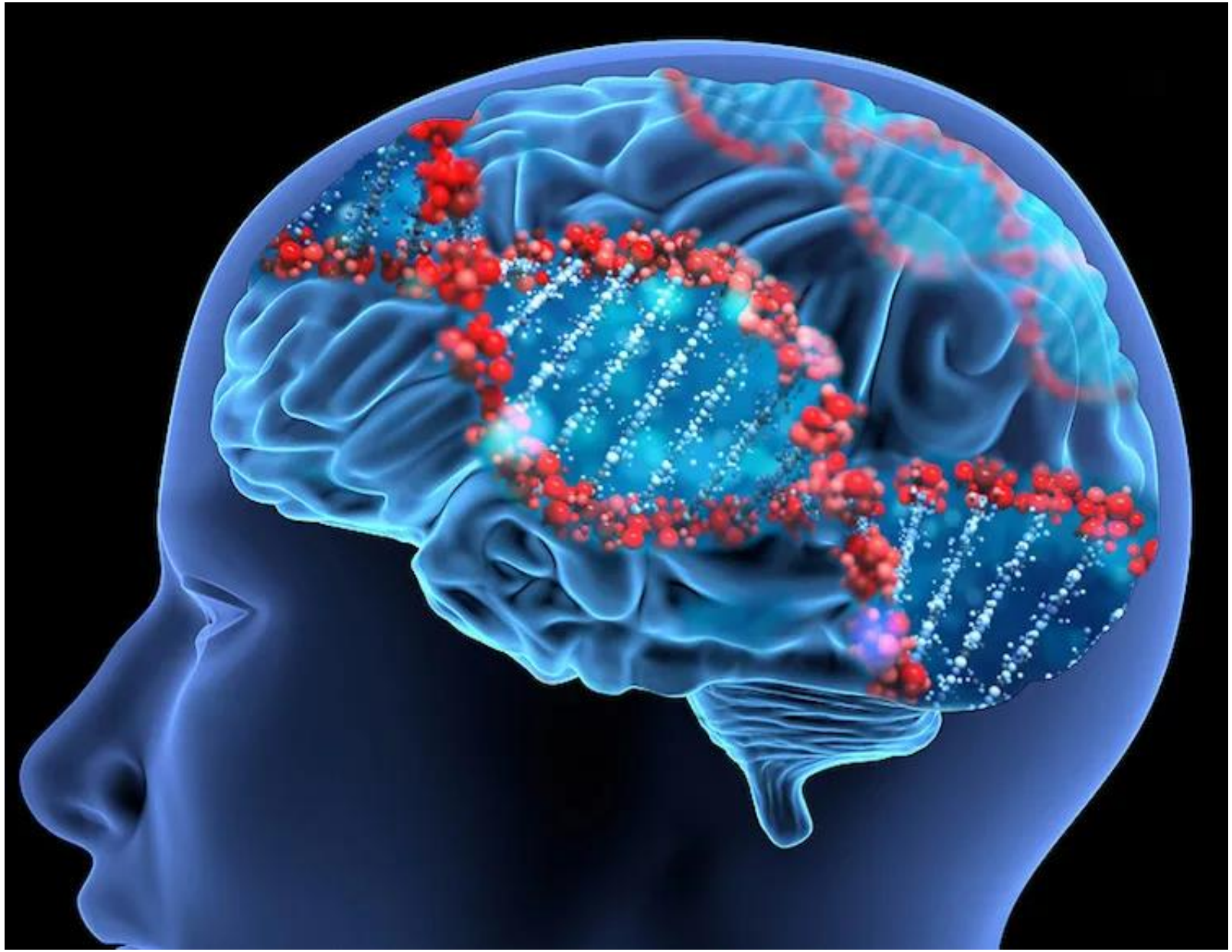

LEAL THERAPEUTICS

Introduction

APRIL 2024

Disclaimer

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Leal's team has deep experience in development of CNS therapeutics, including ASOs and small molecules

Leadership

Asa Abeliovich, MD, PhD
CEO & Founder, Director

Xianglin Shi, PhD
Chief Technology Officer

Eduardo Paredes, PhD
VP, CMC

Herve Rhinn, PhD
SVP, Discovery & Bioinformatics

Laura D. Heckman, PhD
VP, Translational Sciences

Lawrence Severt, MD, PhD
VP, Clinical Development

A formula for success: experienced team, platforms and targets validated by human data, major unmet needs in the CNS

Board of Directors

Athena Countouriotis, MD
(Chairperson)
- Co Founder & CEO, Avenzo; Former CEO, Turning Point Therapeutics

Franz Hefti, PhD
- Former CEO Prevail, Acumen; CSO Avid; EVP Rinat; SVP Merck; Director Genentech

Carl Gordon, PhD, CFA
- Managing Partner, OrbiMed

Mona Ashiya, PhD
- Partner, OrbiMed

Asa Abeliovich, MD, PhD

Track record of building breakthrough CNS companies and forming strategic partnerships

Leal is third CNS company Asa Abeliovich has founded or co-founded with OrbiMed support:

Company	Description	Strategic partnerships or acquisitions
alector	▪ Antibody therapeutics for Alzheimer's and other neuro-degenerative diseases ▪ $176M IPO at $1.3B valuation in 2019	▪ Partnership with AbbVie ($205M upfront) for Alzheimer's Disease TREM2, CD33 Abs ▪ Partnership with GSK ($700M upfront) for Progranulin FTD Sortilin Ab
Prevail Therapeutics	▪ Gene therapy for Parkinson's Disease and other neuro-degenerative diseases ▪ IPO raised $125M	▪ Advanced Gene Therapy Programs to clinic: GBA-Parkinson's, Neuronopathic Gaucher's, Progranulin FTD ▪ ~$1B acquisition by Eli Lilly in 2020
Leal Therapeutics	▪ Precision therapeutics for major unmet needs in the CNS	▪ *Partnerships TBD*

Advancing pipeline of precision CNS therapeutics

Our Approach

- Precision medicines for patients with neurodegenerative or neuropsychiatric disorders
- State-of-the-art nucleic acid and small molecule technology platform capabilities

Program	Target / pathway	Indication	Modality	Leads	Preclinical	DC	IND-enabling	Clinical
LTX-002	*SPTLC1* / Lipid metabolism	**ALS,** PN, AD, PD	**ASO**					
LTX-001	*GLS1* / Glutamate presynaptic	**Schizophrenia,** MDD, ALS	**Small molecule**					
LTX-003	Complement	**AD,** FTD, AMD	**ASO**					
LTX-004	Lipid trafficking	**AD,** DLB	**ASO**					
LTX-005	*GRIN2A* / Glutamate NMDAR	**Refractory Epilepsy,** MDD/TRD	**ASO**					

