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Background

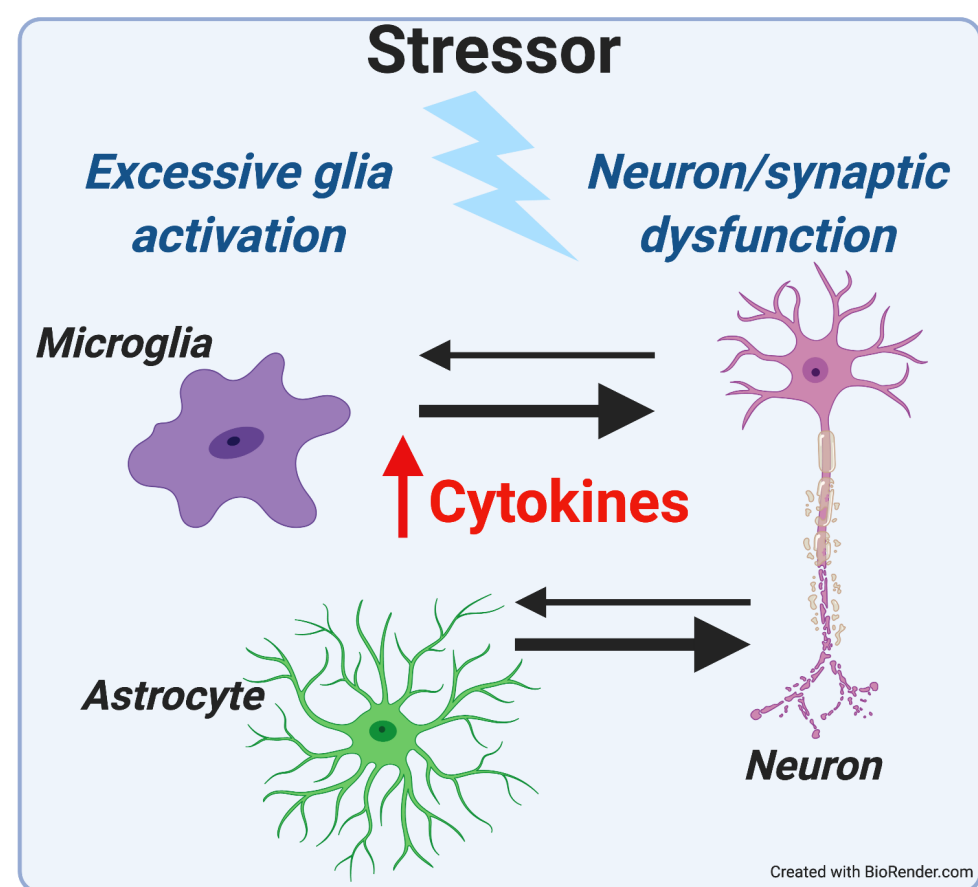
Dysregulated proinflammatory cytokine production from activated glia contributes to CNS disease progression and susceptibility. We developed a small molecule drug candidate [MW01-6-189WH (aka MW189)] as a selective CNS-penetrant suppressor of stressor-induced proinflammatory cytokine dysregulation linked to synaptic and cognitive impairment in animal models of progressive and acute onset CNS disorders [1,2].

MW189 was developed using the classic functional/phenotypic approach that screened for novel CNS-penetrant compounds with drug-like properties. Compounds were prioritized for ability to restore dysregulated neuro-inflammatory pathways back toward homeostasis without suppressing basal physiological cytokine levels and without having immunosuppressive or non-selective anti-inflammatory action. Like many approved drugs and ones used daily in health care, MW189 does not have a consensus molecular target. We know, however, that it is not binding any of the standard protein kinase or GPCR targets based on large-scale screens for kinase inhibitors and GPCR agonist/antagonists [3,4].

MW189 was successfully subjected to three phase 1 clinical studies of safety, tolerability, pharmacokinetics and pharmacodynamic endpoint engagement [3]. Intravenously administered MW189 for short term treatment of intracerebral hemorrhage is in progress (NCT05020535), with a strong safety profile to date [5,6].

Therefore, our goal is to reposition MW189 from acute care with short term treatment via intravenous administration to repeat oral administration over an extended time to Alzheimer's disease patients.

