cerevel

Transforming the Possible in Neuroscience

A Different Kind of Biopharma Company

R&D Event

January 2021

Forward-Looking Statements

This presentation contains forward-looking statements that are based on management's beliefs and assumptions and on information currently available to management. In some cases, you can identify forward-looking statements by the following words: "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue," "ongoing" or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. These statements involve risks, uncertainties and other factors that may cause actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain.

Forward-looking statements in this presentation include, but are not limited to: statements about the potential attributes and benefits of our product candidates, including with respect to receptor subtype selectivity, activity, side effect and tolerability profile and relevant indications; the format and timing of our product development activities and clinical trials, including the design of clinical trials and the timing of initiation, completion and data readouts for of clinical trials; the timing and outcome of regulatory interactions; the ability to compete with other companies currently marketing or engaged in the development of treatments for relevant indications; the size and growth potential of the markets for product candidates and ability to serve those markets; the rate and degree of market acceptance of product candidates, if approved; the potential of our development approach; and the intended results of our strategy.

We cannot assure you that the forward-looking statements in this presentation will prove to be accurate. Furthermore, if the forward-looking statements prove to be inaccurate, the inaccuracy may be material. Actual performance and results may differ materially from those projected or suggested in the forward-looking statements due to various risks and uncertainties, including, among others: that clinical trial results may not be favorable; uncertainties inherent in the product development process (including with respect to the timing of results and whether such results will be predictive of future results); the impact of COVID-19 on the timing, progress and results of ongoing or planned clinical trials; other impacts of COVID-19, including operational disruptions or delays or to our ability to raise additional capital; whether and when, if at all, our product candidates will receive approval from the FDA or other regulatory authorities, and for which, if any, indications; competition from other biotechnology companies; uncertainties regarding intellectual property protection; and other risks identified in our SEC filings, including those under the heading "Risk Factors" in our prospectus filed with the SEC on December 4, 2020.

In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. The forward-looking statements in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this presentation.

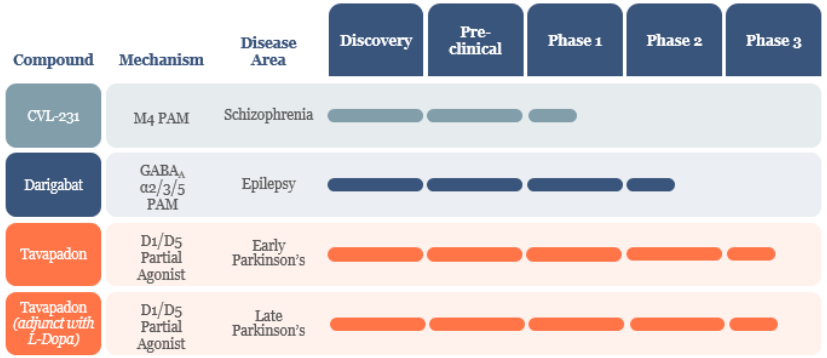
Cerevel:
Transforming the Possible in Neuroscience