Note: DC = Development Candidate; MDD = Major Depressive Disorder; PN = peripheral neuropathy; AMD = Age-related Macular Degeneration; DLB = Dementia with Lewy Bodies; AD = Alzheimer's Dementia; PD = Parkinson's Disease

Leal CNS programs address major unmet needs with recognized value

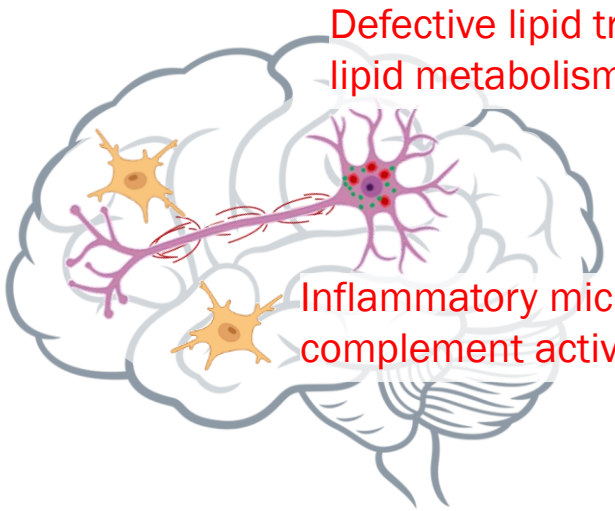
Program	Indication(s)	Stage	Comparable programs and ascribed value	
LTX-002	ALS	IND-enabling	AMYLYX	Recently approved Relyvrio projected peak sales up to ~$1B in ALS, prior to Ph3 failure
			IONIS Biogen	Qalsody/tofersen approval in SOD1 ALS based on NfL as surrogate marker; projected peak sales ~$300M
			DTx Pharma Novartis	$1B acquisition of DTx by Novartis ($500M up front), lead program preclinical stage for rare PN (CMT1A)
LTX-001	Schizophrenia	IND-enabling	Bristol Myers Squibb Karuna Therapeutics	$14B acquisition of Karuna by BMS; lead program M1/M4 agonist in schizophrenia
			abbvie cerevel	$8.7B acquisition of Cerevel by AbbVie; lead programs include schizophrenia/psychosis
			Intra-Cellular Therapies Acadia	Significant peak sales projected for Caplyta (>$4B; Intra-Cellular; approved in schizophrenia, BPD) and Nuplazid ($500M+; Acadia; approved in PD psychosis)
LTX-003 & LTX-004	AD	Preclinical	Eisai Biogen Lilly	Approval of Leqembi/lecanemab (Eisai/Biogen) in AD; positive Phase 3 data for donanemab
			Denali Therapeutics	~$3B market cap; lead programs in neurodegeneration
LTX-005	Drug-resistant Epilepsy, MDD/TRD	Preclinical / Dev. Candidate	Neumora	Lead program in MDD, >$600M raised in private capital, ~$1.7B market cap post-IPO
			rapport therapeutics	$150M Series B raised to support precision medicines pipeline in psychiatry, treatment-resistant epilepsy
			Sage Therapeutics Biogen	Biogen/Sage >$3B collaboration (>$1B up front) driven by lead program in postpartum depression, MDD
			axsome	Blockbuster projected peak sales for Auvelity (>$1B; Axsome; approved in MDD)

Comparable companies and clinical programs in Leal's therapeutic areas have been ascribed significant value

Note: BPD = bipolar depression; MDD = Major Depressive Disorder; TRD = Treatment Resistant Depression; PN = Peripheral Neuropathy; CMT1A = Charcot-Marie Tooth disease type 1A; AD = Alzheimer's Disease. Market data as of April 2024.

Developing novel precision CNS therapeutics that target key pathogenic pathways

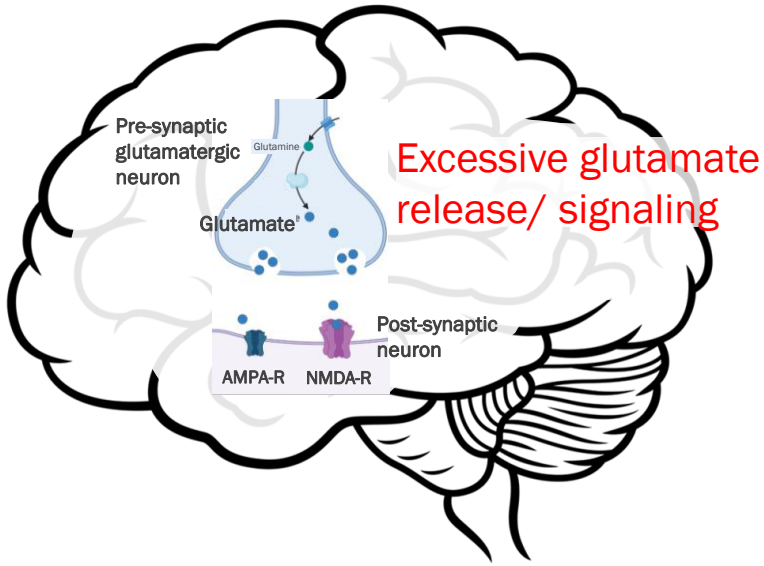
Lipid trafficking/metabolism, inflammatory dysregulation



RNA, Small Molecule Therapeutic Platforms

- **ALS, Peripheral Neuropathy**
- **Age-related Macular Degeneration**
- **FTD,** Alzheimer's Disease, Parkinson's disease

Glutamate Physiology dysregulation



- **Schizophrenia,** MDD
- **Focal epilepsies**, Syndromic epilepsies
- **ALS**, FTD, Alzheimer's Disease

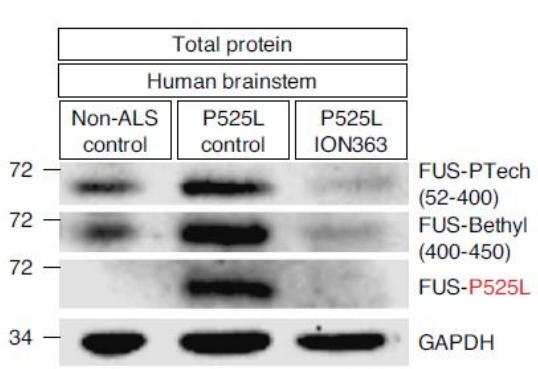
Note: graphics made using Biorender, Powerpoint

ASOs are a validated and exceptionally precise modality for the CNS

Recent clinical, biomarker, and imaging data confirm that IT-delivered ASOs can potently suppress target expression in key brain regions, are well-tolerated, and are remarkably long-acting in the CNS (~Q3-6M dosing)

