ACI-7104 in VαcSYn Phase 2 - Interim results

NASDAQ: ACIU | December 2025

AC Immune

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AC Immune – pioneering precision prevention of neurodegeneration

Next generation Precision Medicine for neurodegenerative diseases

Focused pipeline with active immunotherapies and intracellular targeted small molecule programs

Key differentiation: Precision Prevention enabled by leadership in targeting toxic proteins

Differentiated technology platforms validated through multiple clinical candidates and pharma partnering deals

Partnering: strategic, risk-mitigating, timely, monetization with >CHF 4.3 billion in potential milestones

Cash reserves on Balance sheet
Funding to the end of Q3 2027

- Based in Lausanne, Switzerland
- ~120 employees
- Listed on NASDAQ: ACIU
- 100.9 million shares outstanding[1]
- Cash resources of CHF 108.5 million[2]

Takeda
Janssen Pharmaceutical Companies of Johnson & Johnson
Lilly
LANTHEUS

(1) As of September 30, 2025; excluding treasury shares; (2) As of September 30, 2025 (~USD 136 million)

Pipeline focused on Precision Prevention for neurodegenerative diseases

Core Value Drivers in Active Immunotherapies and Intracellular Targeting

Modality	Candidate	Partner	Indication	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
Active Immunotherapy	ACI-35.030 (JNJ-2056)	Janssen	Alzheimer's disease (*pTau*[1])			FDA Fast Track		
	ACI-24.060	Takeda	Alzheimer's disease (*Abeta*[2])			FDA Fast Track		
			Alzheimer's disease: Down Syndrome					
	ACI-7104.056		Parkinson's disease (*a-syn*[3])					
Intracellular Targeting	ACI-19764		Neuro-inflammation (*NLRP3* [4])					
	Morphomer Tau	Lilly	Alzheimer's disease (*Tau*)					
	Morphomer® a-syn		Parkinson's disease (*a-syn*)					
Tracer	PI-2620	LANTHEUS	Alzheimer's disease, PSP[5] and others (*Tau*)				FDA Fast Track	

(1) Phosphorylated Tau; (2) amyloid beta; (3) alpha-synuclein; (4) (NOD)-like receptor protein 3; (5) Progressive supranuclear palsy

AC Immune's four core value drivers

Combining biomarker-based clinical development, validated targets and strong collaborations

ACI-35.030 anti-pTau

The only active immunotherapy in a prevention study for pre-symptomatic Alzheimer's disease

ACI-24.060 anti-Abeta

Biomarker-driven development targeting the hallmark protein in Alzheimer's disease and Alzheimer's in Down syndrome

ACI-7104.056 anti-a-syn

Active immunotherapy targeting pathological a-syn in early-stage Parkinson's disease

Intracellular targeting

Small molecule programs targeting intracellular pathologies:

- Tau (Lilly)
- a-syn
- NLRP3 inflammasome

Parkinson’s disease

Pathological deposition of alpha-synuclein

Most common neurodegenerative movement disorder
Affects ~1% of the population over 65 years

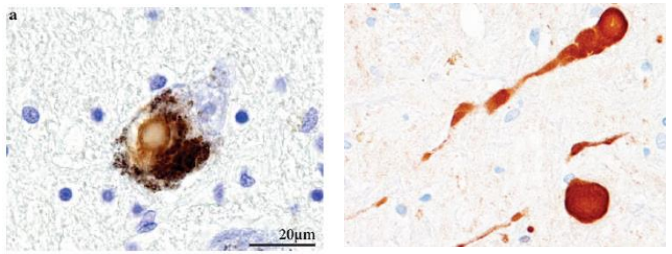
Etiology
5-10% genetic, 90-95% idiopathic, unknown cause

Cardinal motor symptoms
Tremor, rigidity, bradykinesia

Common non-motor symptoms
Sleep disorder, depression, cognitive impairment

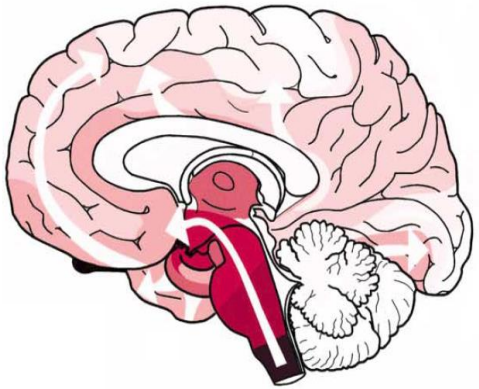
Pathological hallmarks
Neuron loss, alpha-synuclein aggregates – Lewy bodies

Main component of Lewy bodies: Alpha-synuclein



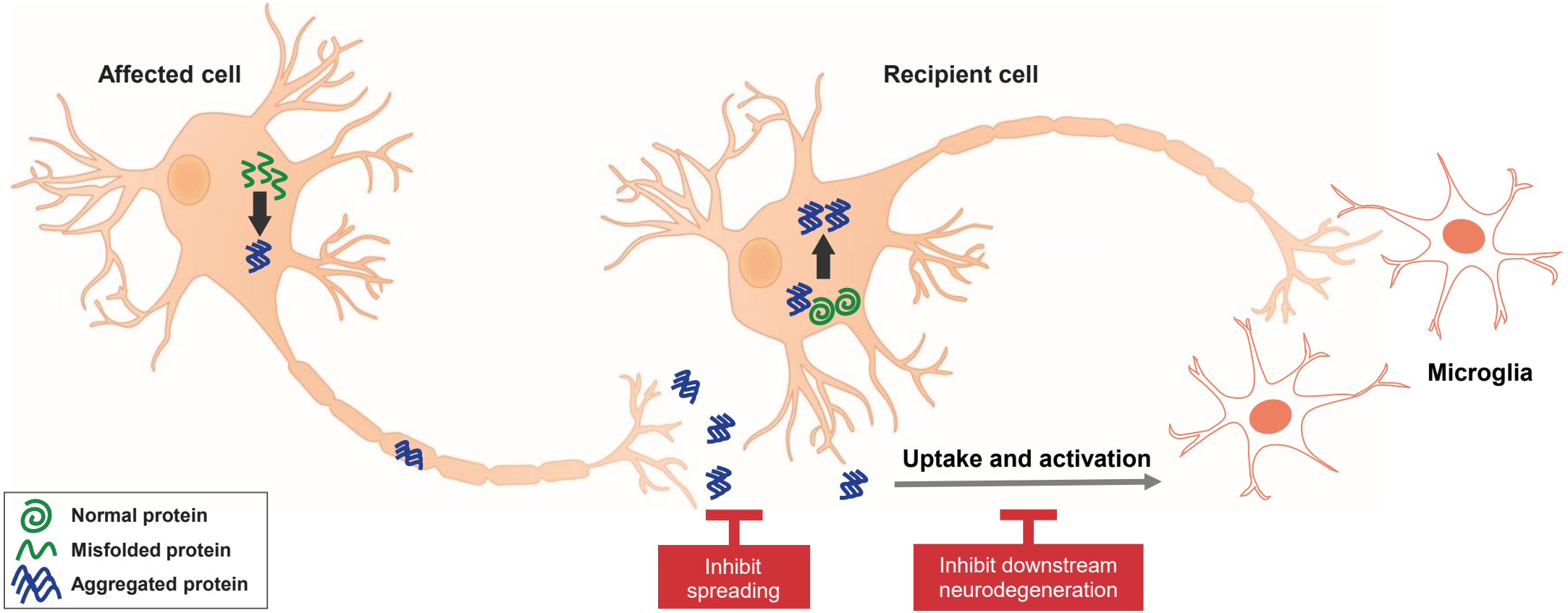
Halliday *et al.* 2011

Progression of pathology



Braak *et al.* 2003

Pathological oligomeric a-syn[1] is causally linked to PD[2] and other NDD[3]



