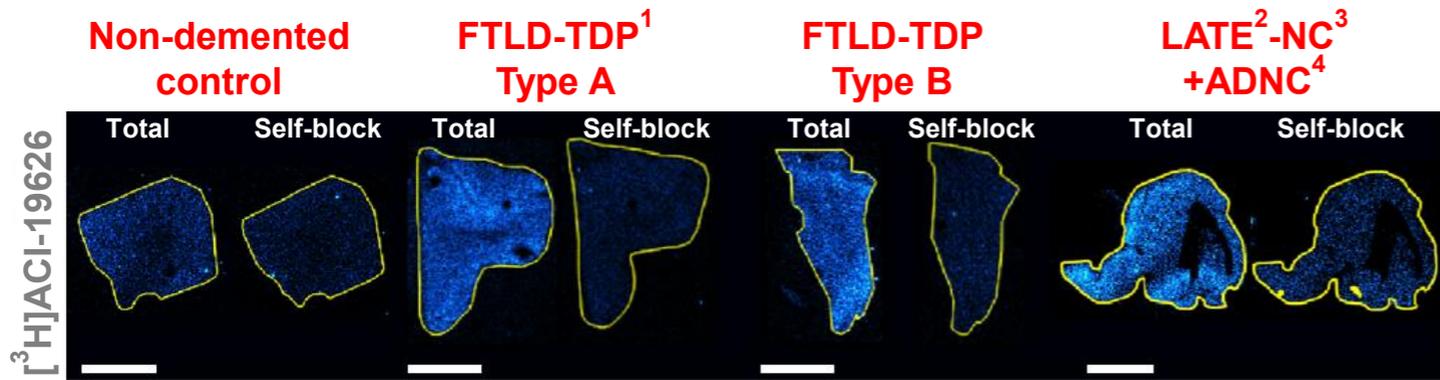
- Non-peptidic, small molecules with CNS⁵-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, α-synuclein)
- Pharmacokinetics suitable for brain PET imaging

- 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

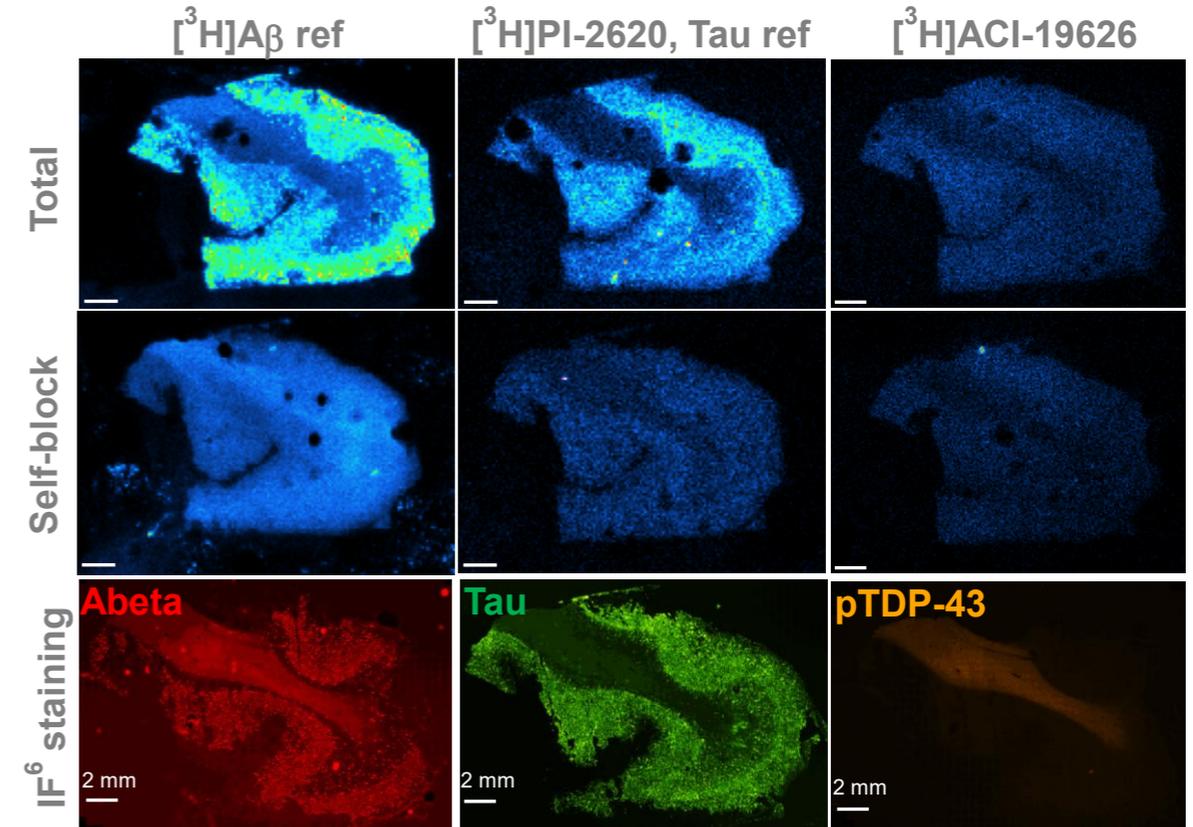
ACI-19626 binding profile, affinity and selectivity