Autopsy data: Leal ASO potency in mice can translate to CNS target engagement with repeat IT dosing in patients

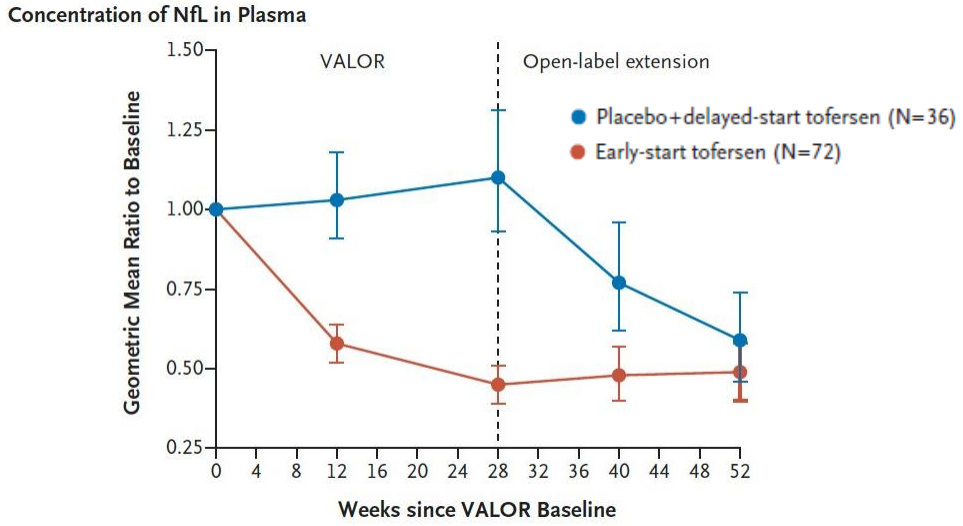
ALS Patient autopsy data[1]



Intrathecal dosing Q1M for 10 months using Fus ASO led to >80% target reduction in patient brainstem, cortex, and spinal cord

Surrogate endpoint data: Neurofilament light chain (NfL) reduction seen as early as 3 months, sustained for 12 months after tofersen treatment in ALS patients

Plasma biomarker (surrogate endpoint) data[2]

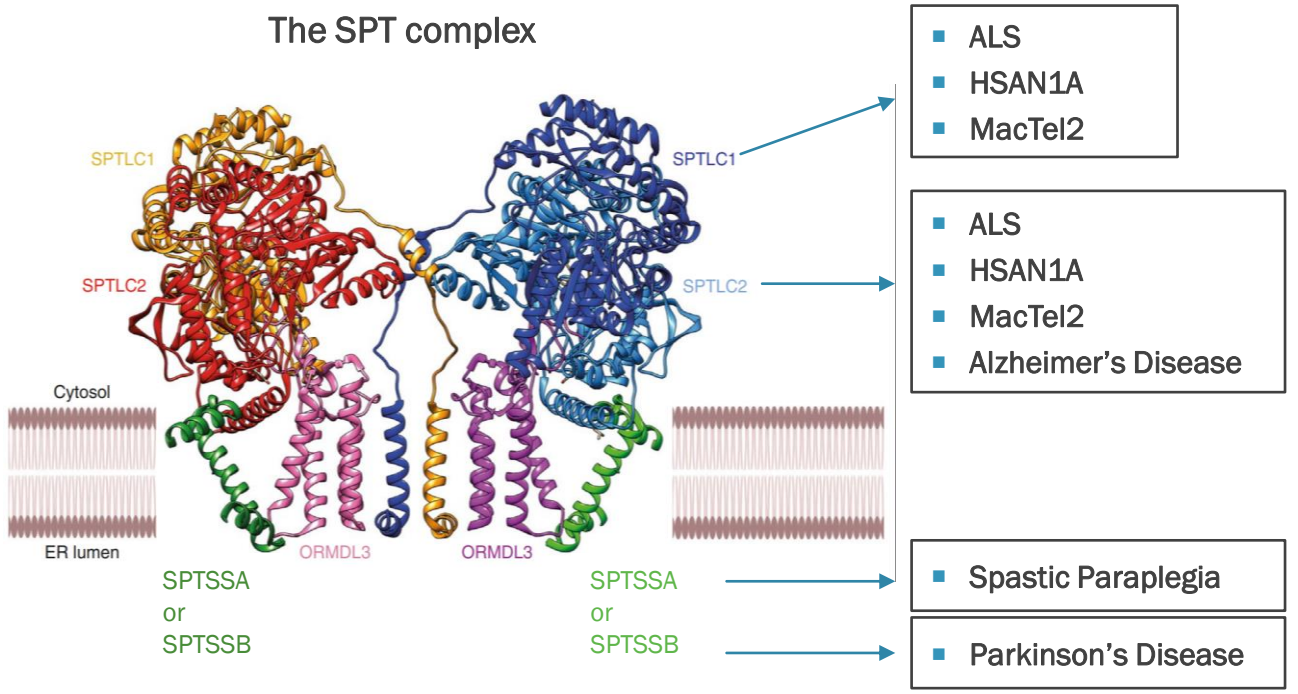


NfL concentration in plasma was reduced by 60% in tofersen-treated faster-progression subgroup and increased 20% with placebo at week 28 (3 loading doses at 2week intervals, followed by 5 doses at 4week intervals).

Source: 1 Korobeynikov et al., 2022, Nature Medicine; Pascoal et al Brain 2020, Pascoal et al Brain 2021; 2 Miller et al. NEJM 2022

Leal's *SPTLC1* ASO program targets sphingolipid dysregulation in ALS; validated by human genetics, human biomarker, and model system data

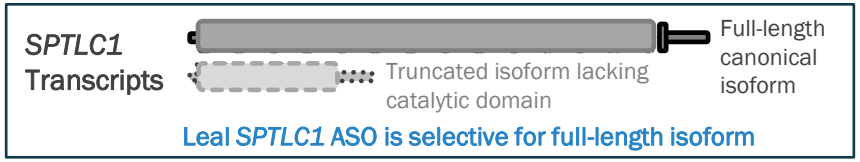
- *SPTLC1* encodes an essential subunit of serine palmitoyltransferase (SPT), the rate-limiting enzyme in sphingolipid biosynthesis
- Human genetics, lipid biomarker data, functional genomics and preclinical models support targeting *SPTLC1*
- Potential indications include ALS (sporadic and genetic forms), peripheral neuropathy (diabetic, chemo-induced, HSAN1A), MacTel 2
- SPT complex associated with Alzheimer's, Parkinson's



Note: ALS = Amyotrophic Lateral Sclerosis; HSAN1A = hereditary sensory and autonomic neuropathy type 1A; MacTel 2 = Macular Telangiectasia Type 2
Source: Data on file

