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DT-101 | a Novel AMPAR PAM Demonstrating Favorable Tolerability, PK and Target Engagement in Phase 1 Healthy Volunteer Trial

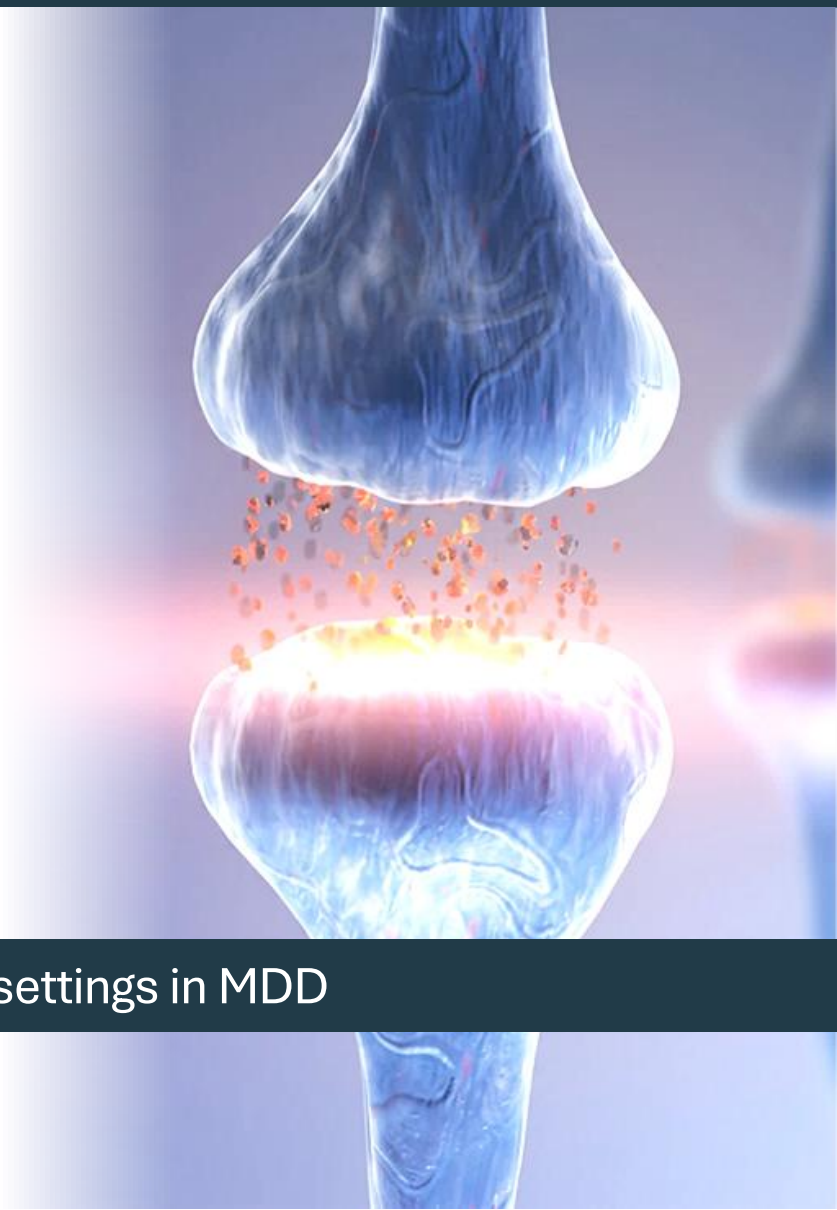
Prof Simon Ward, Co-Founder & CSO

ASCP Miami
May 2026
Presentation

DT-101 | Novel AMPAR PAM in Phase 2 for MDD

DT-101 background

- DT-101 is a next-generation AMPA receptor allosteric potentiator
- Designed to modulate synaptic plasticity via selective potentiation of AMPAR-mediated neurotransmission
- Mechanism aligned with glutamate-based downstream pathways in MDD implicated in esketamine response
- Pharmacokinetic profile characterized by transient, pulsatile exposure consistent with synaptic priming biology