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

Autoradiography in AD⁵ tissue sections



- Broad potential to detect TDP-43 pathology in FTLD-TDP, LATE, AD, FTD⁷-MND⁸ and ALS⁹
- Optimal *in vitro* binding potential ($B_{max}/K_d > 10$) for further development as brain PET tracer¹⁰
- 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; * B_{max}/K_d ratio

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

Study design and preliminary results



- Healthy volunteers
- Genetic FTD¹

- Sporadic FTD
- Sporadic ALS²
- Suspected LATE³



Safety profile

- Good safety and tolerability
- Dosimetry profile within accepted limits



Brain pharmacokinetic profile

- Demonstrated fast brain uptake (SUV⁴ >1)
- Demonstrated fast washout
- Feasibility of kinetic modeling under exploration



Data from 4 HV⁵ and 4 C9orf72⁶ FTD patients

- 0-90 min dynamic scan
- Reference region: cerebellum grey matter⁷

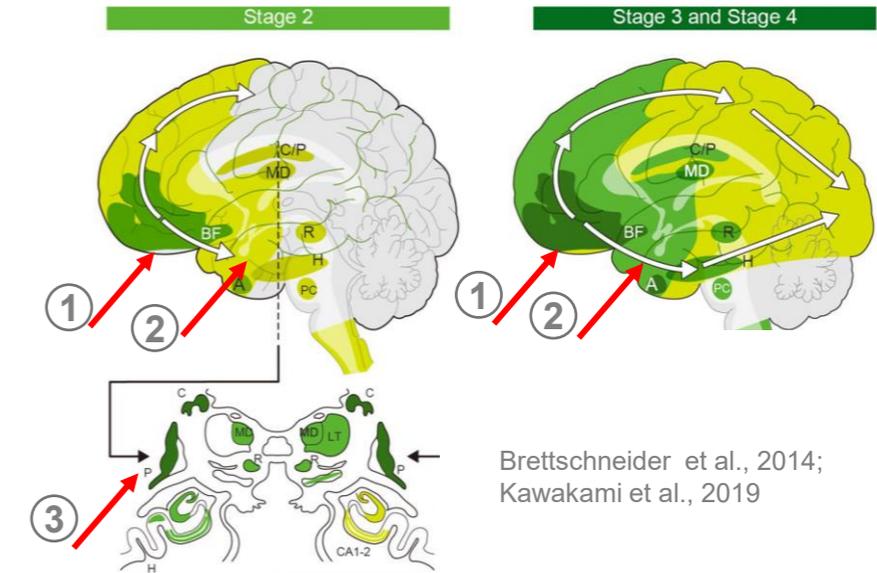
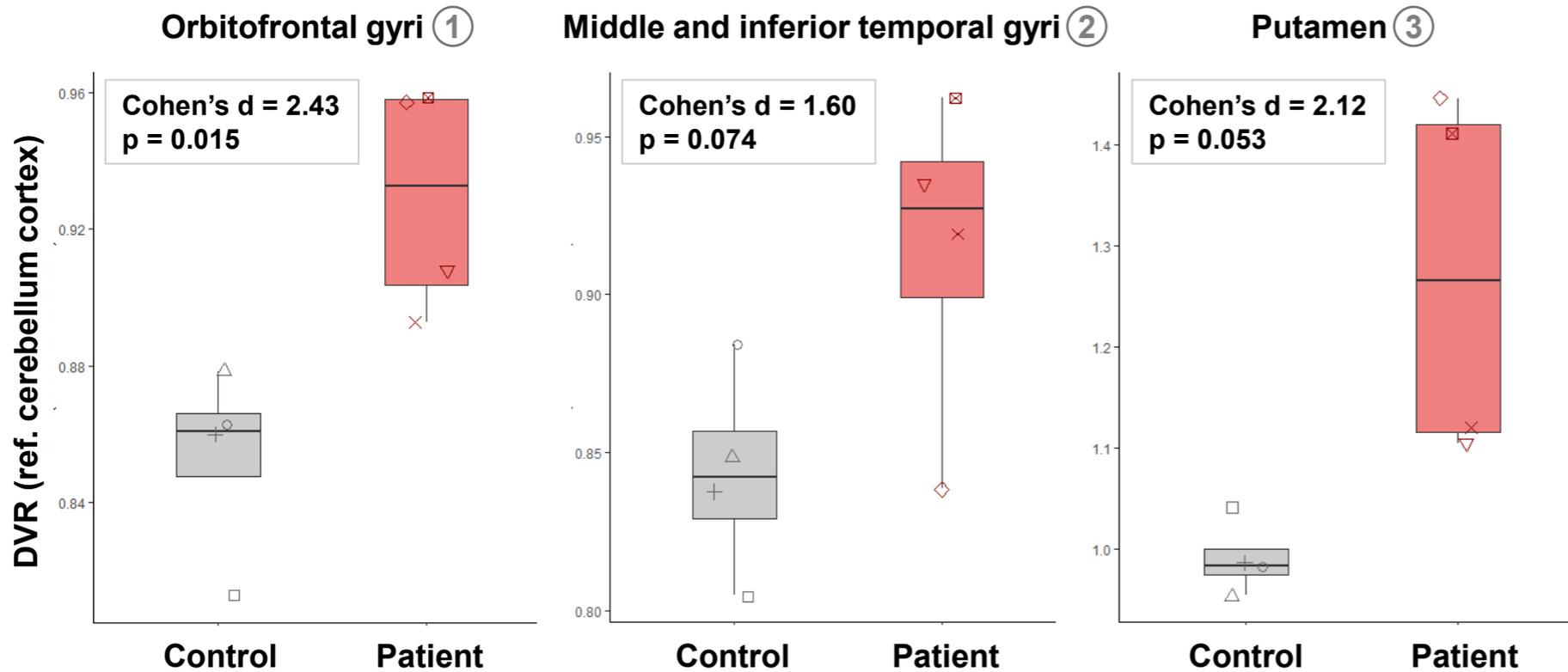