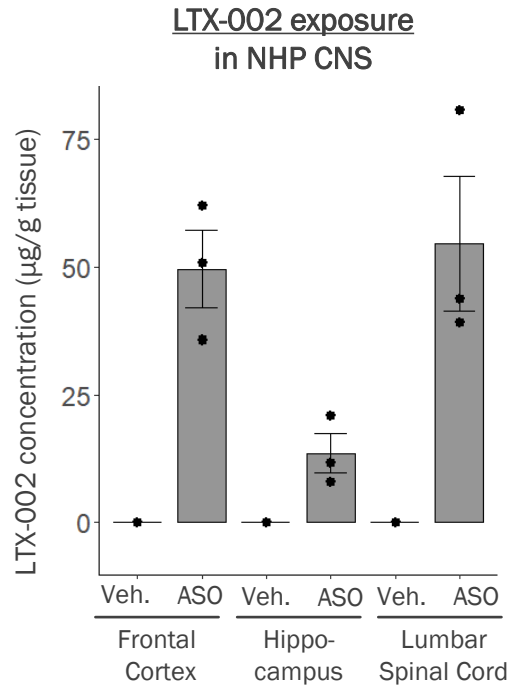
In NHP, *SPTLC1* ASO LTX-002 showed safety, target engagement, and biodistribution to key CNS regions

- ASO levels in NHP brain tissue exceeded effective levels in rodents in Leal programs with ASOs that target rodent sequences (>50% KD achieved with levels >10 µg/g)
  - Brain tissue levels met or exceeded published PK in NHP ASO studies dosed similarly[1]
- LTX-002 knocked down *SPTLC1* ~30-40% in NHP cortex with acute IT dosing
  - LTX-002 specifically targets full-length *SPTLC1* transcript; does not reduce truncated transcript that lacks catalytic domain:



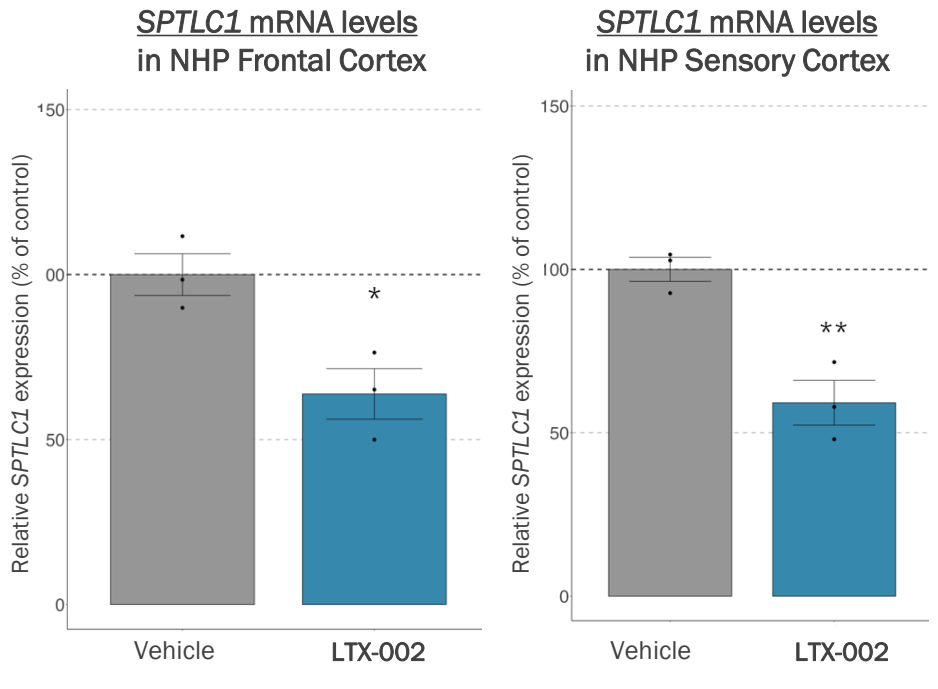
- No safety signals observed in-life, no adverse findings on histopathology or neuropathology

LTX-002 distributed to key CNS areas



Each dot represents an animal, bars show mean +/- SEM. PK assessed by LCMS 2 weeks post final dose; animals received 2 doses of 20mg IT 2 weeks apart. N=3 per group.

LTX-002 significantly engaged target in NHP CNS (IT dosing)



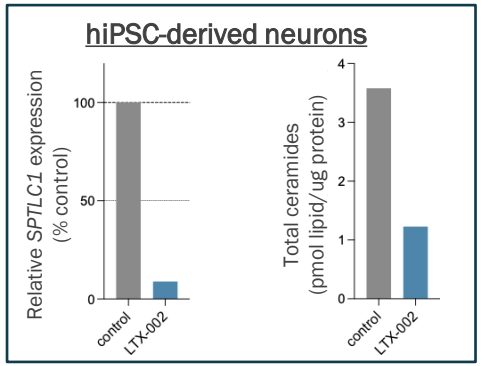
Each dot represents an animal, bars show mean +/- SEM. *SPTLC1* expression measured by RT-qPCR 2 weeks post- second dose; animals received 2 doses of 20mg IT 2 weeks apart. N=3 per group. *p<0.05, **p<0.01 for Treatment vs. Vehicle by unpaired t-test.

