DT-101 – A Novel AMPAR PAM Demonstrates Favorable Tolerability and Functional Biomarkers in Phase 1 Healthy Volunteer Trial

Ward SE[1], Swettenham JB[1], Hyder R[2], Lock R[3], Singh KD[2], Atack JR[1]

1. Draig Therapeutics; 2. Cardiff University; 3. Aucuba Sciences

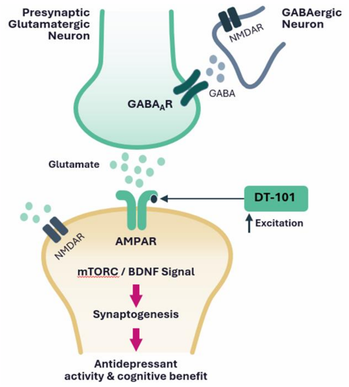
BACKGROUND

DT-101: Next-gen AMPAR-PAM

DT-101 is a next-generation AMPA receptor allosteric potentiator (positive allosteric modulator (PAM):

- Designed to modulate synaptic plasticity via selective potentiation of AMPAR-mediated neurotransmission
- Mechanism aligned with glutamate-based downstream pathways in major depressive disorder (MDD) implicated in esketamine response
- Pharmacokinetic profile characterized by transient, pulsatile exposure consistent with synaptic priming biology
- Phase 2 studies ongoing in monotherapy and adjunct settings in MDD

DT-101: A validated approach to restore synaptic connectivity in MDD



MDD is a disorder of disrupted connectivity

- 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

AMPAR is the synaptic plasticity target in MDD

DT-101 PHASE 1 STUDY DESIGN OVERVIEW

Objective: Randomized, 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 of DT-101 vs placebo

Part B: Multiple Ascending Dose

14-day MAD; n=25; 9, 18, 27 mg of DT-101 vs placebo; neuroimaging (MEG) for target engagement

Part C: Target Engagement

Single dose 3-way crossover; n=19; 9, 18 mg of DT-101 vs placebo; neuroimaging (MEG) for target engagement

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.

DT-101 PHASE 1 STUDY RESULTS

Favorable safety & tolerability profile in Phase 1

- 66 Healthy volunteers exposed 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 placebo
- No clinically meaningful changes in chemistry, hematology, urinalysis, ECG, EEG or vital signs**

	SAD (n=37)					
	Pbo	1mg	3mg	9mg	18mg	36mg
AEs	**2 (22%)**	0	0	0	0	1 (17%)
SAEs	**0**	0	0	0	0	0

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

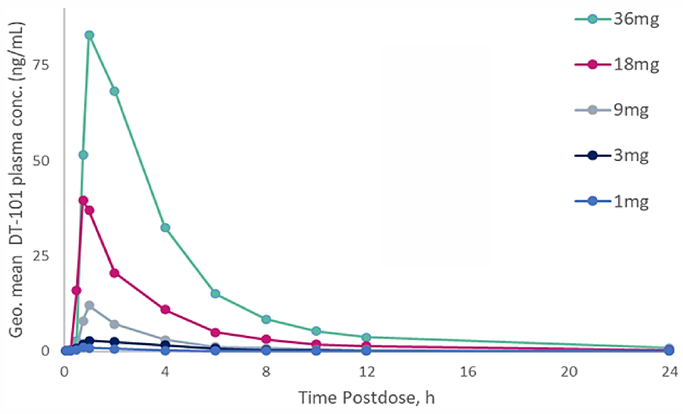
No safety signal observed across all cohorts

**Favorable profile replicated in additional, independent study (n=15).*
***Two participants (Part B, 9mg, 27mg) experienced a transient elevation in CRP, not considered to be related to investigational product.*

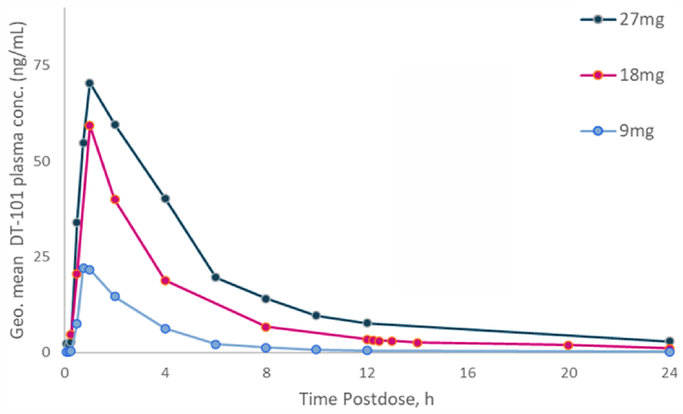
DT-101 demonstrates dose-dependent exposure with pulsatile kinetics

- Exposure increasing with dose in SAD & MAD
- Moderate half-life (6–10 h) observed (in line with pre-clinical data)
- Complete distribution into CSF (confirmed by CSF sampling)

Part A: SAD (Day 1)

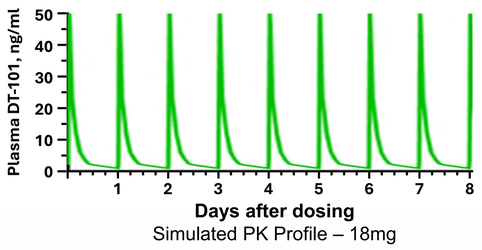


Part B: MAD (Day 14)



Desired pulsatile profile

Pulsatile kinetics maximize synaptic plasticity to unlock fast and durable effects



Simulated PK Profile – 18mg

Ph1 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 artifact sensitivity

Consistent dose-dependent effect across multiple MEG paradigms

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

Visual Gamma

- Stimulus-driven gamma band activity
- Translational marker of E/I balance
- ✓ Dose-dependent increase
- ✓ Correlates with plasma exposure

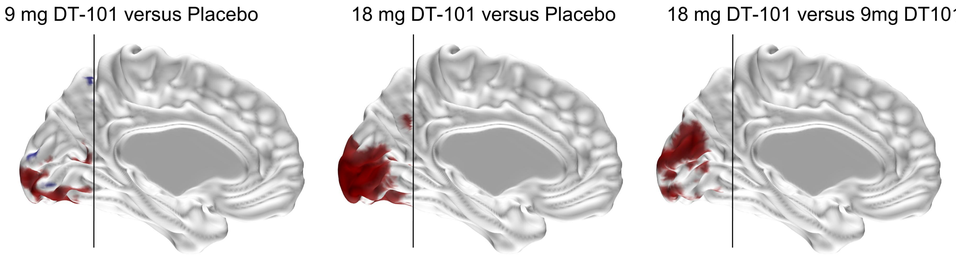
Auditory Steady-State

- Established biomarker of cortical E/I balance
- ✓ Dose-dependent response

Resting–State Network

- Intrinsic brain activity (no task)
- ✓ Dose-dependent response

Visual Gamma:
Dose-dependent increases in oscillatory activity



CONCLUSION

- **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: Tarian-1: monotherapy & Aeron-1: adjunctive**

Disclosures
SEW, JBS, JRA: Cardiff University, Draig Therapeutics; RH, KDS: Cardiff University; RL: Aucuba Sciences.
Funded by Wellcome Trust grants awarded to SW (222159/Z/20/Z &103096/Z/13/Z).

References
1. Suzuki K et al. Neuropharmacology. 2023; 235:109308. doi:10.1016/j.neuropharm.2022.109308
2. Duman RS et al. Nat Med. 2016; 22:238–249. doi:10.1038/nm.4050