- FIH⁸ Part 1 is focused on C9orf72 FTD cases
- FIH Part 2 aims to explore additional patient populations, including ALS
- Confirmed safety and favorable pharmacokinetics

(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

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

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

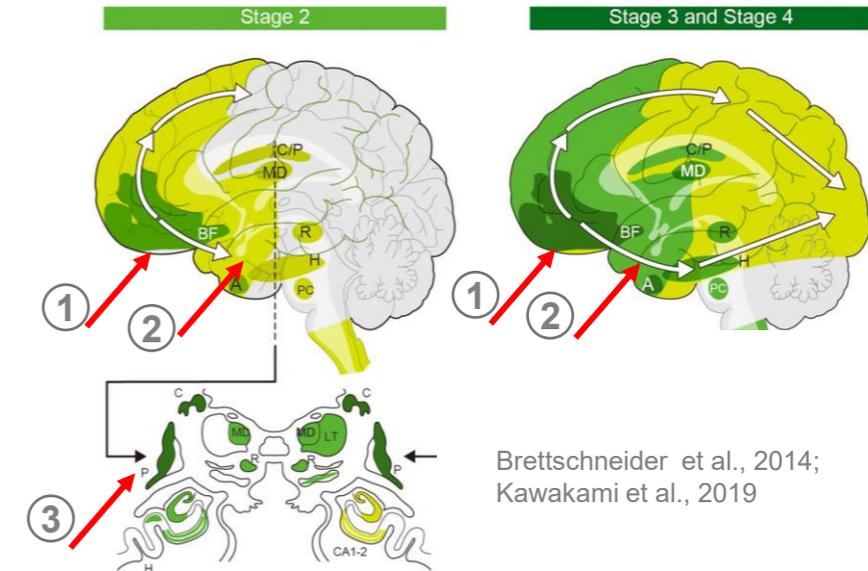
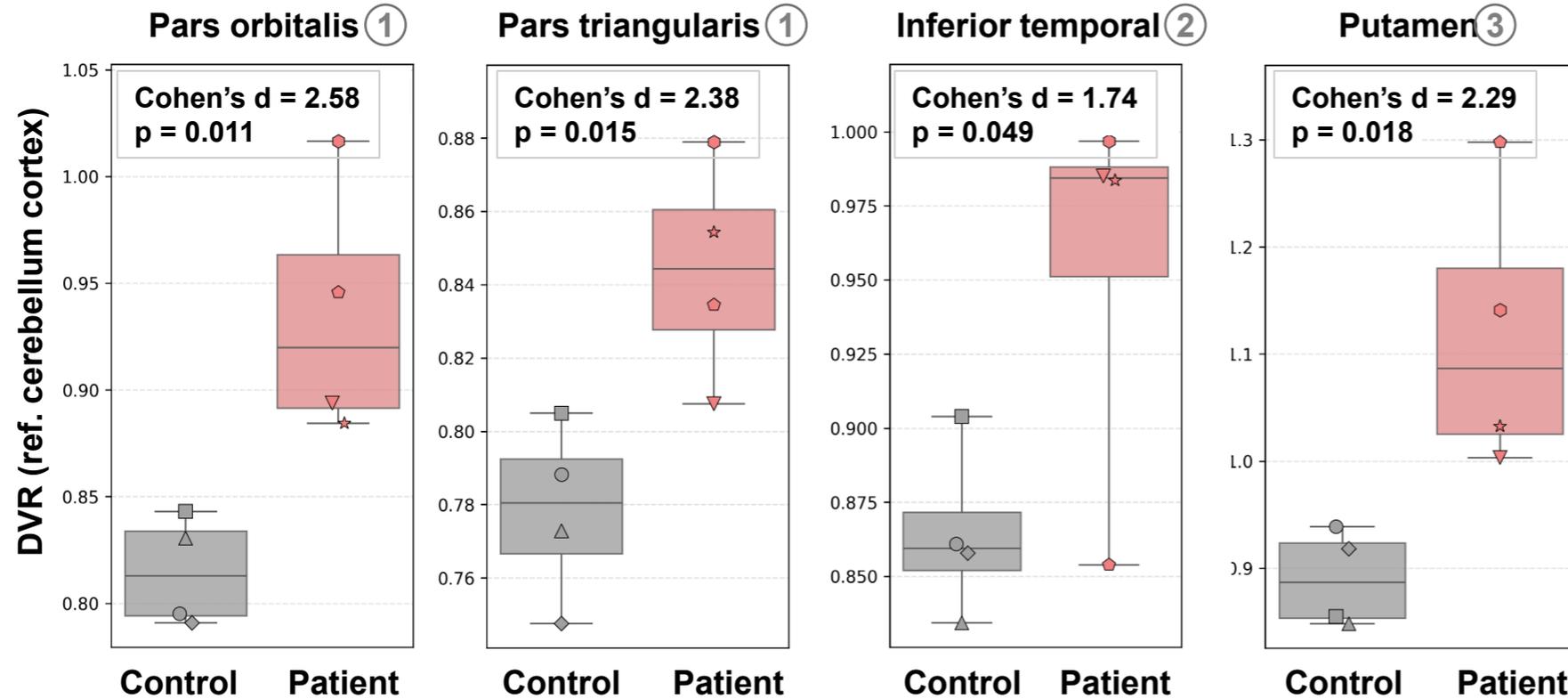


- Preliminary data indicates higher tracer uptake in C9orf72 FTD patients compared to healthy controls in relevant brain regions
- Refinement of the kinetic modelling is ongoing to assess to what degree uptake reflects specific binding and validate reference tissue approaches

(1) First in human; (2) distribution volume ratio; (3) two tissue compartment model; (4) healthy volunteers; (5) frontotemporal dementia