- A-syn misfolding and aggregation are the molecular basis for a-synucleinopathies, e.g. PD, DLB[4] and MSA[5]
- Seeding and spreading of a-syn are potential drivers of disease progression

(1) Alpha-synuclein; (2) Parkinson's disease; (3) Neurodegenerative diseases; (4) Dementia with Lewy bodies; (5) Multiple system atrophy

Immunological potential of ACI-7104

The optimized a-syn peptide-conjugate formulation

ACTIVE Immune Therapy

Generates target-specific antibody response

Safely engages target-unrelated T-cells to enhance & maintain response

Key outcomes

Immunogenicity	✓
Target specificity	✓
Selective for aggregated α-syn	✓
Sustained antibody response	✓
Boosting	✓
Evidence of memory B cells	✓
Preclude activation of T cells specific for α-syn	✓

- ACI-7104 delivers the clinical validated modified a-syn peptide antigen[1] which provided:
  - Robust a-syn immunogenicity with a well tolerated profile in PD patients
  - Long lasting antibody responses supporting a disease prevention approach

(1) Volc et al., Lancet Neurol. 2020;

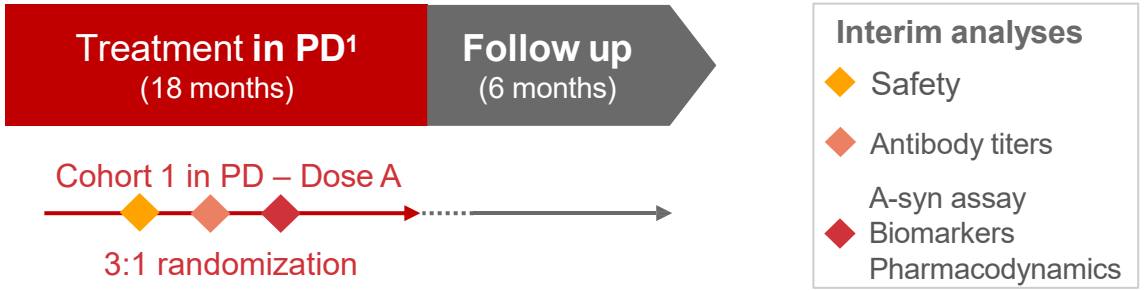
VacSYn: Adaptive biomarker-based Phase 2 study of ACI-7104 in early PD

Placebo-controlled Phase 2 Study Overview (clinicaltrials.gov identifier: NCT06015841)

- Seamless transition
  - All participants from Part 1 will contribute to final analysis
- Biomarker based interim analyses
  - Early immunogenicity to tailor dose and/or dose regimen
  - Apply disease-relevant biomarkers for early transition to filing

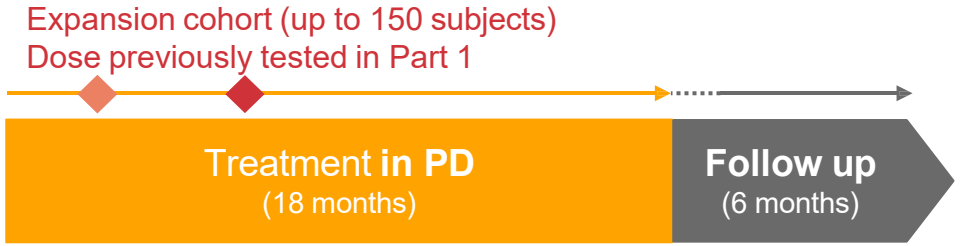
Part 1: Safety & PK/PD

- Key immunogenicity measures
- Measures of pathological a-syn (a-syn oligomers and aggregates)



Part 2: Proof of Concept in Early PD

- Motor and Non-Motor Functioning (UPDRS[2] based)
- Degeneration of dopaminergic terminals (DaT SPECT[3] imaging)
- Advanced MRI (including ASL[4] and DTI[5])
- Digital biomarkers of motor and non-motor function
- Functional and patient reported outcomes



(1) Participants must have idiopathic PD and be stable on up to 300 mg of L-Dopa treatment and dopaminergic deficit determined by Dopamine Transporter Single Photon Emission Computed Tomography; (2) Unified Parkinson's disease rating scale; (3) Dopamine Transporter Single Photon Emission Computed Tomography; (4) Arterial spin labeling; (5) Diffusion tensor imaging

VacSYn an adaptive biomarker-based Phase 2 study of ACI-7104 in early PD[1]

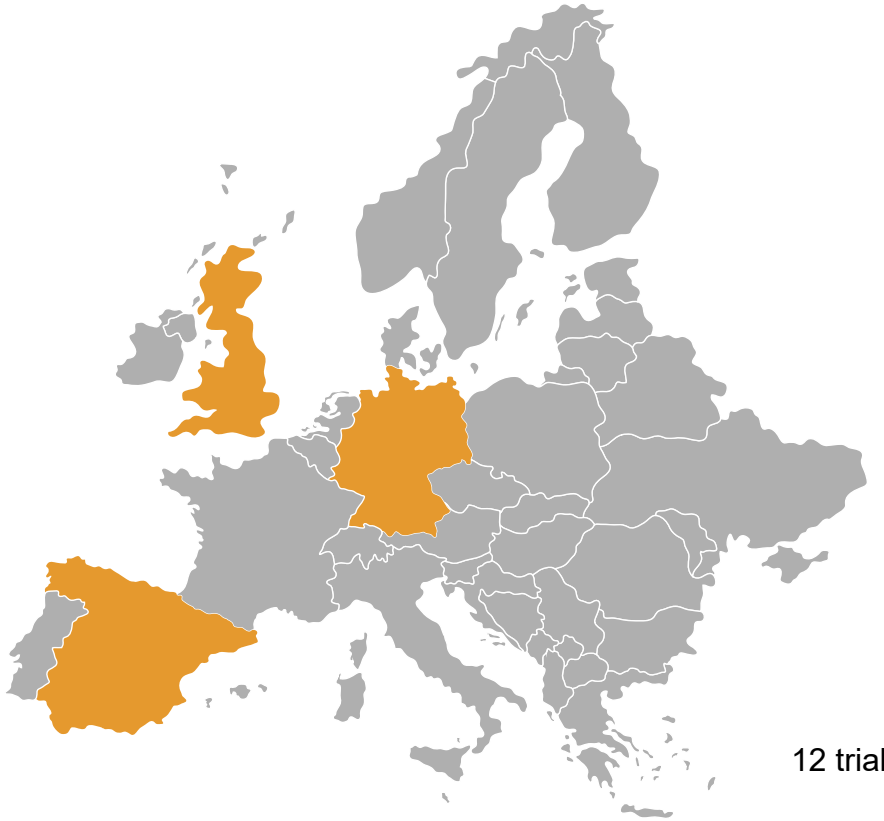
Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Aged ≥40 to ≤75 years
- Diagnosis of clinically established early PD[1] (confirmed by DaT-SPECT[2])
- ≤ 2 years from time of onset motor symptoms
- H&Y[3] Stage I to II
- Monotherapy treatment with L-Dopa[4] at 300 mg per day or treatment naïve

Key Exclusion Criteria

- Carriers of certain familial PD[1] gene mutations
- Parkinsonian syndrome other than idiopathic PD[1]
- Significant CNS[5] disease[6]



12 trial sites

- Total enrolment: 34 patients
- In the following analyses, the number of subjects beyond week 50 are expected to increase as participants reach later timepoints

(1) Parkinson's disease; (2) Dopamine Transporter Single Photon Emission Computed Tomography; (3) Hoehn & Yahr scale; (4) Levodopa; (5) Central Nervous System; (6) Parkinsonian syndrome other than idiopathic PD, including but not limited to, progressive supranuclear palsy, multiple system atrophy, drug induced parkinsonism, essential tremor, vascular parkinsonism, primary dystonia.