Phase 2 studies ongoing in monotherapy and adjunctive settings in MDD

DT-101 | a validated approach to restore synaptic connectivity in MDD

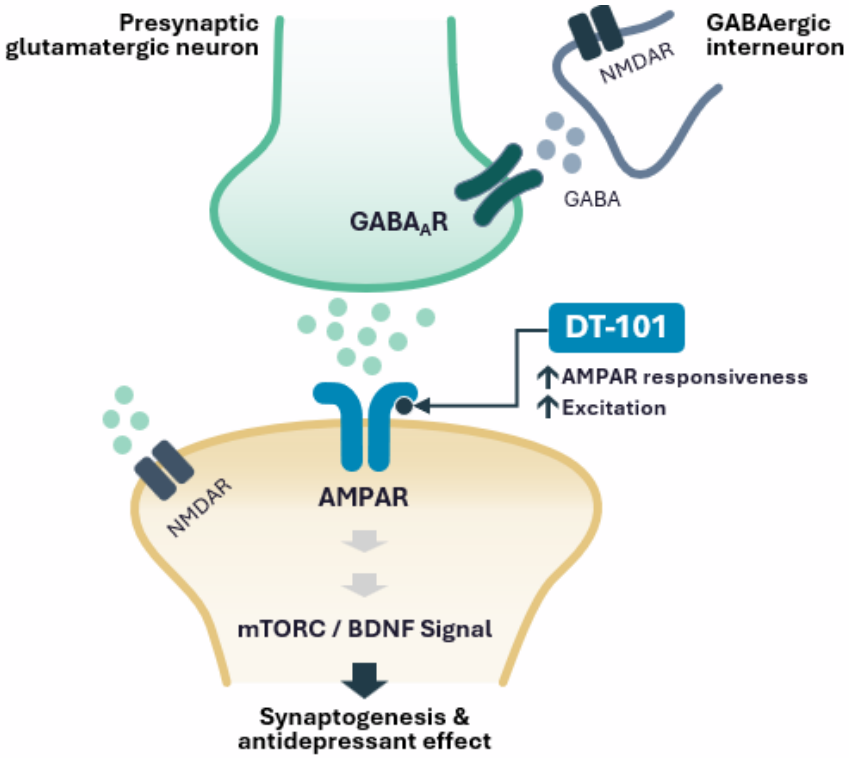
MDD is a disorder of reduced plasticity and network dynamics

- Monoamine therapies limited by lack of impact on underlying circuit dysfunction
- Modalities targeting synaptic plasticity are driving unprecedented antidepressant effects

AMPAR in MDD

- AMPAR is the central regulator of synaptic plasticity, mood & cognition
- Ketamine efficacy driven by AMPAR activation[1,2]
- AMPAR PAMs clinically validated in MDD with good safety

DT-101: Selective AMPAR potentiation



AMPAR is the synaptic plasticity target in MDD

1. Suzuki et al. (2023) 2. Miller et al. (2016)

DT-101 Phase 1 study overview

Objective: Randomised, double-blind, placebo-controlled 3-part study to assess safety and tolerability, pharmacokinetic and pharmacodynamic effects in healthy volunteers (n=81)

Part A

Single ascending dose

- 5 dose level SAD
- n=37
- 1, 3, 9, 18, 36 mg

Part B

Multiple ascending dose

- 14-day MAD
- n=25
- 9, 18, 27 mg
- Neuroimaging (MEG)

Part C

Target engagement

- Single dose 3-way crossover
- n=19
- 9, 18 mg
- Neuroimaging (MEG)

Safety & tolerability

- All AEs were mild to moderate and resolved; No AEs leading to withdrawal
- No SAEs were observed

PK

- Dose-dependent exposure
- CNS penetration
- Pulsatile kinetics

PD

- Functional effect of target engagement across MEG paradigms
- Modulation of oscillatory dynamics

EEG and MEG = electro- and magnetoencephalography; HVs = healthy volunteers; SAD and MAD = single- and multiple-ascending dose, generally with a 2 + 6 placebo:drug design for each dose