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

DVR² estimates from Logan analysis using corrected IDIF³ *

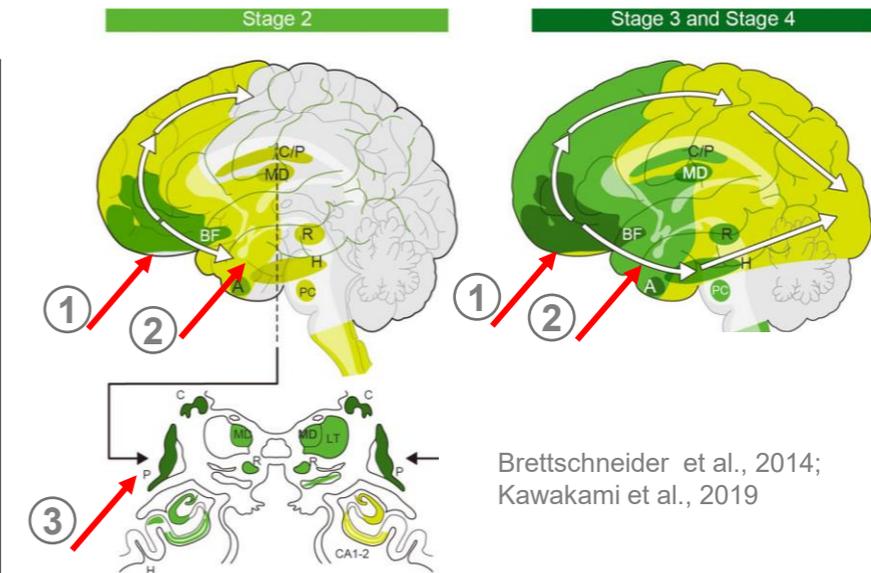
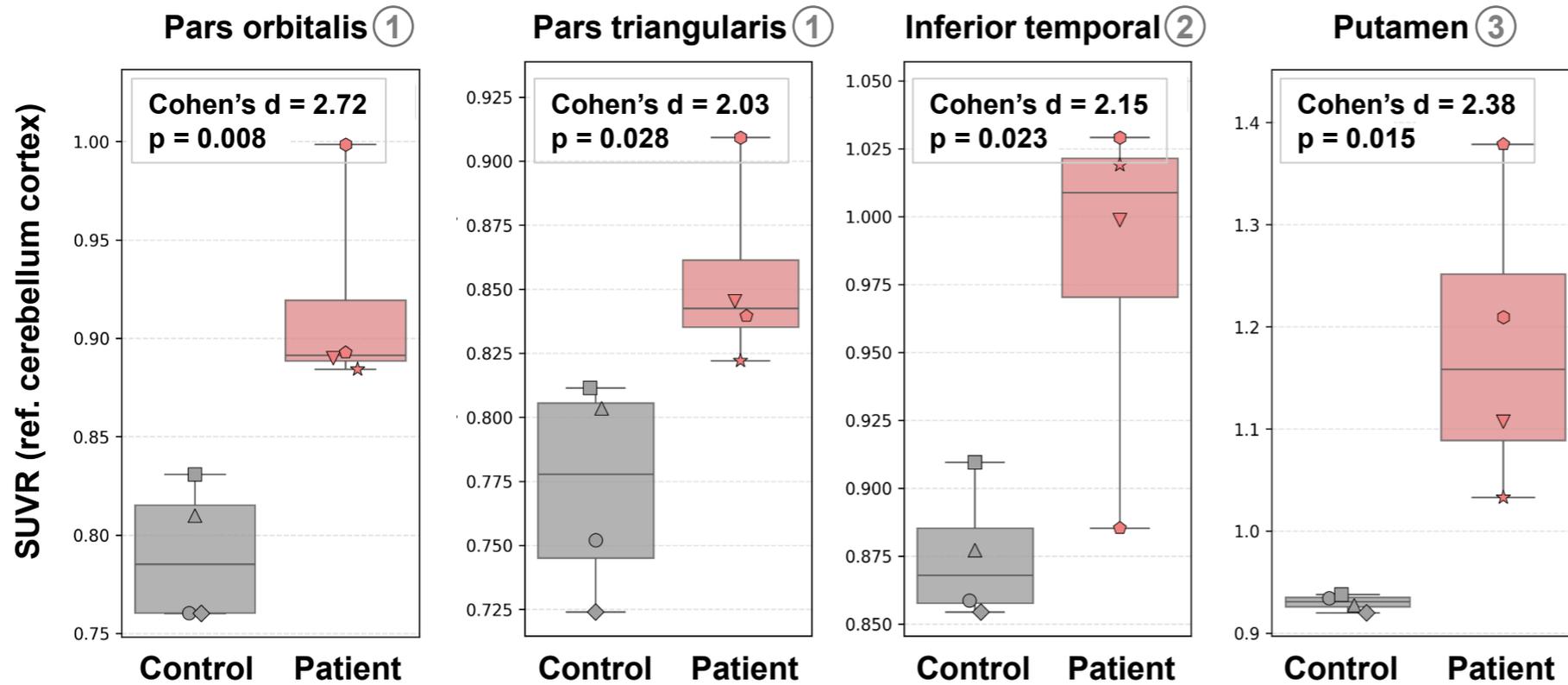


- Preliminary data indicates higher tracer uptake in C9orf72 FTD⁴ patients compared to healthy controls in cortical and subcortical regions where TDP-43 pathology is expected based on *post-mortem* studies