The therapeutic rationale is that restoring cytokine balance will support synaptic function and memory performance, directly addressing the glial neuroinflammation–neuronal synaptic function axis, a key driver of homeostasis and disease pathogenesis.



References

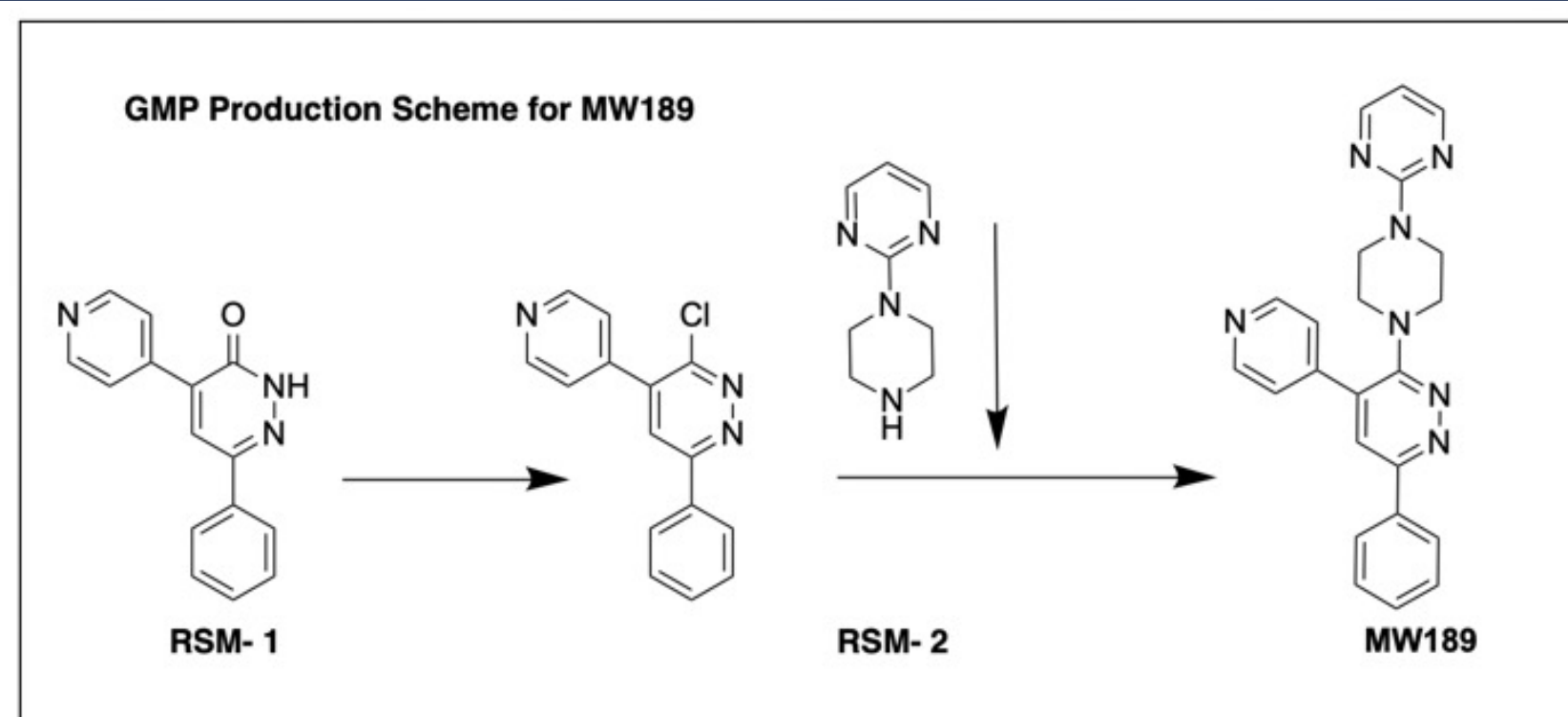
- [1] Hu W, et al. (2007) Bioorg Med Chem Lett 17: 414-418. PMID: 17079143.
- [2] James ML, et al. (2012) Anesthesiology 116: 1299-1311. PMID: 22487803.
- [3] Van Eldik LJ, et al. (2021) Clin Pharm Drug Dev 10: 131-143. PMID: 32255549.
- [4] Roy SM, et al. (2019) J Med Chem 62: 5298-5311. PMID: 30978288.
- [5] Avadhani, et al. (2024) Neurocrit Care 40: 807-815. PMID: 37919545.
- [6] Sorensen G, et al. (2025) J Clin Transl Sci 9:e215. PMID: 41040632.