Favorable safety & tolerability profile in Phase 1

- 66 healthy volunteers exposed to drug across SAD, MAD and target engagement cohorts
- Safe and well-tolerated across all dose levels
- No SAEs observed across dose range and no discontinuations due to AEs
- All AEs mild-moderate in severity, resolving on their own; most common = headache
- Incidence and nature of AEs comparable to Pbo
- No clinically meaningful changes in chemistry, hematology, urinalysis, ECGs, or vital signs*

	SAD (n=37)						MAD (n=25)				Target engagement (n=19)		
	Pbo	1mg	3mg	9mg	18mg	36mg	Pbo	9mg	18mg BID	27mg	Pbo	9mg	18mg
AEs	**2 (22%)**	0	0	0	0	1 (17%)	**2 (33%)**	3 (43%)	2 (33%)	3 (50%)	**1 (5%)**	1 (5%)	2 (11%)
SAEs	**0**	0	0	0	0	0	**0**	0	0	0	**0**	0	0

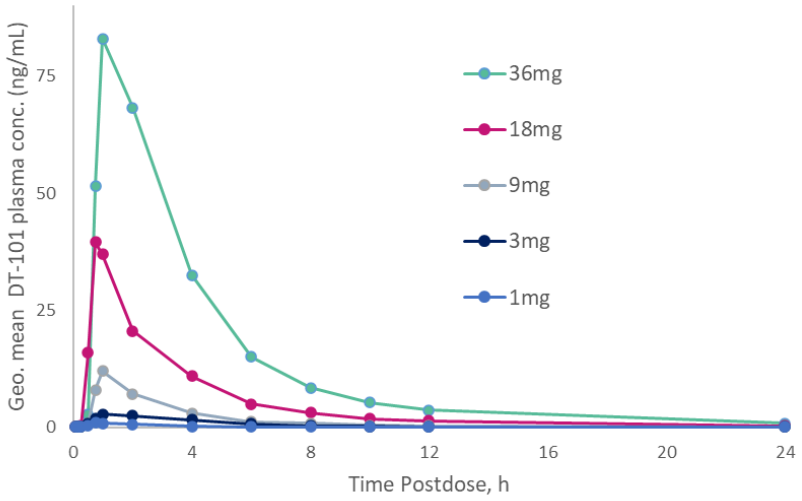
No safety signal observed across all cohorts

*Two participants (Part B, 9mg, 27mg) experienced a transient elevation in CRP, not considered to be related to investigational product

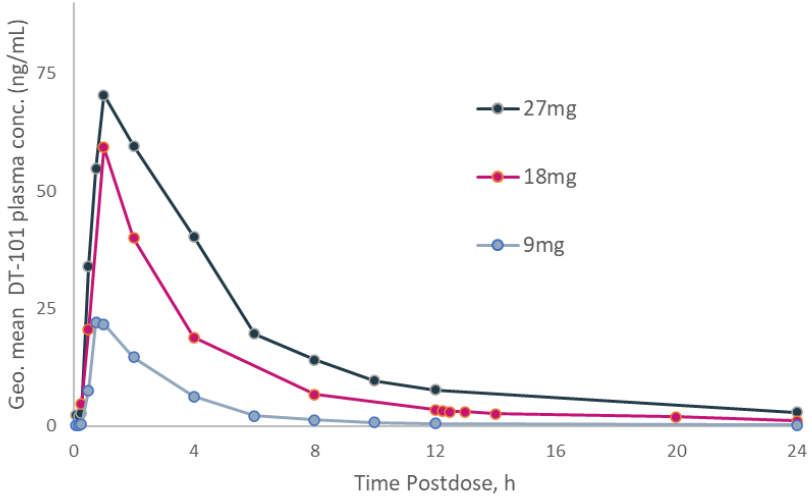
DT-101 demonstrates dose-dependent exposure with pulsatile kinetics