(1) First in human; (2) distribution volume ratio; (3) image-derived input function; (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

[¹⁸F]ACI-19626 FIH¹ study preliminary results: SUVR²

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

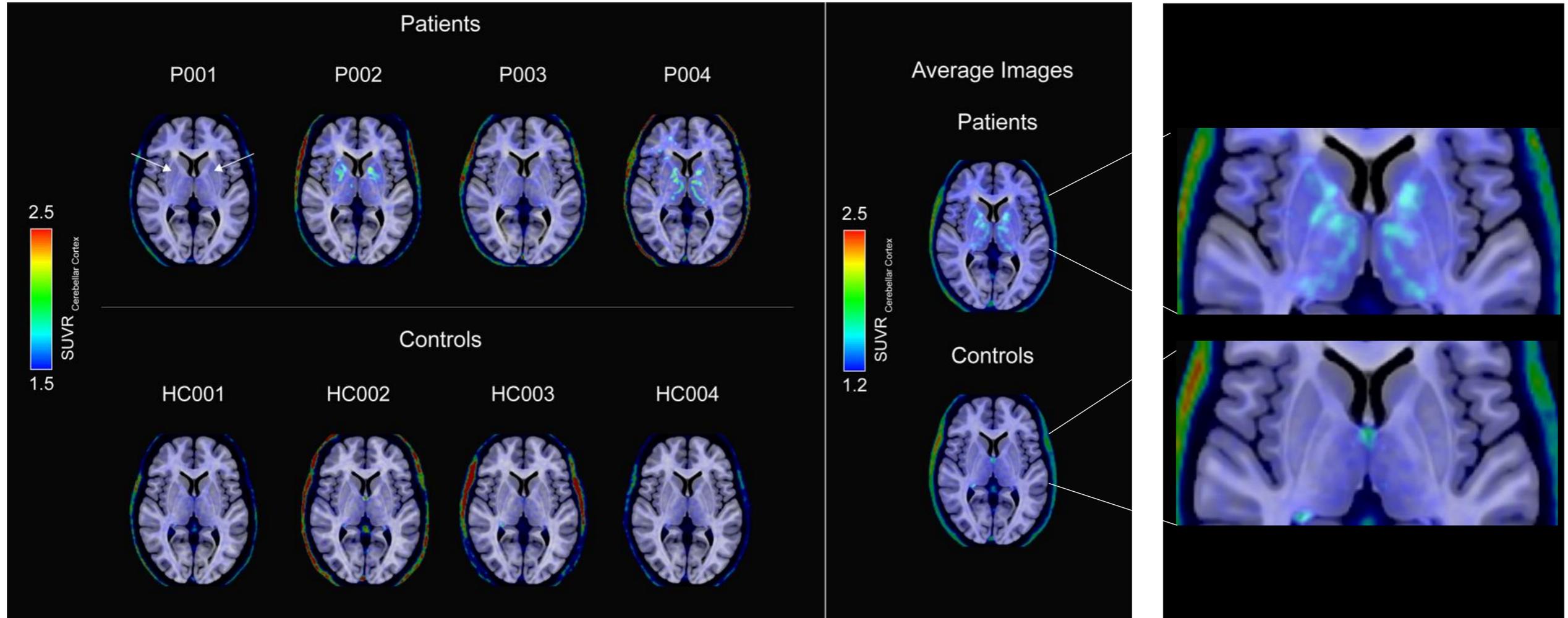


- Preliminary data indicates higher tracer uptake in C9orf72 FTD³ cases compared to healthy controls in subcortical and cortical regions where TDP-43 pathology is expected based on *post-mortem* studies

(1) First in human; (2) standardized uptake volume ratio; (6) frontotemporal dementia; *Post-hoc analysis from a third-party external to the study, for informational purposes only and does not constitute official, finalized data

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

SUVR² analysis, 15-40 min scan, using cerebellum cortex as reference region*



- Preliminary data indicates higher tracer uptake in C9orf72 FTD³ 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

[¹⁸F]ACI-19626 as first-in-class TDP-43 PET¹ tracer

Conclusions

Promising preliminary clinical data

- Preliminary data in healthy volunteers and genetic FTD² subjects suggests higher PET tracer uptake in patients in some relevant brain regions
- Binding data to be confirmed in a larger number of subjects

Clinical development status

- Exploration of ACI-19626 binding in additional patient populations including ALS³ is ongoing
- PET data analysis ongoing to validate reference tissue approaches

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

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