Note: IT = intrathecal

Source: Data on file; 1 Jafar-Nejad et al. 2021

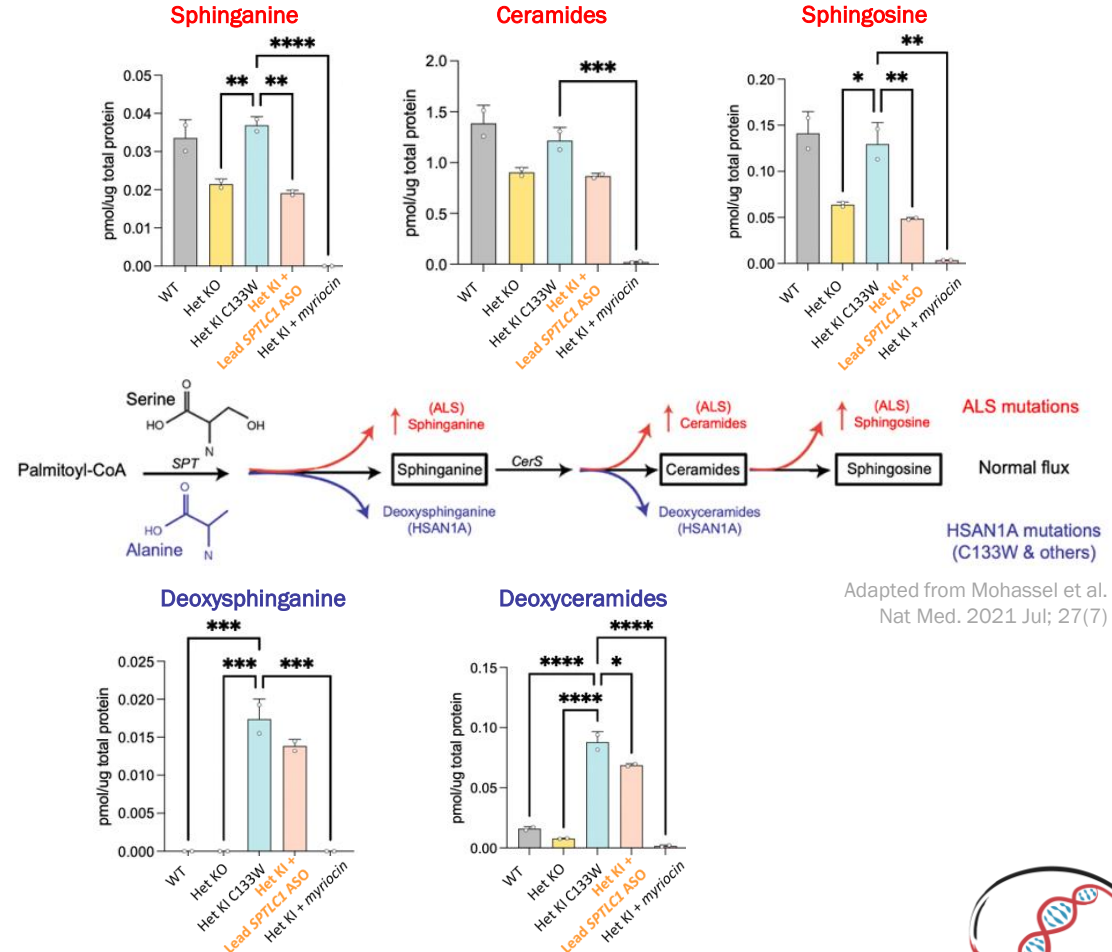
LTX-002 reduced levels of toxic sphingolipids in human iPSCs with clinical *SPTLC1* mutation

- Study assessed effect of *SPTLC1* knockdown with LTX-002 on sphingolipid levels in hiPSCs with HSAN1A-causing *SPTLC1* GOF mutation
  - Myriocin (non-selective SPT inhibitor) used as positive control
- LTX-002 knockdown of *SPTLC1* mRNA by ~50% in mutant hiPSC significantly reduced levels of toxic deoxysphingolipids and canonical sphingolipids, supporting approach in ALS
- LTX-002 knockdown of *SPTLC1* by ~90% in WT hiPSC-derived neurons reduced ceramide levels



Neuronal cultures across 6 plates were pooled for single lipid analysis

LTX-002 decreased downstream sphingolipid levels in iPSCs with clinical *SPTLC1* mutation

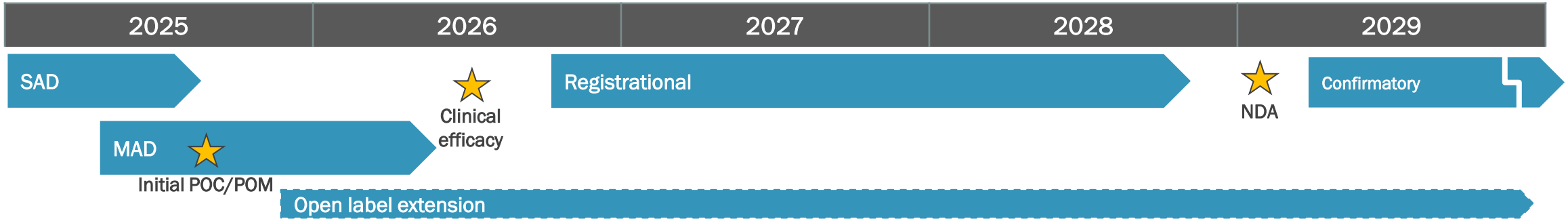


Adapted from Mohassel et al. Nat Med. 2021 Jul; 27(7)

Source: Data on file. Statistics were performed for differences versus SPTLC1 het KI C133W by ANOVA followed by Dunnett's. ****:p<0.0001, ***:p<0.001, **:p<0.01, *:p<0.05; N=2 technical replicates.

SPTLC1 in ALS: clinical development path

Potential development path



- POC/POM: NfL and ceramide/sphingolipid levels (n=~5-10)
- Initial clinical endpoints include Δ in ALSFRS-R from baseline, Δ in FVC
- Nested SAD/MAD in patients with ALS (sporadic or genetic)
- Doses in the MAD at Days 1, 29, 85
- N= ~60 for SAD/MAD, N= ~125 for Registrational
- Registrational: 28-week assessment period, dosing IT ~Q3M
- OLE for all participants in SAD, MAD, and Registrational trials; Safety data and long-term clinical benefit
- Endpoints: Δ in ALSFRS-R from baseline; Δ in FVC, Δ in strength by dynamometry, time to ventilatory support or death
- Δ in NfL as surrogate endpoint to support accelerated approval

Patient criteria:

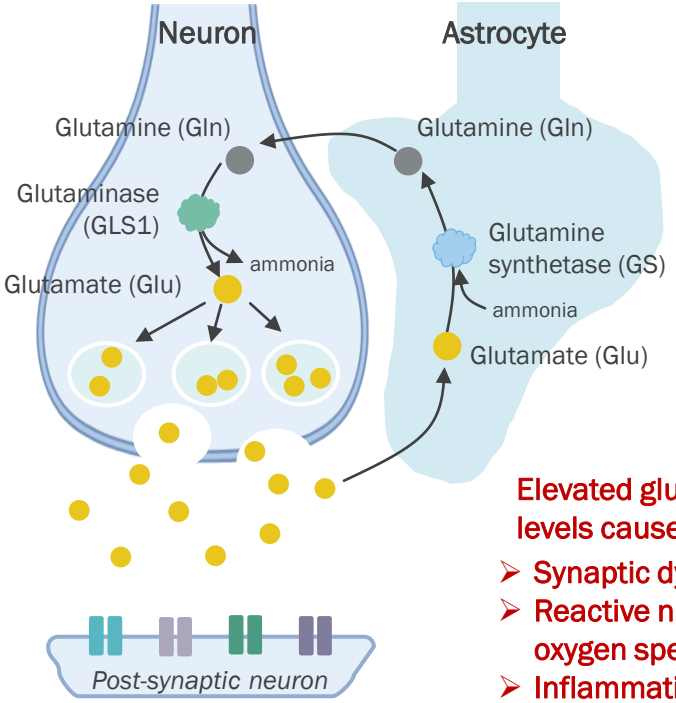
- ALS: sporadic or genetic (SPTLC1 or other)
- Definite/probable/possible ALS per revised El Escorial criteria
- Onset of symptoms ≤ 24 months, FVC ≥50% at screening; *stratified by biomarker, rate of clinical progression*

