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Treating Neuroinflammation, Treating Disease

A Randomized, Double-Masked, Placebo-Controlled Phase 2a Study of the Safety, Tolerability, and Pharmacokinetics of NTRX-07, a Selective CB2 Receptor Agonist, in Mild Cognitive Impairment and Mild-to-Moderate Alzheimer's Disease

J. F. Foss[1,2], M. Kiraly[1], T. Giordano[1], N. Osman[4], P. Kovács[3], G. Csukly[3]

[1]NeuroTherapia, Inc., Gates Mills / Cleveland, OH USA · [2]Cleveland Clinic, Cleveland, OH USA · [3]CRU Global. · [4]Osman Clinical Pathways, NV USA

AAIC 2026 · London
Phase 2a | NTRX-07-C201
EU CT: 2024-517957-29
NCT07058688
joseph.foss@neurotherapia.com
www.neurotherapia.com

Background — Microglial Network

NTRX-07 (formerly MDA7) is an oral, brain-penetrant, **selective CB2 receptor agonist** (>100-fold CB2/CB1) without CB1 psychoactivity; CB2 is upregulated on activated **microglia** at sites of AD pathology.

In the **pathological network model**, Aβ, tau, and neuroinflammation form a self-amplifying circuit in which chronically dysregulated microglia act as the **central amplifier** of neurodegeneration, only partly explained by amyloid burden. NTRX-07 engages this **microglial node**, redirecting microglia from disease-associated toward homeostatic, phagocytic states:

CB2 agonism › Microglia → homeostatic › ↓ TLR4 / NF-κB MyD88 › ↓ Neuro-inflammation › ↑ Aβ clearance & synaptic plasticity

Preclinical (APP/PS1): reduced microglial activation, enhanced Aβ clearance, restored LTP, improved learning/memory.[1]

Phase 1a/1b: safe to 90 mg/day active moiety; main effect mild transient orthostatic BP change.[2]

Objectives & Endpoints

- **Primary —** Safety & tolerability: TEAEs, vitals, clinical labs, 12-lead ECG over 28 days.
- **Secondary —** Pharmacokinetics: Cmax, AUC of NTRX-07.
- **Exploratory —** MMSE-2, ADAS-Cog, ADCS-ADL, CBI, TMT.

-CSF biomarkers (Aβ40/42, Aβ42/40, NfL, GFAP, pTau, IL-8).

-Free-water / CDM diffusion MRI; qEEG & P300 ERP.

Methods

Design. Randomized, double-masked, placebo-controlled Phase 2a; 28 days once-daily oral dosing + post-treatment follow-up; 6 European sites (Hungary, Poland, Czech Republic).

Population. Adults 66–80 y with MCI or mild-to-moderate AD and typical age-related comorbidities.

Dosing. 90 mg/day NTRX-07 (NTRX-07-SDD) or matching placebo once daily.

Analysis. Descriptive safety; non-compartmental PK; exploratory within-subject change-from-baseline for efficacy, biomarker & imaging endpoints.

Study Schematic

Screening Day −30 to −2 › Once-daily dosing 28 days › Follow-up ~Day 35

PK sampling Day 1, 14 & 28. CSF/plasma biomarkers, free-water/CDM MRI, and qEEG/P300 at baseline and Week 4. Safety (AEs, vitals, labs, ECG) collected throughout.

Subject Disposition

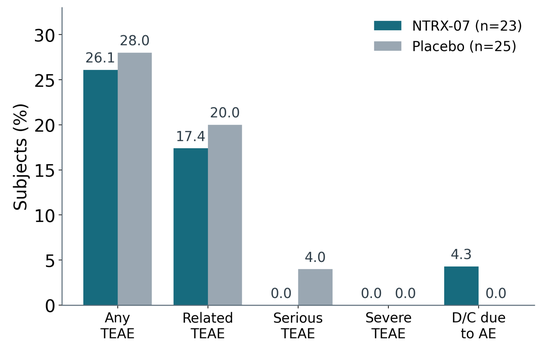
94	Screened	
	48	Randomized
Treated	48	23 NTRX-07 25 placebo
	47	Completed Day 28
	1	Early termination (AE-related)