Good PK exposures

SAD
Day 1

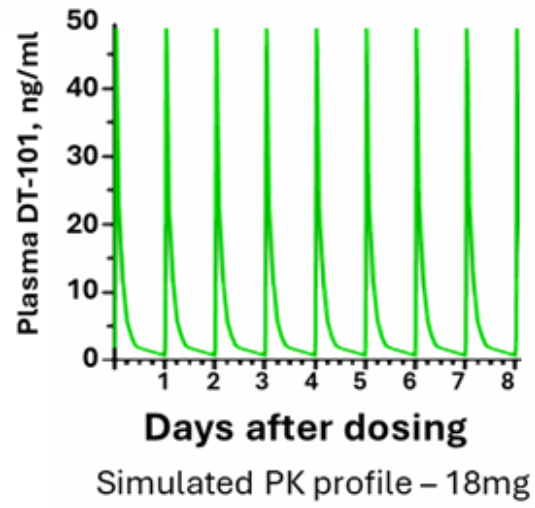


MAD
Day 14



Dose-proportional exposure observed across SAD & MAD cohorts
Moderate half-life (4-9 h) observed (in line with preclinical data)
Good distribution into CSF ($Kp_{u,u}$ ≈ 0.6 by CSF sampling)

Desired pulsatile profile



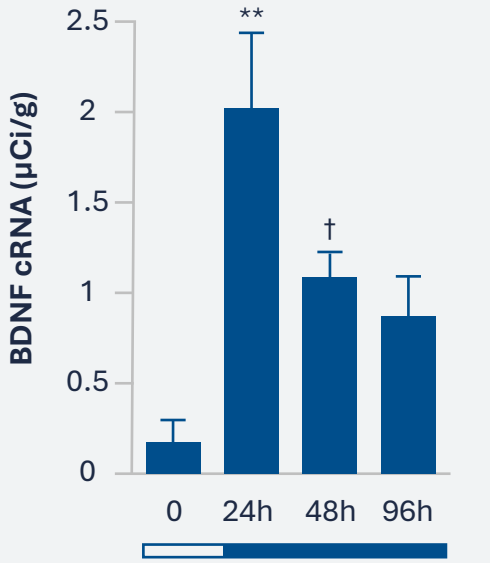
Pulsatile kinetics maximizes synaptic plasticity to unlock fast and durable effects

PK values presented as geomeans

DT-101's pulsatile PK optimal for synaptic plasticity

Transient AMPAR potentiation optimal

1. Continuous receptor occupancy is not required for efficacy[1-8]
2. Prolonged AMPAR PAM exposure dampens plasticity signalling[9]
3. Clinical data support transient, peak-driven plasticity activation (ketamine, osavampator & psychedelics)



CX614 dosing in hippocampal slide model

Figure adapted from Lauterborn et al., J Pharmacol Exp Ther 2003[9]

Pulsatile kinetics enable metaplasticity

- Pulsatile exposure primes neuronal circuits; amplifying response to subsequent stimuli[10,11]
- Recovery periods enable consolidation

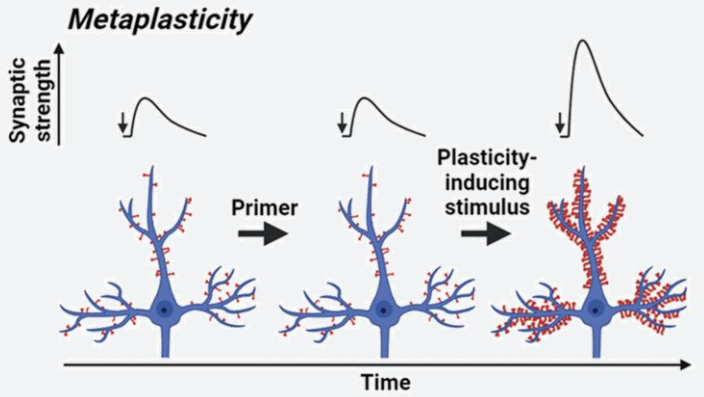


Figure adapted from Brown et al., Mol Psychiatry 2024[10]

Pulsatile kinetics maximizes synaptic plasticity to unlock fast and durable effects

1. Hara et al. (2021); 2. Ward et al. (2010); 3. Ward et al. (2011); 4. Mendez-David et al. (2017); 5. Autry et al. (2011); 6. Li & Wolf (2011); 7. Caldeira (2007); 8. Laio et al. (2025); 9. Lauterborn et al. (2003); 10. Brown et al. (2024); 11 Brown et al. (2025).