VacSYn: Patient baseline characteristics and interim safety/tolerability findings

Placebo-controlled Ph 2 Study: No safety concerns raised by DSMB[1,5]

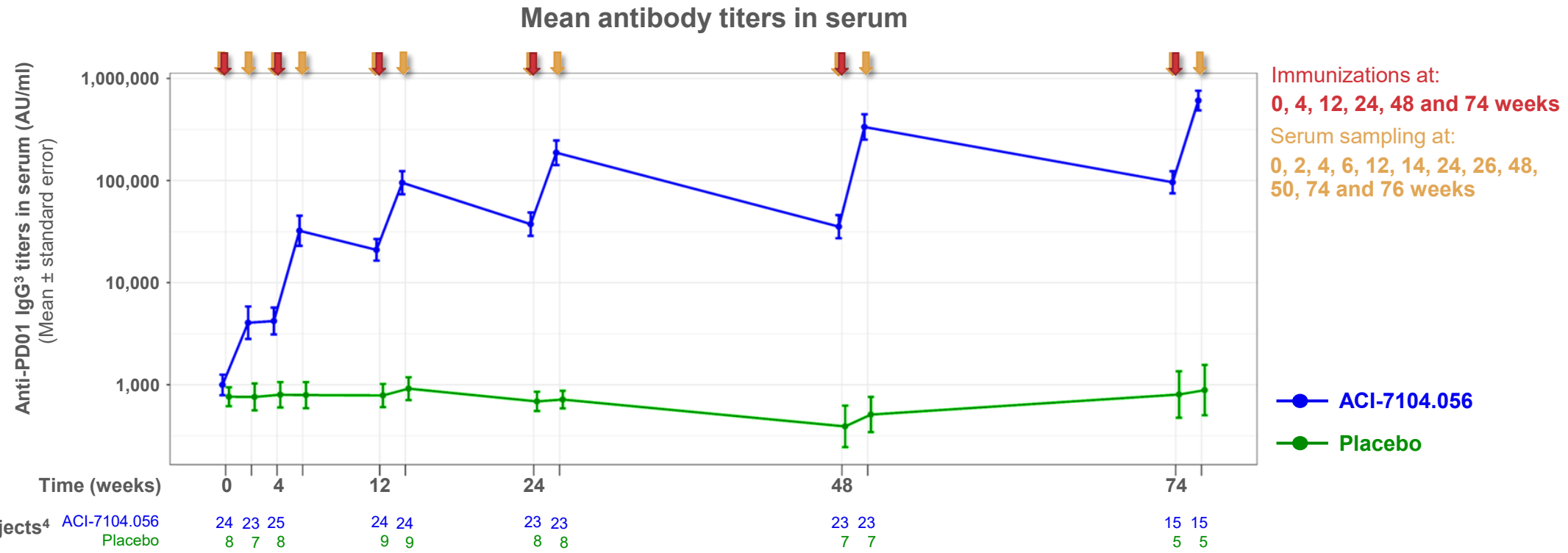
Baseline profile	Unit	Total
Total number of patients	n	34
Age	Years mean (std)	62.1 (6.7)
Sex		
Male	n (%)	22 (65%)
Female	n (%)	12 (35%)
Hoehn and Yahr stage		
Stage I	n (%)	16 (47%)
Stage II	n (%)	18 (53%)
MDS-UPDRS scores		
Part 1: Non-motor experiences of daily living	mean (std)	4.09 (3.1)
Part 2: Non-motor experiences of daily living	mean (std)	4.09 (3.2)
Part 3: Motor examination	mean (std)	21.09 (9.8)
Time since initial PD Diagnosis	Months mean (std)	10.3 (7.5)
PD Treatment		
treatment-naïve	n (%)	11 (32%)
L-Dopa 300mg/day	n (%)	23 (68%)

1. **Overall good safety/tolerability to date**[1]
2. **No SAE**[2] **considered related to the study drug, incl. 1 subject who died during participation in the study (unlikely related to the study drug)**
3. **Two AE leading to discontinuation from the study**[3] **unrelated or unlikely related to study drug**
4. **Most common AEs are transient and generally of mild severity: Injection Site Reactions (55.9%) and headaches (14.7%) and fatigue (11.8%)** [4]
5. **No significant MRI**[6]**, lab, ECG**[7] **abnormalities reported to date**

(1) Data Safety Monitoring Board; (2) Serious Adverse Events: Upper limb fracture, osteoarthritis, perforated appendicitis and intraabdominal sepsis (in the same subject), radical prostatectomy are considered unrelated to study drug, death of unknown cause is considered unlikely related to study drug; (3) One worsening of preexisting generalized anxiety disorder unrelated to study drug and one SAE of death of unknow cause post extraction date; (4) incidence in the pooled active and placebo subjects; (5) Extraction date September 5, 2025; (6) Magnetic Resonance Imaging; (7) Electrocardiogram

ACI-7104 induces robust antibody response in early PD[1]