Baseline Characteristics

Parameter	NTRX-07 (n=23)	Placebo (n=25)
Age, mean (SD), y	73.3 (3.9)	74.1 (4.1)
Female, n (%)	16 (69.6)	19 (76.0)
MMSE-2, mean	21.1	20.8
ADAS-Cog, mean	19.7	24.4

Arms well balanced on MRI, MMSE & demographics; placebo had higher baseline ADAS-Cog burden

Primary Endpoint — Safety & Tolerability



Comparable overall tolerability: any TEAE 26.1% (NTRX-07) vs 28.0% (placebo); related 17.4% vs 20.0%.

No severe TEAEs in either arm; the only serious TEAE (pneumonia) occurred on placebo and was unrelated.

Active-arm pattern: mild autonomic/orthostatic events plus GI events (nausea, vomiting; probably related, one subject).

Placebo pattern: more heterogeneous intercurrent events (anaemia, infections, fracture), incl. the only SAE.

One active-arm discontinuation for mild, probably-related nausea/vomiting.

Other Safety Assessments

No clinically meaningful changes were observed in either treatment arm across routine safety domains:

Hematology · Chemistry · Urinalysis No signal	**Vital signs** No signal
12-lead ECG No signal	**Physical examination** No signal

Consistent with the overall benign tolerability profile of NTRX-07.

Adverse Event of Special Interest

Orthostatic hypotension / autonomic signal

1 / 23	1 / 25	1 vs 0
NTRX-07 4.3%	Placebo 4.0%	Related active only

No count imbalance for the AESI itself.

The single active-arm case occurred on the first dose, was mild, non-serious, and resolved the same day (relationship: possible); it clustered with sinus bradycardia and a positive orthostatic test in the same subject.

Interpretation: clinically manageable, monitorable autonomic/orthostatic tolerability pattern rather than a frequency signal.

Secondary Endpoint — Pharmacokinetics

28-day repeat once-daily dosing · N=21

146	1.0	392
Cmax ng/mL · mean	Tmax h · median	$AUC_{0–10h}$ ng·h/mL · mean

Parameter	Median (IQR)	Mean
Cmax (ng/mL)	139 (86–166)	146
Tmax (h)	1.0 (0.5–3.0)	~1.0
$AUC_{0–10h}$ (ng·h/mL)	343 (210–481)	392

Secondary PK objective met. Rapid absorption (median Tmax ~1 h) with measurable peak and total exposure.

Trough and early post-dose (1.5 h) concentrations were broadly stable from Day 14 to Day 28.

Reproducible once-daily exposure over 28 days → supports dose selection for Phase 2b.

Exploratory Endpoints: cognition, function, CSF biomarkers, diffusion MRI, and qEEG/P300 were prespecified hypothesis-generating endpoints without formal efficacy powering.

Exploratory — Cognition & Function

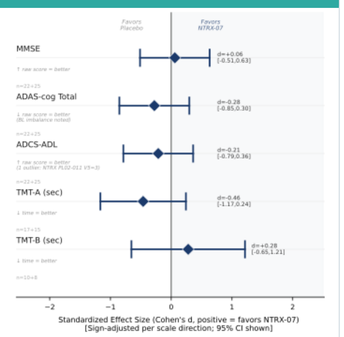
MMSE-2 Stable in both arms (Δ +0.3 active vs +0.1 placebo).

ADAS-Cog Broadly stable; placebo entered worse (24.4 vs 19.7)

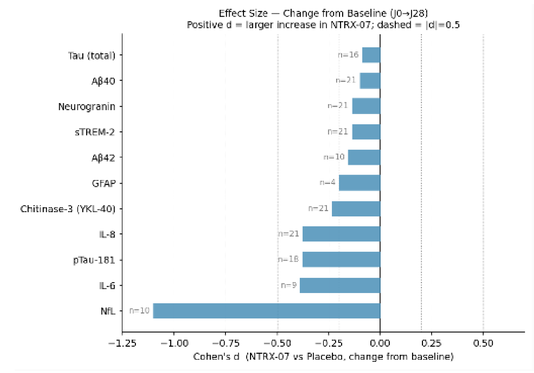
ADCS-ADL Transient active improvement (Days 7–21), not sustained at Day 28.