Phase 1 target engagement enables clinical translation

Magnetoencephalography (MEG)

- Sensitive, translational readout of functional target engagement in Ph1
- Measures neuronal activity via magnetic fields
- The magnetic correlate of EEG with superior spatial resolution and lower artefact sensitivity

Consistent dose-dependent effect across multiple MEG paradigms

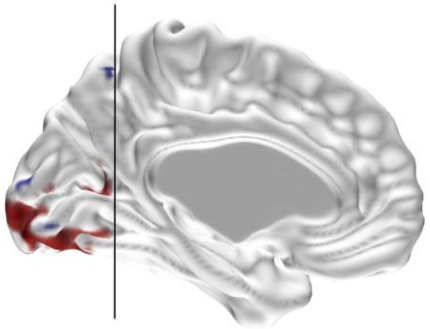
MEG paradigm	Measure	DT-101 effect
Visual gamma	Visual stimulus-driven oscillatory activity	✓
Auditory steady-state response (ASSR)	Sound processing/cortical circuit synchrony	✓
Resting state	Intrinsic brain activity without stimulus	✓

- Functional effect of DT-101 AMPAR target engagement in healthy volunteers confirmed
- DT-101 modulates oscillatory activity indicative of E/I balance

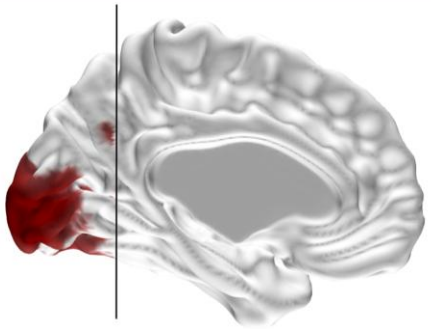
DT-101 MEG data confirm functional effect of target engagement

Visual gamma: dose-dependent increases in oscillatory activity across multiple frequency bands

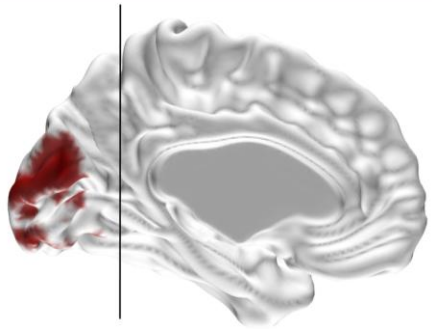
9 mg DT-101 vs Pbo



18 mg DT-101 vs Pbo



18 mg vs 9 mg DT-101



Visual gamma

- Stimulus-driven gamma band activity
- Translational marker of E/I balance

✓ **Dose-dependent increase**

✓ **Correlates with plasma exposure**

Auditory steady-state

- Established biomarker of cortical E/I balance

✓ **Dose-dependent response**

Resting–state network

- Intrinsic brain activity (no task)

✓ **Dose-dependent response**

Consistent, dose-dependent modulation of cortical oscillatory activity across paradigms

Robust translational evidence supporting DT-101 in MDD

- Favorable safety & tolerability profile demonstrated in healthy volunteers
- Linear human PK with excellent CNS exposure, supporting once daily oral dosing
- Clear evidence of target engagement & pharmacological activity demonstrated via MEG
- Phase 2 dose selection supported by exposure–PD correlations

Robust Phase 2 MDD program ongoing:

1. Tarian-1: monotherapy
2. Aeron-1: adjunctive

MEG = magnetoencephalography

THANK YOU

DT-101 Poster Presentations
Poster Session II (11:30 AM – 1:15 PM Thu May 28))

- T61 The Use of Magnetoencephalography (MEG) in a First-In-Human Trial to Demonstrate the Functional Consequences of Target Engagement by DT-101, a Novel AMPA Receptor Positive Allosteric Modulator

- T65 DT-101 – a Novel alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Receptor (AMPAR) Positive Allosteric Modulator Demonstrates Favorable Tolerability and Functional Biomarkers in Phase 1 Healthy Volunteer Trial

ASCP Miami
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Presentation