100% responder rate observed for anti-PD01[2] antibody titers in serum

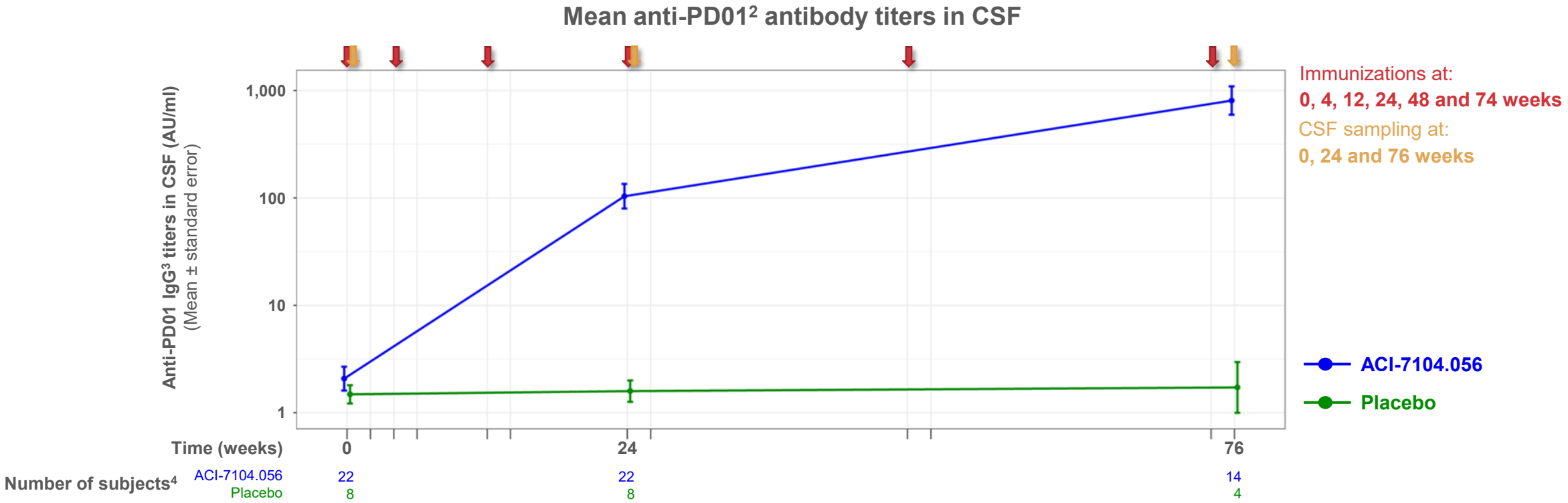


- From week 14 onwards, all participants exhibited anti-PD01 IgG antibodies in serum
- From the 2nd to the 6th immunization, antibody responses were boosted after each dose
- The placebo group did not show any detectable signal

(1) Parkinson's disease; (2) Modified a-syn peptide antigen; (3) Immunoglobulin; (4) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Antibody titers in CSF[1] increase with successive immunizations

ACI-7104.056 generates antibodies against modified a-syn that cross the blood-brain barrier

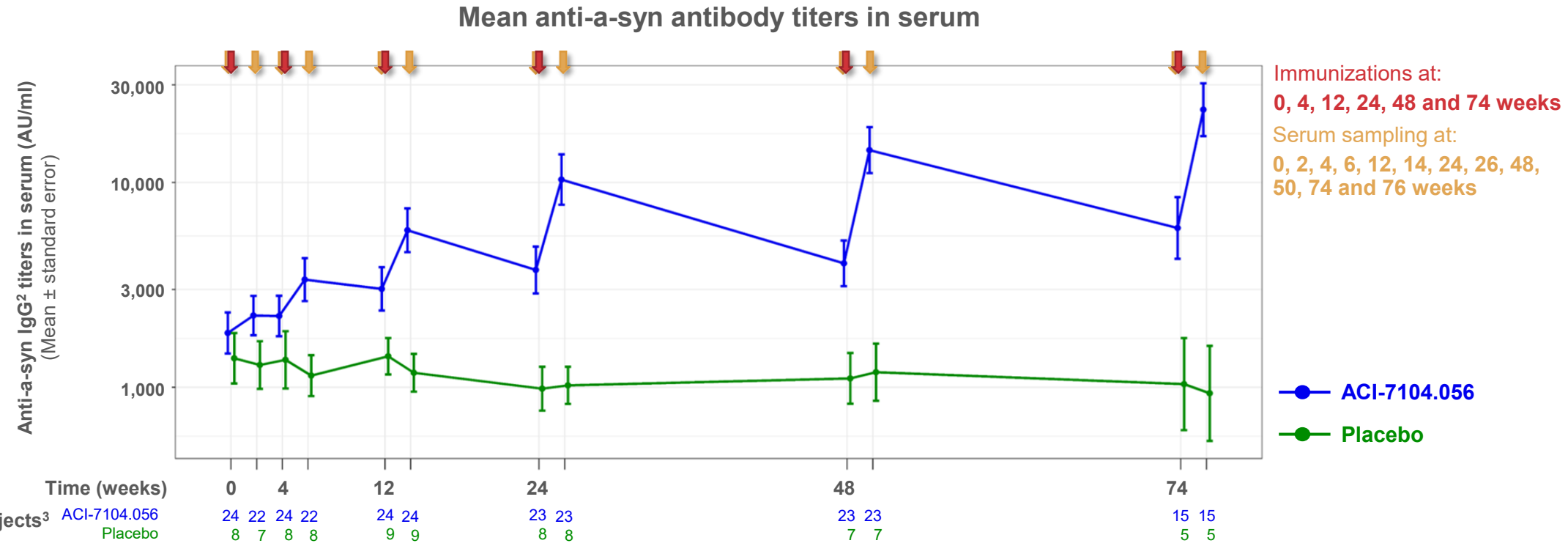


- On average, IgG antibody levels in CSF were an order of magnitude higher after the 6th immunization (week 76) compared to the 3rd immunization (week 24)
- Antibody exposure in the CNS is enhanced with increasing number of doses

(1) Cerebrospinal fluid; (2) Modified a-syn peptide antigen; (3) Immunoglobulin; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Repeated ACI-7104.056 immunizations boost anti-a-syn[1] antibody responses

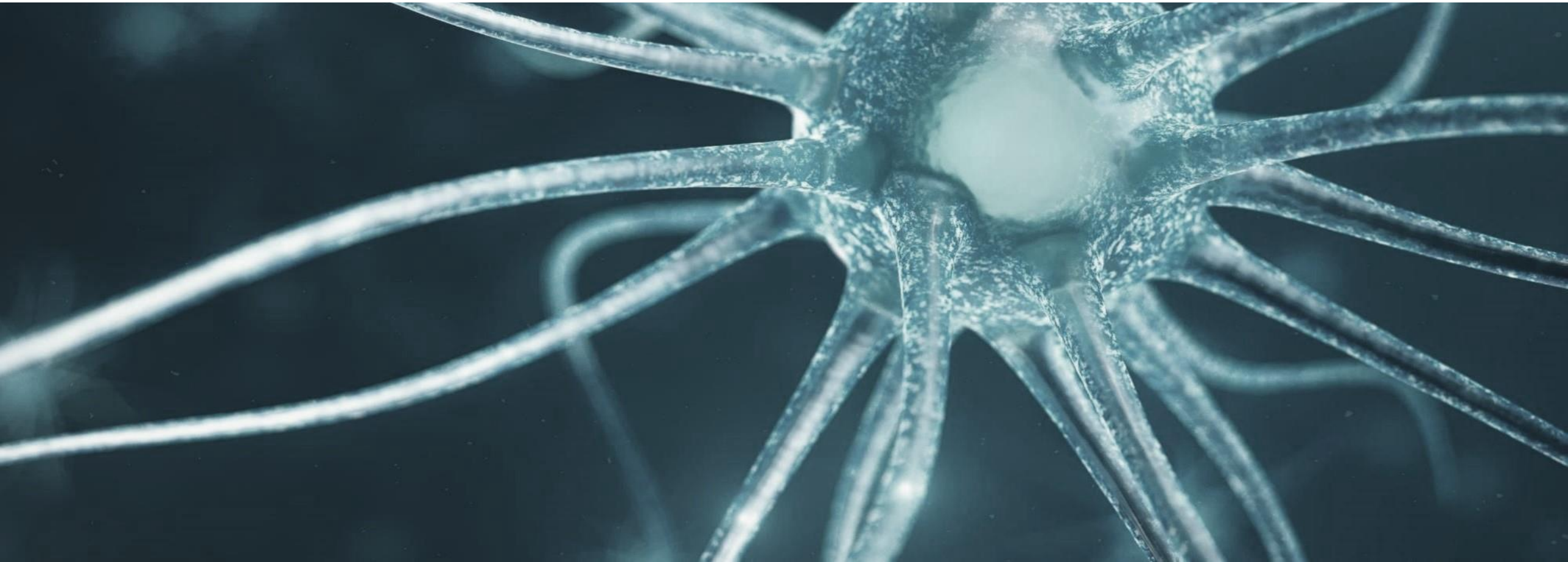
Anti-a-syn antibody titers in serum increase steadily over 76 weeks