TMT No consistent change

Exploratory endpoints; no powered efficacy claim.



Exploratory — CSF Biomarkers



Paired CSF subset: 15 NTRX-07 / 17 placebo (descriptive).

Directionally favorable (active): Changes from baseline were systematically lower in the NTRX-07 group relative to the Placebo group.

Caveats: small subset, baseline imbalance (higher placebo burden) → hypothesis-supporting, not confirmatory.

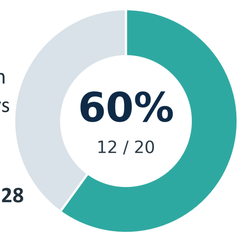
Exploratory — MRI (Cortical Disarray, CDM)

CDM AngleR (diffusion-MRI cortical microstructure) relates to neuroinflammation — CSF sTREM2/PGRN and plasma GFAP.[3]

NTRX-07 showed greater reduction (improvement) in cortical AngleR vs placebo.

12 / 20 active cases were AngleR responders (reduced AngleR over 28 days).

Reductions in AngleR are consistent with reduced cortical microstructural disarray potentially linked to decreased neuroinflammatory burden.



Exploratory; supports the neuroinflammation hypothesis.

Exploratory — EEG (qEEG & P300)

- No robust procognitive signal in resting qEEG or P300 ERP over 28 days.
- Most notable observation: a distinct favorable Alpha1 (~10 Hz) effect.
- Probable baseline neurophysiologic imbalance between arms; P300 evidence was weak/noisy.
- Considered methodologically exploratory and signal-generating rather than decision-grade.

EEG may reflect disease-biology differences not captured by routine baseline summaries — a candidate for deeper follow-up in future studies.

Conclusions

1. NTRX-07 90 mg/day for 28 days in MCI/mild-to-moderate AD was well tolerated — overall TEAE burden comparable to placebo, no severe TEAEs, and the only SAE (pneumonia) on placebo and unrelated.
2. The principal active-arm finding was a mild, monitorable autonomic/orthostatic pattern; one active subject discontinued for mild, probably-related nausea/vomiting.
3. The secondary PK objective was met: rapid absorption, measurable exposure and stable Day 14→28 levels, supporting reproducible once-daily exposure and dose selection.
4. Exploratory **CSF biomarkers, and CDM-MRI signals were directionally supportive** / hypothesis-generating, limited by small n, 28-day duration, and baseline imbalance.
5. **Taken together, the tolerability, PK, and directional biomarker/imaging findings support advancement to a larger, longer Phase 2b program (NTRX-07-C202).**

Acknowledgments, Disclosures, Funding & References

Acknowledgments. We thank the patients and their families for their participation. We also thank the investigators: Prof. Jakub Hort, MD, PhD at Motol University Hospital, Prague; Katerina Sheardova, MD, PhD at Neuro Health Centrum, Brno; Prof. Agnieszka Slowik at University Hospital in Kraków; Dr. Marzena Zboch MD, Alzheimer Center, Wroclaw; Prof. Dr. Anita Kamondi MD, PhD, DSc at the National Institute for Neurology and Neurosurgery, Budapest; and Prof. Dr. János Réthelyi at Semmelweis University, Department of Psychiatry, Budapest.

Disclosures. Authors are employees/consultants of NeuroTherapia, Inc. and may hold stock or stock options.

Funding. Sponsored by NeuroTherapia, Inc. With support from the Alzheimer's Association Part the Cloud fund (Grant # PTC-24-1267901).

References. 1. Wu J, et al. Eur J Pharmacol 2017;811:12–20. 2. Foss J, et al. Alzheimers Dement 2020. 3. Torso M, et al. J Prev Alzheimers Dis 2022 (CDM/AngleR). 4. Ridgway G, et al. CTAD 2024.

Note. *Preliminary topline data; final CSR pending. Exploratory endpoints are hypothesis-generating.*