- Tofersen SOD1 ALS accelerated approval based on NfL as surrogate endpoint plus clinical benefits trends

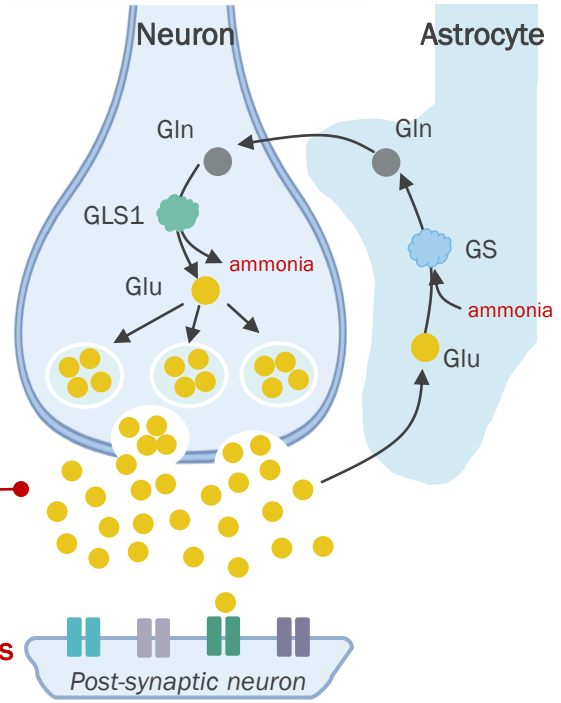
Note: POM: Proof of Mechanism; POC = Proof of Concept

Glutaminase-1 (GLS1) Program Summary: first-in-class novel oral small molecule enables therapeutic reduction of brain glutamate levels

Physiological glutamate system



Pathologic glutamate system



Elevated glutamate levels cause:

- Synaptic dysfunction
- Reactive nitrogen / oxygen species stress
- Inflammation, Mitochondrial dysfunction
- Excitotoxicity

- Glutamate (Glu) is the major excitatory neurotransmitter of the brain; GLS1 is rate-limiting enzyme to generate pre-synaptic Glutamate
- Extensive physiologic, biomarker/Imaging, and pharmacological data support targeting excessive glutamate in schizophrenia/TRS, epilepsies, MDD/TRD, BD
  - GLS1 and Glutamate pathway also implicated in ALS, AD, Dementia-psychosis, other CNS disorders
- Common genetic variants that reduce expression of GLS1 in humans and lead to increased glutamine levels are associated with reduce psychiatric disease in large "PheWAS" UK Biobank dataset re-analysis by Leal
- Existing GLS1 inhibitors do not cross BBB and/or are non-specific; do not impact CNS Glu levels significantly

Graphics made with Biorender, Powerpoint

Note: TRS = treatment-resistant schizophrenia; MDD = major depressive disorder; TRD = treatment-resistant depression

Source: Marwaha et al Lancet 2022, Lazar and McIntyre 2019, Barker-Haliski and White Cold Spring Harbor Perspectives in Medicine 2015, Fang and Wang Seizure 2015, Montanari et al Int. J. Mol. Sci 2022; Merritt et al JAMA 2021; Egerton et al Neuropsychopharm 2012; Li et al Frontiers in Psych 2021

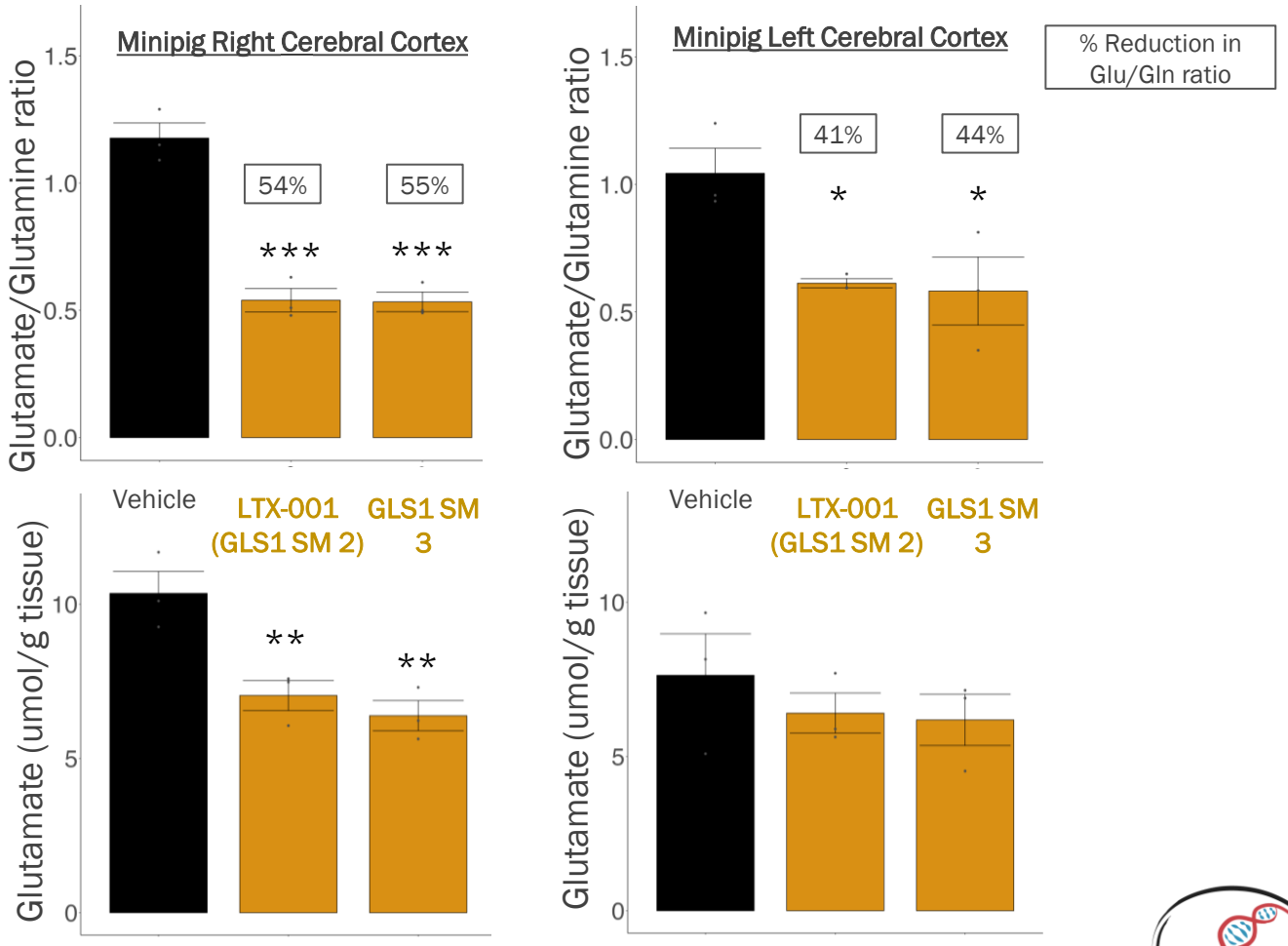
GLS1 oral SM Lead compounds demonstrated compelling PK/PD/Safety in minipig, rat CNS