- From the 2nd to the 6th immunization, antibody responses were boosted after each dose
- The placebo group did not show any detectable signal

(1) Native alpha-synuclein; (2) Immunoglobulin; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

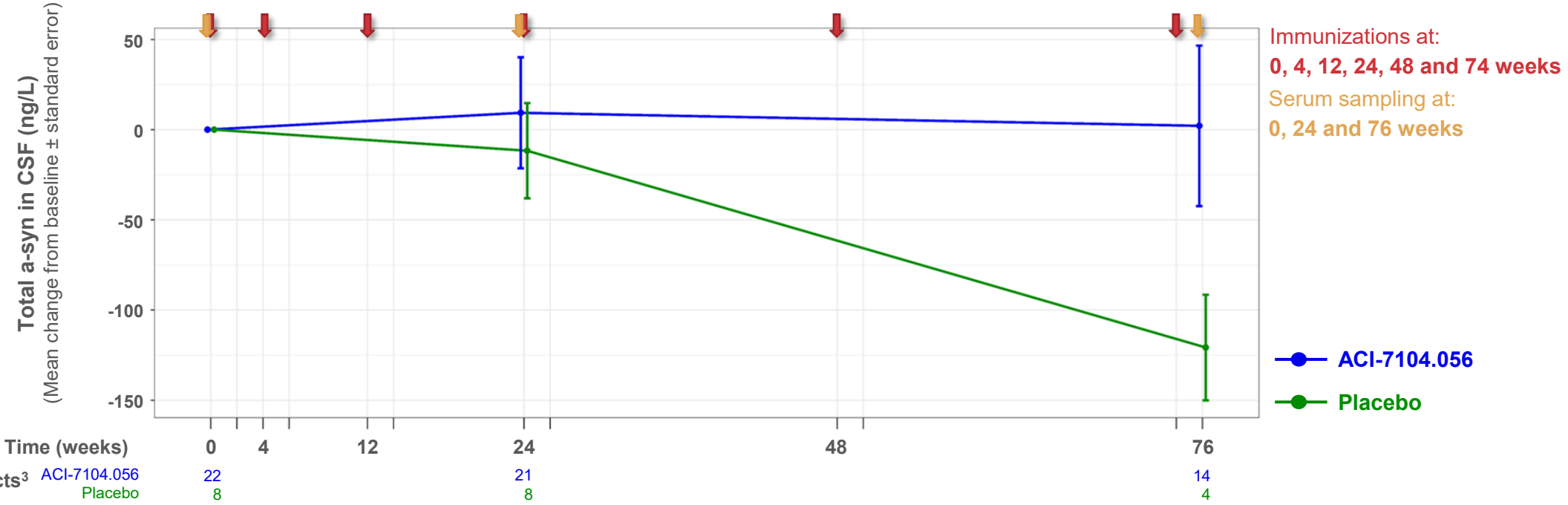
Disease-relevant biomarkers



Immunization with ACI-7104 stabilizes total a-syn[1] levels in CSF[2]

ACI-7104-induced anti-a-syn antibodies demonstrate target engagement in CSF

Total a-syn in CSF[3] (change from baseline)



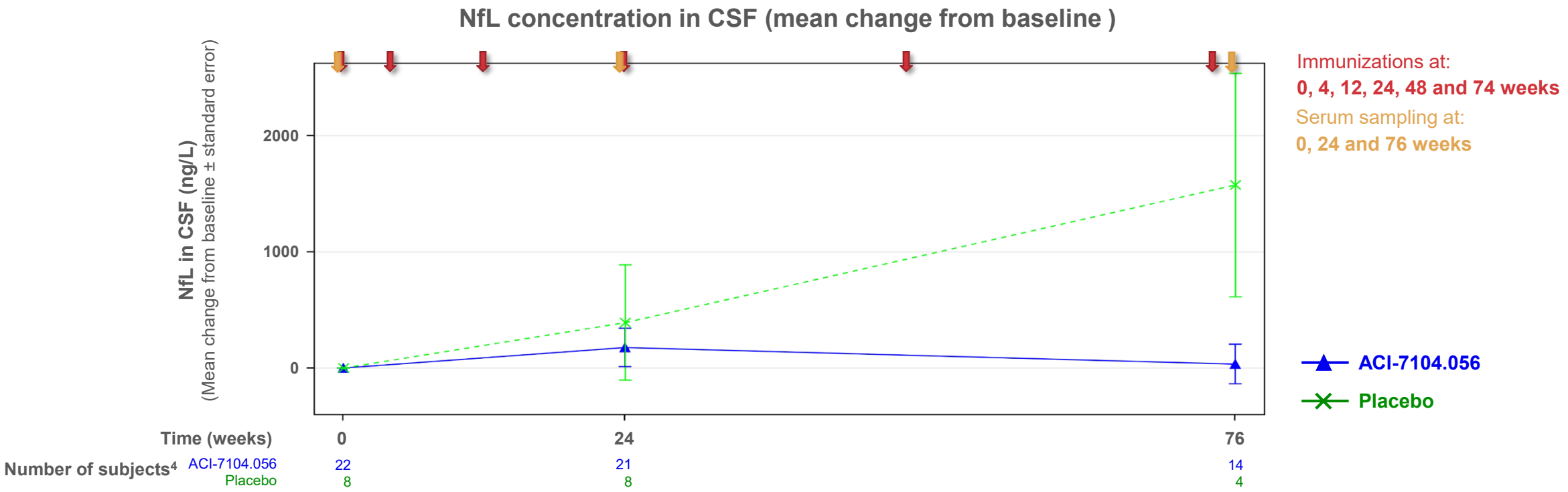
Post-hoc analysis showed a statistically significant difference (p = 0.018, one-sided Welch t-test) at week 76 between active and placebo groups.

- Total CSF a-syn levels in treatment arm suggest stabilization of the target or increased brain clearance
- In the placebo group, a decrease in total CSF a-syn was observed over time

(1) Alpha-synuclein; (2) Cerebrospinal fluid; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints. One patient with very high a-syn levels at only week 24, likely an outlier value, needs further technical investigation and was removed here.