Non-clinical and clinical studies of MW189

Previous Nonclinical Studies: Models, Endpoints, Outcomes						
Category	Model/Study	Species	Dosing Route	Primary Endpoints	Key Outcomes / Findings	Notes
AD related	Aβ oligomer infusion model	Mouse	Oral; repeat dosing (study-specific regimens)	Hippocampal cytokines; synaptic proteins (PSD-95, synaptophysin); Y-maze cognition	↓ IL-1β, TNFα, S100B; preserved synaptic proteins; improved memory; no systemic immunosuppression	Supports inflammation–synapse mechanism
AD related	APP/PS1 knock-in (chronic administration)	Mouse	Oral; chronic	Synaptic proteins; LTP; cognition; amyloid plaque burden	Prevention of synaptic protein loss; LTP rescue; improved cognition; no change in plaque burden	Mechanism complementary to anti-amyloid
TBI	Closed-head TBI	Mouse	Oral; effective when first dose ≤6 h post-injury; lowest effective dose ~0.1 mg/kg	Vestibulomotor & memory tests; microglial activation; neuronal loss	Improved motor/cognitive outcomes; ↓ microglial activation; ↓ neuronal loss	Therapeutic window beyond acute dosing
ICH	Collagenase-induced ICH	Mouse	Oral	Edema; vestibulomotor function	↓ Edema; improved vestibulomotor performance	Translational relevance to BEACH trial
Other	Seizure, radiation injury, multiple sclerosis, mixed VCID/AD	Rodent models	Oral; model-specific	Inflammation markers; functional outcomes	Broad protection via selective suppression of dysregulated cytokine responses; cognitive/functional improvements	Class effect observed across MW151/188/189

Previous Clinical Studies: Designs, Endpoints, Outcomes					
Study / Phase	Population	Dosing & Route	Primary Endpoints	Key Outcomes / Findings	Status / Notes
Phase 1a SAD (NCT01357421)	Healthy adults	IV 0.025–0.25 mg/kg (single)	Safety/tolerability; PK; ECG (QTc)	Well-tolerated; linear PK; no QT prolongation	Completed
Phase 1a Endotoxin PD	Healthy adults + LPS (2 ng/kg)	IV 0.25 mg/kg	Plasma cytokines (TNFα, IL-10) over 12 h	On-mechanism PD: ↓ TNFα, ↑ IL-10; no clinically significant AEs	Completed
Phase 1b MAD (NCT02942771)	Healthy adults	IV BID 0.075–0.30 mg/kg x 5 days	Safety/tolerability; PK (linearity, accumulation)	Well-tolerated; linear PK; no accumulation; mild infusion site reactions at highest dose	Completed
Phase 2a BEACH (NCT05020535)	Intracerebral hemorrhage patients	IV 0.25 mg/kg within 24 h of bleed; BID x 5 days	Safety/tolerability to Day 7; PK; edema; CSF/plasma biomarkers	110 patients recruited; excellent safety; no test-article-related SAEs resulting in death; interim PK consistent with Phase 1	Ongoing; recruitment complete