- Lead compounds significantly decreased Glu/Gln ratio in multiple regions of minipig CNS
- Assessed dose in minipig is allometric equivalent to effective dose in mice[1]
- No in-life safety signals
- Rat, minipig MTD/DRF studies support broad safety margin based on repeated dosing and mouse efficacy data (studies completed and ongoing)

Key parameters in minipig following oral dosing	LTX-001 (GLS1 SM 2)	GLS1 SM 3
$T_{1/2}$ (h)	7.5	6.2
T_{max} (h)	1.0	0.5
C_{max} (ng/mL)	6100	2700
AUC_{inf} (h*ng/mL)	34591	7376
Cortex con. (nM) 4h post dose	369	319
Plasma con. (nM) 4h post dose	7055	1655
Cortex/Plasma ratio	5.2%	19.3%

Note: 1 Assessed dose (3 mg/kg PO) was selected by using allometric scaling (Nair 2016) of efficacious dose in mice (25 mg/kg PO in mice) and rounding to next whole mg/kg.
Source: Data on file

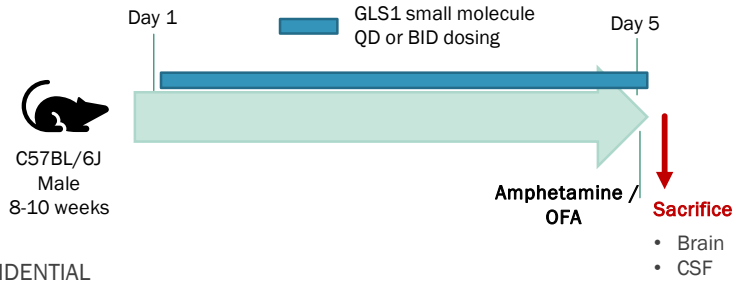
Significant reduction in glutamate-to-glutamine ratio and glutamate in minipig CNS



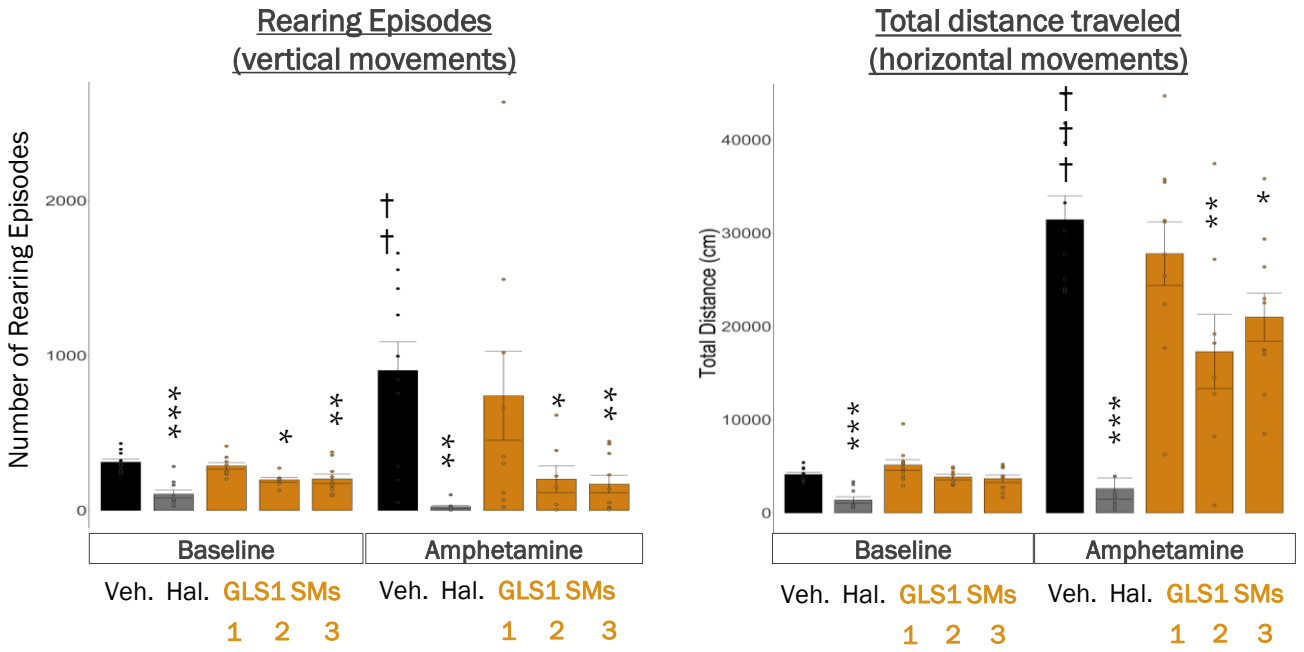
Each dot represents an animal; bars show mean +/- SEM. PK & PD assessed 4 hours after the second PO dose given 1 day apart[1]. N=3 per group. *p<0.05, **p<0.01 ***p<0.001 for differences vs. Control by ANOVA.