Stabilization of NfL[1] levels suggests potential slowing of neurodegeneration

Neurofilament light chain in CSF[2] remains at baseline levels after treatment with ACI-7104.056

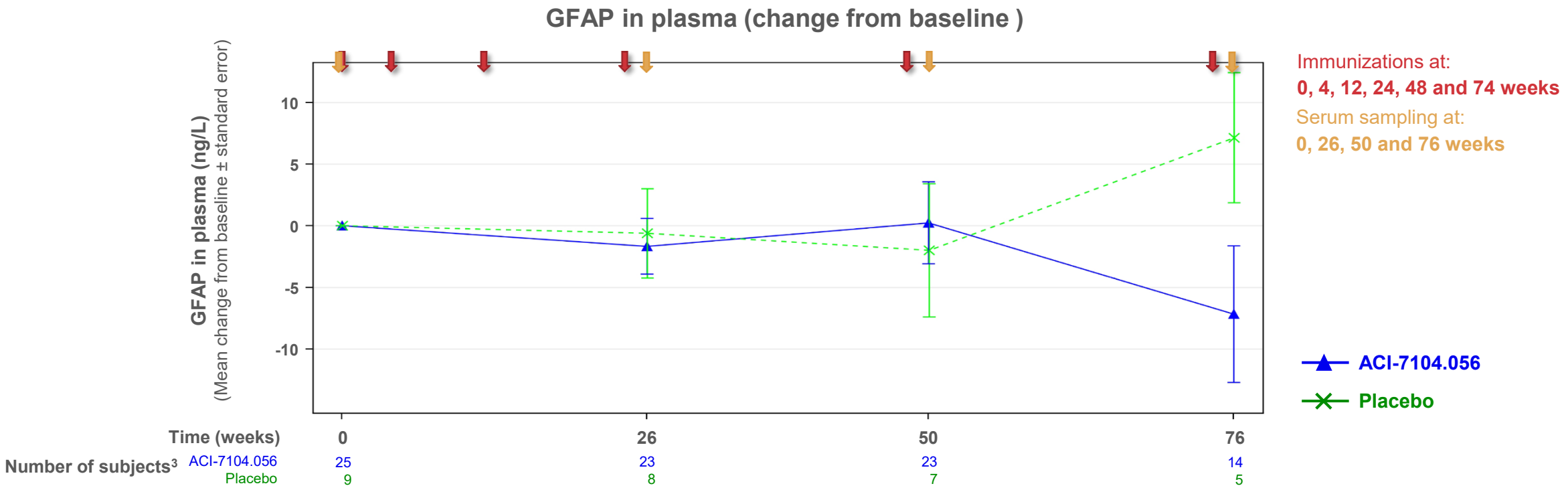


- NfL in CSF remained stable in the ACI-7104.056 group which indicates slowing of disease
- In the placebo group, NfL levels in CSF increase over time, as previously reported in PD[3]

(1) Neurofilament light chain; (2) Cerebrospinal fluid; (3) Parkinson's disease; Mollenhauer *et al.*, Movement Disorders, 2021; (4) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Treatment with ACI-7104.056 might regulate GFAP[1] levels in plasma

GFAP is a biomarker for astrocytic activation, neuroinflammation and neuronal damage

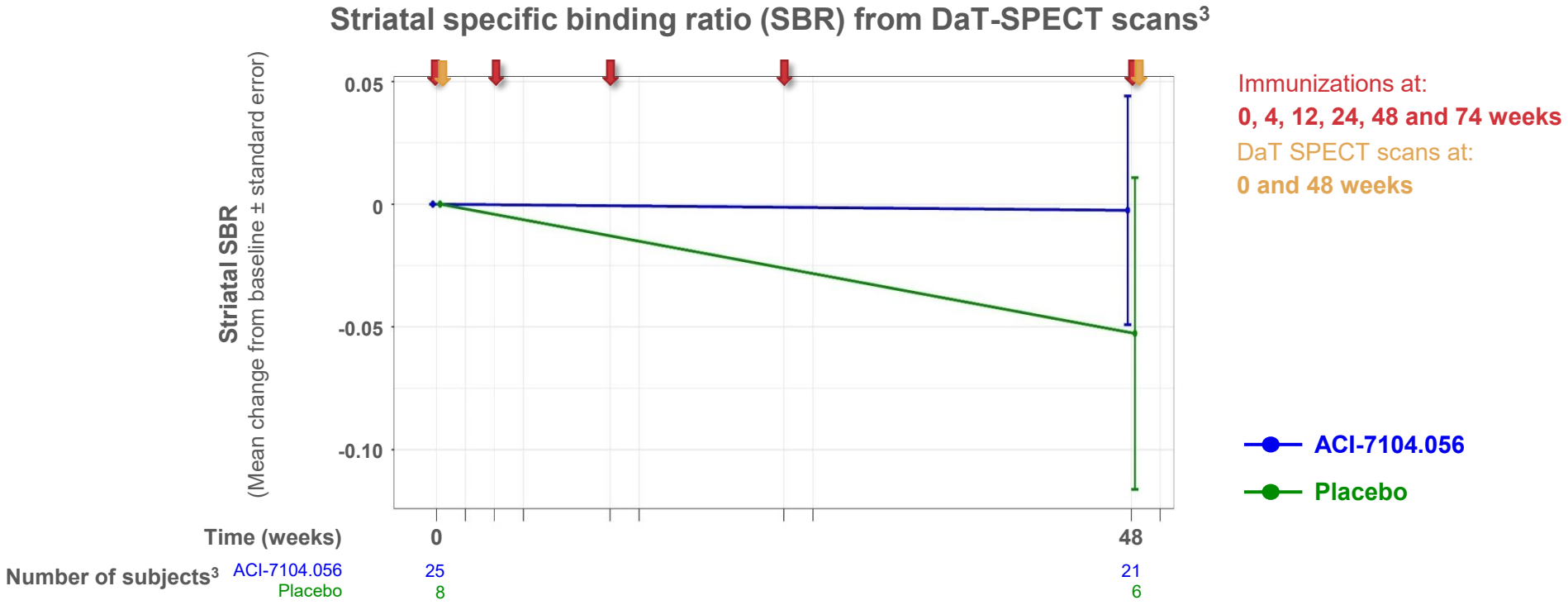


- GFAP plasma levels tend to decrease in the ACI-7104.056 treatment group
- In the placebo group, plasma GFAP was elevated at week 76, as expected in PD[2] patients

(1) Glial fibrillary acidic protein; (2) Parkinson's disease; Lin *et al.*, BMC Medicine, 2023; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Dopamine transporter imaging suggests stabilization of PD[1] pathology

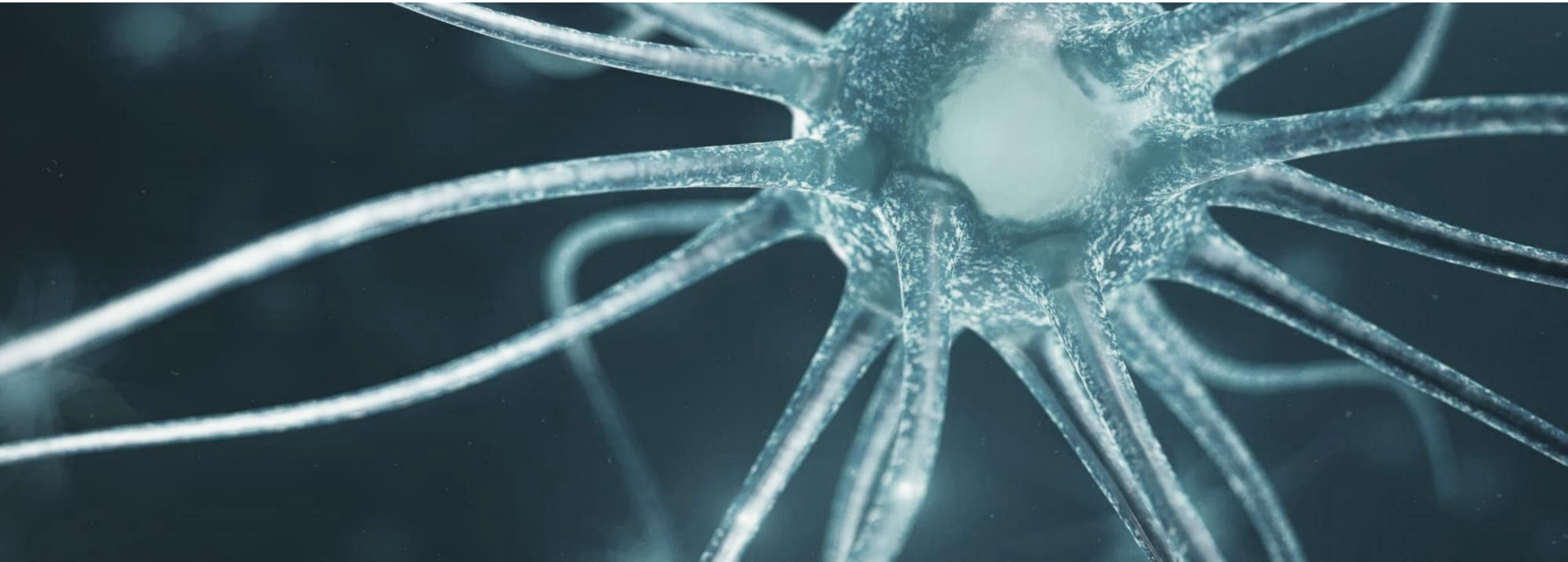
DaT-SPECT[2] scans show trends of slowing degeneration of midbrain dopaminergic neurons