GMP Phase 2-compliant clinical drug available

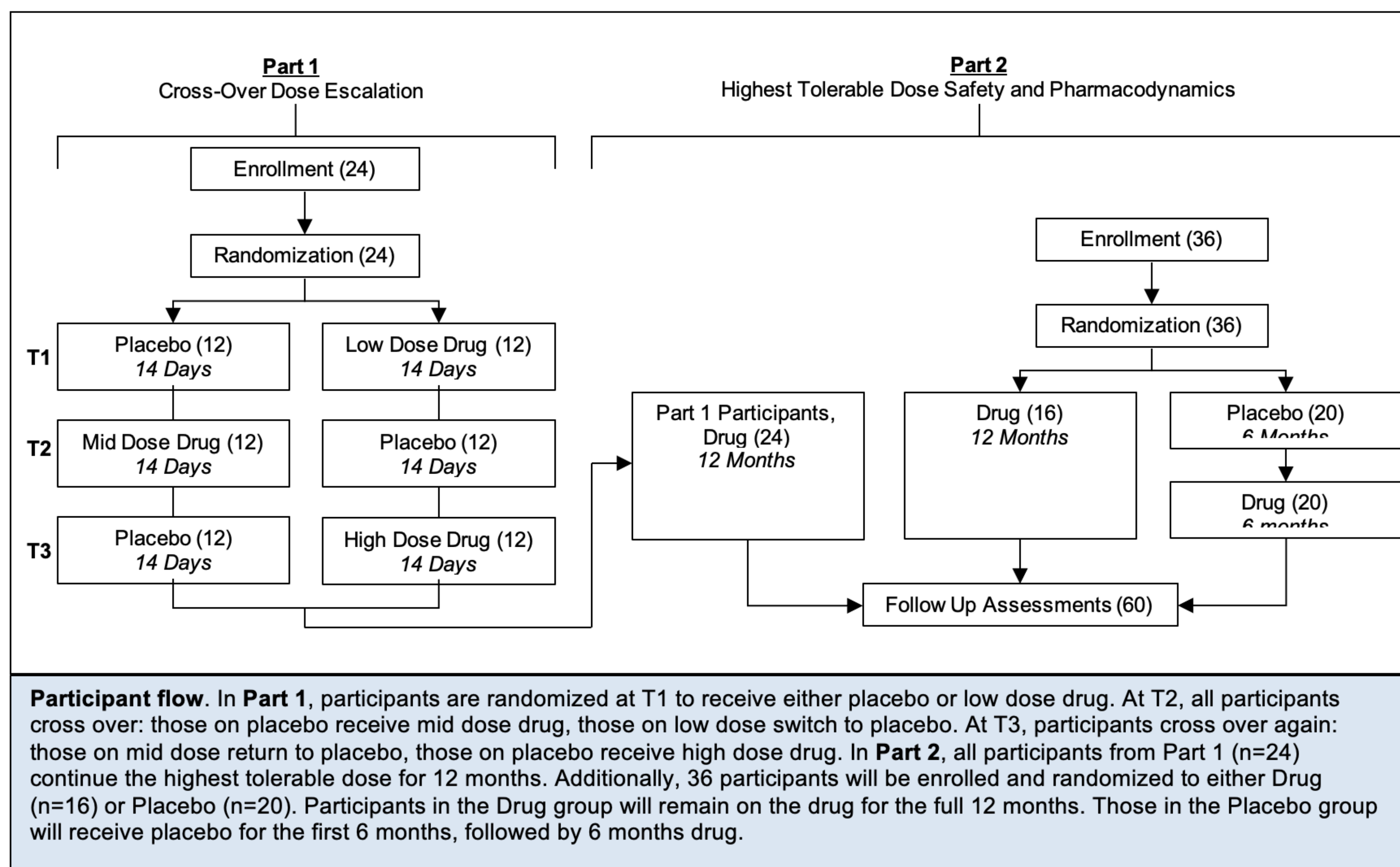


MW189 Molecule Summary	
Chemistry	Value/Properties
Molecular weight (CAS # 886208-76-0)	395.47
cLogP (ACD v18)	3.28
Polar surface area	70.93
pKa (base)	3.71 ± 0.09 (potentiometric)
Chemical stability: 6mo time point Accelerated, 25°C ± 2°C; 60% RH ± 5%	99.5% purity All tests within acceptance criteria
Chemical stability: 24mo time point Long-term, 5°C ± 3°C; RH not controlled	94.6% purity All tests within acceptance criteria
Metabolism, Absorption, Distribution	Value/Properties
CYP inhibitor screens	CYP2C9 inhibitor. Not an inhibitor of CYP1A2, 2B6, 2C19, 2D6, 2E1, 3A4/5
CYP substrate screens	CYP3A4 substrate. Not a substrate of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2A6, 2E1, 2J2, 4F2
CYP induction screens	Weak inducer of CYP1A2, 2B6, 3A4 in screening assay
Drug transporter inhibitor screens	Not a P-gp, MAO-A or MAO-B inhibitor. Inhibitor of OAT3, OATP1B1. Not an inhibitor of OCT2, BCRP, MATE1, MATE2-K, MRP2, OAT1, OCT1
CSF/plasma exposure, based on AUC _{0-inf}	5.81% at 3.75 mg/kg; 8.38% at 0.75 mg/kg
Oral bioavailability	9% in rat; 24-28% in dog
Adverse Pharmacology & Toxicology	Value/Properties
In vitro GPCR binding screen: 55 receptors, ion channels, transporters	All negative
In vitro kinase inhibitor screen: 412 protein and lipid kinases	All negative
Genotoxicity: chromosomal aberration, mouse lymphoma, bacterial mutation, rat micronucleus	All negative
Rat CNS, dog cardiovascular, dog respiratory	All negative
28d rat oral tox, 4wk recovery	No adverse events; well <u>tolerated</u> ; NOAEL=100 mg/kg (highest dose tested)
28d dog oral tox, 4wk recovery	No adverse events; well <u>tolerated</u> ; NOAEL=50 mg/kg (highest dose tested)
6mo rat oral tox, 4wk recovery	No adverse events; well <u>tolerated</u> ; NOAEL=40 mg/kg (highest dose tested)
9mo dog oral tox, 4wk recovery	No adverse events; well <u>tolerated</u> ; NOAEL=30 mg/kg (highest dose tested)

Extended toxicology studies completed

GLP Toxicology and Clinical Safety Margins					
Species	Duration	NOAEL (mg/kg/day)	HED (mg/kg)	HED (mg/day) for 60 kg human	Margin vs 100 mg dose
Rat	6 months	40	6.5	387	3.87×
Dog	9 months	30	16.7	1000	10×

Clinical study outline for phase 2a repeat oral daily administration of MW189 in MCI/early AD trial “*STORM: Proof-of-concept Studies of Oral MW189, a novel anti-neuroinflammatory drug, in Alzheimer's patients*”