LTX-001 and backup compounds showed efficacy in mouse model of psychosis

- Validated mouse model of schizophrenia: amphetamine induces psychosis-like hyperactivity (vertical and horizontal) behavior in rodents
- LTX-001 and backup small molecules significantly reduced amphetamine-induced hyperactive behavior; *consistent with genetic model*
  - LTX-001 (SM 2) and SM 3 showed greater reduction in psychosis behavior than SM 1, consistent with relative potency on brain Glu/Gln
  - Baseline activity largely unaltered by Leal compounds
- Haloperidol as a positive control reduced psychosis behavior with amphetamine treatment, *but at dose tested also reduces baseline activity*



Leal GLS1 small molecules significantly reduced psychotic-like behavior in mice

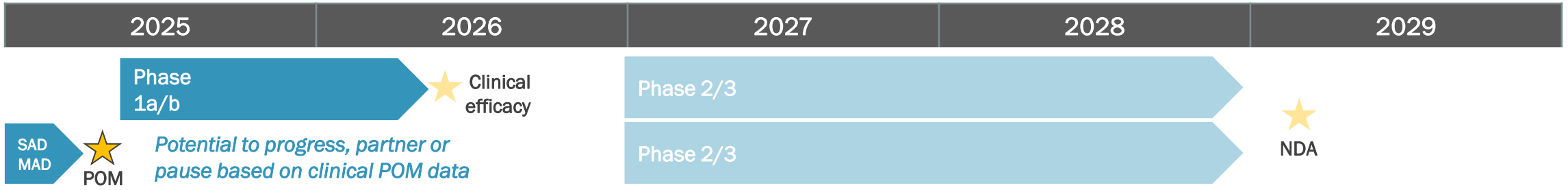


Behavior assessed after 5 days of dosing. Haloperidol dosed once at 0.3 mg/kg IP prior to assay. Means are presented, error bars are SEM. N=7-10 animals per group. ***:p<0.001, **:p<0.01, *:p<0.05, for Treatment vs Vehicle in either Baseline or Amphetamine part of the test by ANOVA followed by Dunnett's test Amphetamine effect: †††: p< 0.001, : ††: p< 0.01 for Amphetamine vs Baseline by paired t-test in Vehicle-treated animals. Grubb's test for outliers performed before stats performed for rearing episodes.

Source: Data on file

Potential for early clinical proof of mechanism in schizophrenia

Potential development path



- POM: Glu/Gln by ^{1}H-MRS in HV, patients (n=5-10)
- Glu and Glu/Gln in CSF and serum of HV, patients
- Mismatch Negativity in patients (N=~10-20)
- SAD in HV/MAD in stable schizophrenia
- Stratify by baseline Glu/Gln
- Phase 1a/b in patients with schizophrenia w/ acute exacerbation
  - N=80 patients with 6-week treatment period
- POC based on 1° endpoint: Δ in PANSS Total Score

- N=~250 per trial
- Schizophrenia with acute exacerbation of symptoms
  - ^{1}H-MRS in subset to stratify for potential response
- 6-week treatment period
- 1° endpoint: Δ in PANSS Total Score
- Other possible endpoints: CGI-S, PANSS Positive/Negative Subscales, PANSS Responder Rate, CDSS, MCCB, BACS, Imaging

Patient criteria: Schizophrenia, significant positive and negative symptoms, breakthrough symptoms on SOC; able to discontinue current antipsychotic; inpatient setting

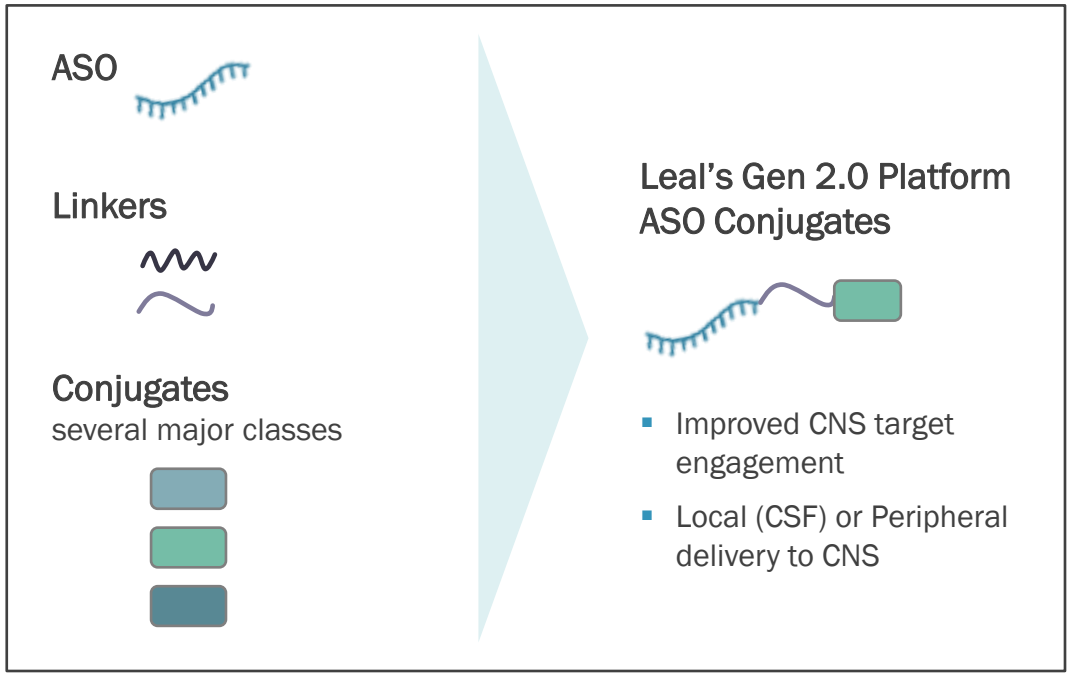
- POM biomarkers including MRS, mismatch negativity and functional brain imaging
- Expanded Phase 1b could potentially provide early POC as demonstrated by emraclidine[1]
- Additional attractive clinical opportunities in MDD, Bipolar Disorder, ALS

Note: POM: Proof of Mechanism; HV: Healthy Volunteers; POC = Proof of Concept; OLE = open label extension
Source: 1 Krystal et al Lancet 2022

Leal has robust internal CMC capabilities and external networks that enable our small molecule and ASO technology platforms

- Leal's Technology team has deep expertise in small molecule and nucleic acid/RNA CMC
  - In-house capabilities to generate preclinical material
  - Network of external CDMOs to support through clinical studies
- Leal Gen 2.0 chemistries include conjugation and modification platforms and have shown emerging feasibility
- **Leal is pursuing both local (CSF) and peripheral delivery approaches to the CNS, including BBB shuttles**

Leal's Gen 2.0 ASO Platform Technologies



Leal's IP strategy creates a foundation to protect pipeline and platform assets

Composition

Methods of use

Platform technology

- >50 provisional or PCT patent applications filed to cover programs and platform
- Filing strategy will protect composition and use as well as platform technology development
- Additional filings to support complementary modality approaches for select targets

Summary: Leal Therapeutics is pioneering precision medicines for high-need CNS disorders

- ✓ Pipeline of 5 programs pursuing human-validated targets in major CNS diseases across neurodegeneration, neuropsychiatric, other neurological indications
- ✓ Lead programs demonstrate compelling *in vivo* PK/PD, safety, and efficacy
- ✓ Platform development focused on optimizing CNS target engagement