- Lower SBR values in striatum indicate reduced dopaminergic input from the midbrain to the striatum, and are linked to disease progression and motor symptoms
- In the ACI-7104.056 arm, minimal progression after 48 weeks suggests stabilized pathology

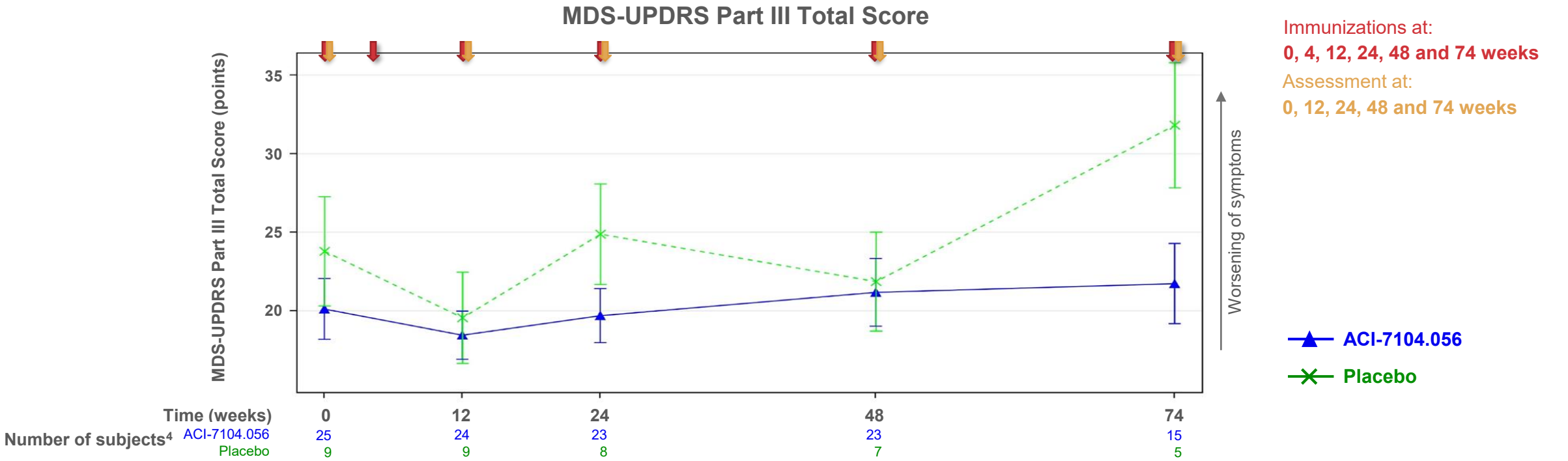
(1) Parkinson's disease; (2) Dopamine transporter single-photon emission computed tomography; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints. One outlier was removed from the placebo group.

Clinical measures



Treatment with ACI-7104.056 limits progression of motor symptoms

MDS-UPDRS[1] Part III examination of motor symptoms suggests faster decline in the placebo group

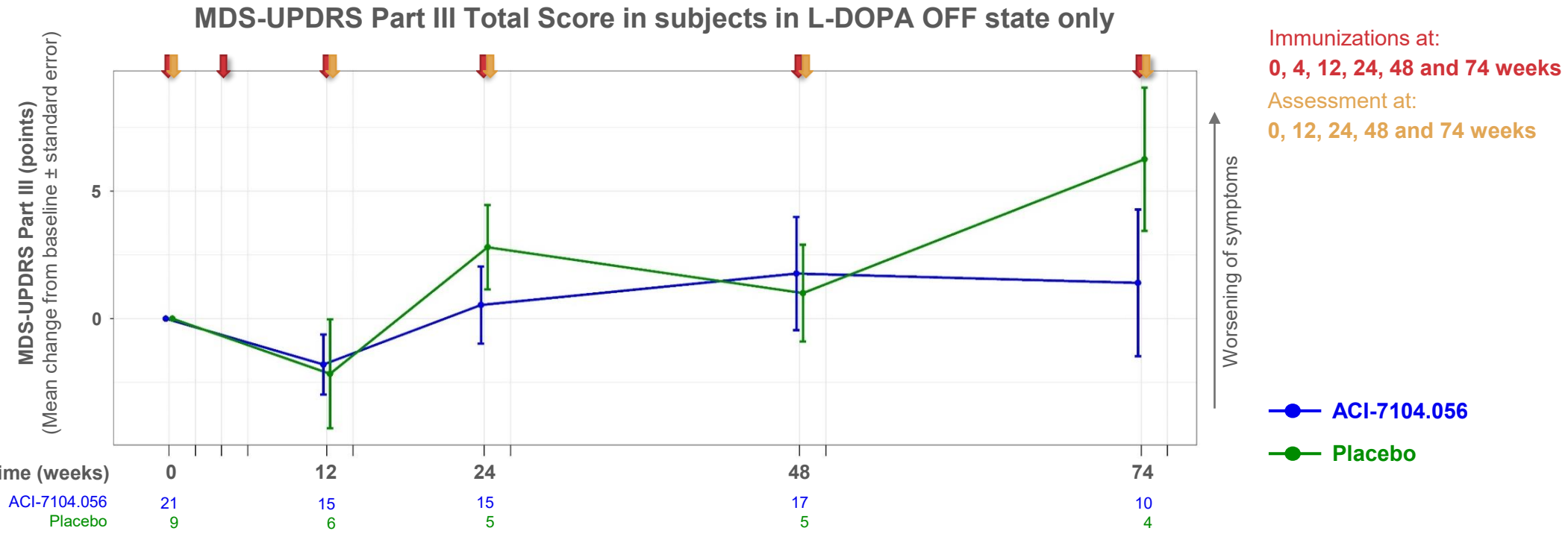


- The MDS-UPDRS Part III score is expected to increase by 2–3 points per year in early PD[2]
- A 5-point-increase is the threshold for meaningful worsening of motor signs[3]
- At week 74, the ACI-7104.056 group did not show signs of meaningful progression, while the placebo arm trends towards an increase in mean MDS-UPDRS Part III total score