Participant flow. In **Part 1**, participants are randomized at T1 to receive either placebo or low dose drug. At T2, all participants cross over: those on placebo receive mid dose drug, those on low dose switch to placebo. At T3, participants cross over again: those on mid dose return to placebo, those on placebo receive high dose drug. In **Part 2**, all participants from Part 1 (n=24) continue the highest tolerable dose for 12 months. Additionally, 36 participants will be enrolled and randomized to either Drug (n=16) or Placebo (n=20). Participants in the Drug group will remain on the drug for the full 12 months. Those in the Placebo group will receive placebo for the first 6 months, followed by 6 months drug.

Proposed Outcome Measures in the STORM Trial			
Type	Name	Time Frame	Brief Description
Primary	Safety/Tolerability	Part 1 and Part 2: At each subject visit	Assess safety and tolerability of oral administration of MW189. Safety variables: Laboratory assessments, vital signs, ECG, AEs
Secondary	Pharmacokinetics/ drug exposure	Part 1: After all subjects are dosed. Part 2: Baseline, 6 and 12 months	Assess plasma MW189 drug exposure. PK parameters: C _{max} , T _{max} , AUC, T _{1/2}
Exploratory	Inflammatory mechanism of action endpoints	Part 2: Baseline, 6 and 12 months	Selected plasma cytokines/chemokines that reflect inflammatory/vascular changes.
Exploratory	AD biomarkers	Part 2: Baseline, 6 and 12 months	Aβ42/40, Total Tau, pTau181, pTau217, NFL, GFAP
Exploratory	MRI	Part 2: Baseline, 6 and 12 months	T1 (volumetrics) and T2 FLAIR (white matter hyperintensities)
Exploratory	Cognitive function tests	Part 2: Baseline, 6 and 12 months	Mnemonic Similarity Task (MST), Integrated Alzheimer's Disease Rating Scale (iADRS)

Conclusions

- Availability of phase 2 GMP compliant oral drug and no safety issues in extended GLP toxicology provide a robust foundation for immediate start of phase 2 trials in MCI & early AD patients.
- The phase 1 clinical safety outcomes with target engagement in healthy adults and a continuing safety record for intravenous administration in acute care for stroke patients extend the tolerability and safety record in humans.
- We conclude that MW189 is a phase 2 clinical candidate with potential for attenuation of glia-based dysregulation linked to synaptic dysfunction in AD patients.