(1) Movement Disorder Society - Unified Parkinson's Disease Rating Scale; (2) Parkinson's disease; Holden *et al.*, Movement Disorders, 2018; (3) Trundell *et al.*, J. of Parkinson's disease, 2025; Horvath *et al.*, Parkinsonism and related disorders, 2015; (4) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

MDS-UPDRS[1] Part III suggests slowing of disease after stratifying by L-DOPA[2] state

In the L-DOPA OFF state, Part III total score also points toward slowed decline in the treatment arm



- Individual scores exhibit lower variability after stratification by L-DOPA ON/OFF state
- In the OFF state, the change from baseline at week 74 in MDS-UPDRS Part III total score shows a more pronounced difference between the active treatment and placebo groups

(1) Movement Disorder Society - Unified Parkinson's Disease Rating Scale; (2) Levodopa; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Conclusion 1 – VacSYn Phase 2 Part 1 interim results

Safety / tolerability

- ACI-7104 has demonstrated a favorable benefit/risk ratio, to date
- No clinically relevant and no serious adverse events related to the study drug
- Most common AEs[1] are transient and generally of mild severity: Injection site reactions and headaches and fatigue

(1) Adverse events

Conclusion 2 – VacSYn Phase 2 Part 1 interim results

Immunogenicity

- 100% responder rate observed for antibodies against the modified a-syn[1] target antigen
- Antibody levels in CSF[2] correlated strongly with levels in serum
- Anti-a-syn antibody levels were boostable and increased up to week 76

(1) Alpha-synuclein; (2) Cerebrospinal fluid

Conclusion 3 – VacSYn Phase 2 Part 1 interim results

Biomarkers

- Stabilization of a-syn[1] in CSF[2] demonstrates target engagement in the CNS[3]
- Total a-syn and NfL[4] in CSF suggest slowing of Parkinson's disease pathology
- Plasma GFAP[5] and Dat-SPECT[6] imaging show trends of disease stabilization

Clinical measures

- ACI-7104-treated subjects showed trend to slowing of disease progression:
  - MDS-UPDRS[7] Part III total score is suggestive of trend for stabilization
  - Stratification by L-DOPA[8] ON/OFF states further enhanced the difference

(1) Alpha-synuclein; (2) Cerebrospinal fluid; (3) Central nervous system; (4) Neurofilament light chain; (5) Glial fibrillary acidic protein; (6) Dopamine transporter single-photon emission computed tomography; (7) Movement Disorder Society - Unified Parkinson's Disease Rating Scale; (8) Levodopa

Summary – next steps

ACI-7104.056 to advance

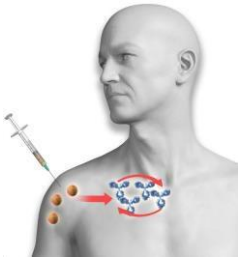
- ACI-7104 stabilized disease-relevant biomarkers and clinical measures
- Suggests potential for meaningful clinical benefit to early-stage Parkinson's Disease patients
- Results support further development of the program and discussion of clinical development plan towards registration with Regulators

ACTIVE Immune Therapy

targeting neurodegenerative diseases

Major advantages

- Long-lasting specific immunity for pathological target, consistent, boostable
- Limited annual dosing (once or twice) after priming year
- Safety profile well suited to long-term use
- Ease of administration and simple logistics for global access
- Cost-effective (attractive healthcare economics across global populations)

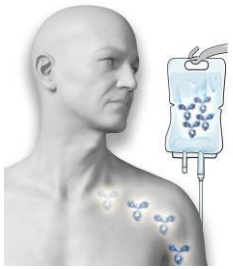


Active immunotherapy

Stimulates the patient's immune system to produce their own polyclonal antibodies

Passive immunotherapy

Externally generated monoclonal antibody requires administration every two to four weeks



Pioneering Precision Prevention

Shifting the treatment paradigm for neurodegenerative disease towards precision medicine and disease prevention

We want to thank the study participants, their families for their participation and commitment, as well as all Investigators and Site personnel for their active participation and support.

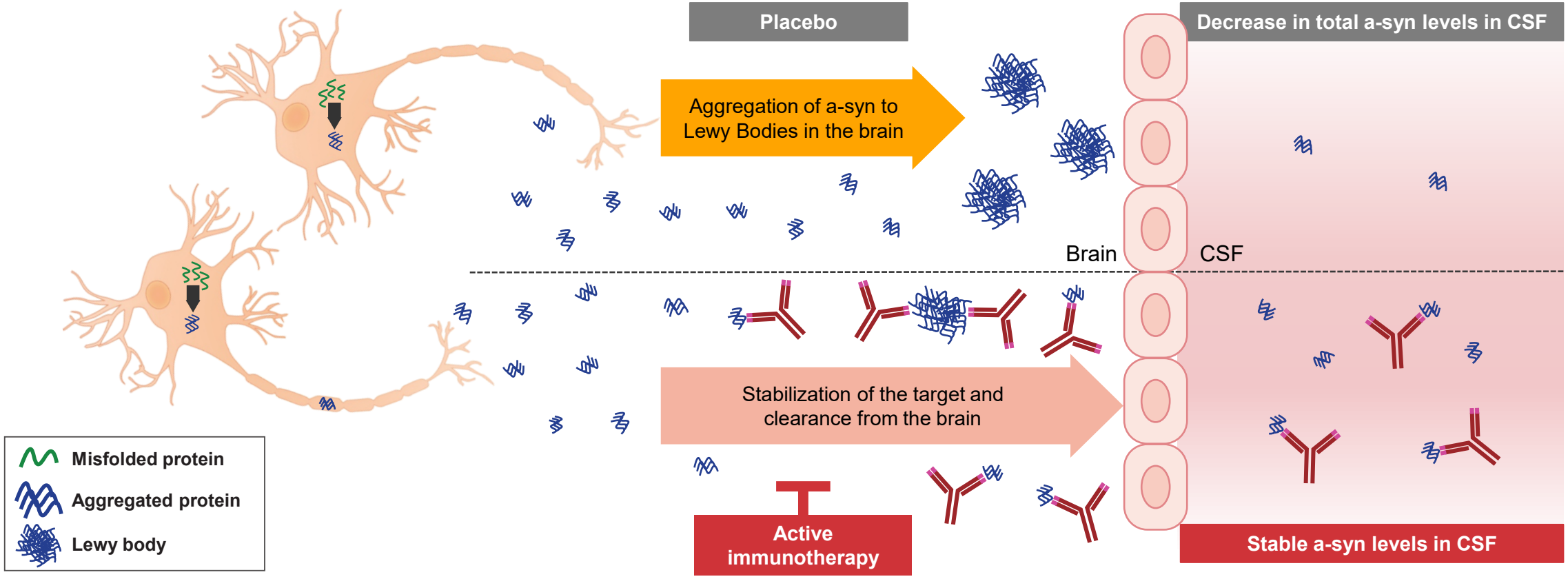
AC Immune

Comment: Prof Werner Poewe

AC Immune

Q&A

Target engagement and brain clearance during active immunotherapy



- Active immunotherapy keeps CSF[1] a-syn[2] levels stable by pulling toxic protein out of brain aggregates
- Placebo shows an expected drop in CSF a-syn as oligomeric a-syn is trapped in Lewy bodies in the brain

(1) Cerebrospinal fluid; (2) Alpha-synuclein