Cerevel is Transforming Possibilities for Tomorrow

Multiple Programs Aimed at Providing New Options for Millions of Patients

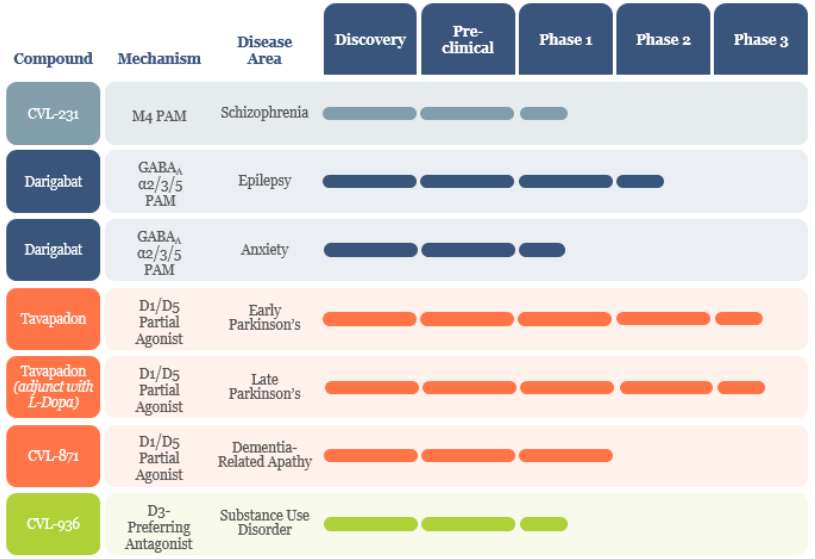
Tangible near-term value creation

- Schizophrenia
- Epilepsy
- Parkinson's



Expansion to other diseases

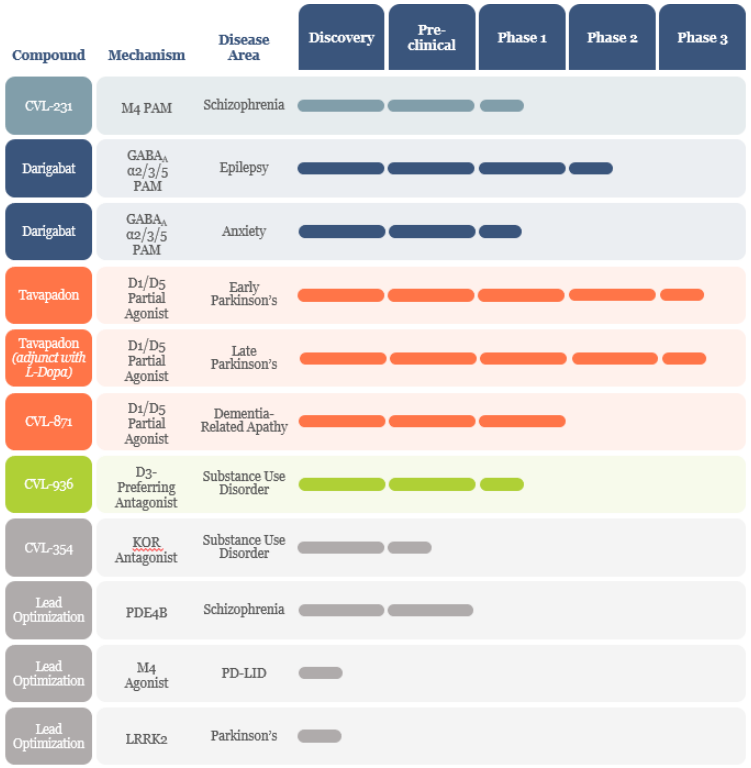
- Alzheimer's Psychosis
- Anxiety
- Apathy
- Substance Abuse Disorder



Long-term discovery efforts

Disease-modifying therapies based on human genetics and novel targets addressing:

- Neuronal loss
- Synaptic health



50M+ Patients WW ⊕ 100M+ Patients WW → Premier Neuroscience Company

Today's Agenda

Time	Topic	Presenter(s)
9:00 – 9:10 AM	Cerevel: Transforming the Possible in Neuroscience	 **Tony Coles, M.D.** *Chief Executive Officer & Chairperson*
9:10 – 10:05 AM	Deep Dive: Darigabat (CVL-865): $GABA_A$ α2/3/5 PAM for Epilepsy / Anxiety	 **Raymond Sanchez, M.D.** *Chief Medical Officer*  **Rachel Gurrell** *Darigabat Scientific Lead*  **Julie Jordan, M.D.** *Darigabat Medical Lead*
10:05 – 10:30 AM	Our Science: A Differentiated Knowledge of Neurocircuitry • PDE4B Inhibitor Program • KOR Antagonist Program	 **John Renger, Ph.D.** *Chief Scientific Officer*  **Phil Iredale, Ph.D.** *Vice President, Biology*  **Georgette Suidan Ph.D.** *KORA Scientific Lead*
10:30 – 11:00 AM	Q&A	All, including Kathy Yi, Chief Financial Officer

Highlights

- Utilizing our differentiated understanding of disease-related biology and neurocircuitry of the brain with advanced chemistry to develop novel therapies for CNS diseases
- Broad portfolio of 11 assets targeting large markets with significant unmet need, including schizophrenia, epilepsy, and Parkinson's Disease
- Progressing towards multiple near and medium-term catalysts, with 8 data readouts and multiple INDs expected over the next 3 years
- Leveraging a seasoned management team with extensive expertise in neuroscience and a strong track record of over 20 prior drug approvals and commercialization

Led by a Seasoned Life Sciences Management Team

Tony Coles, M.D.
Chief Executive Officer & Chairperson

Kathy Yi
Chief Financial Officer

Raymond Sanchez, M.D.
Chief Medical Officer

John Renger, Ph.D.
Chief Scientific Officer

Kenneth DiPietro
Chief Human Resources Officer

Orly Mishan
Chief Business Officer

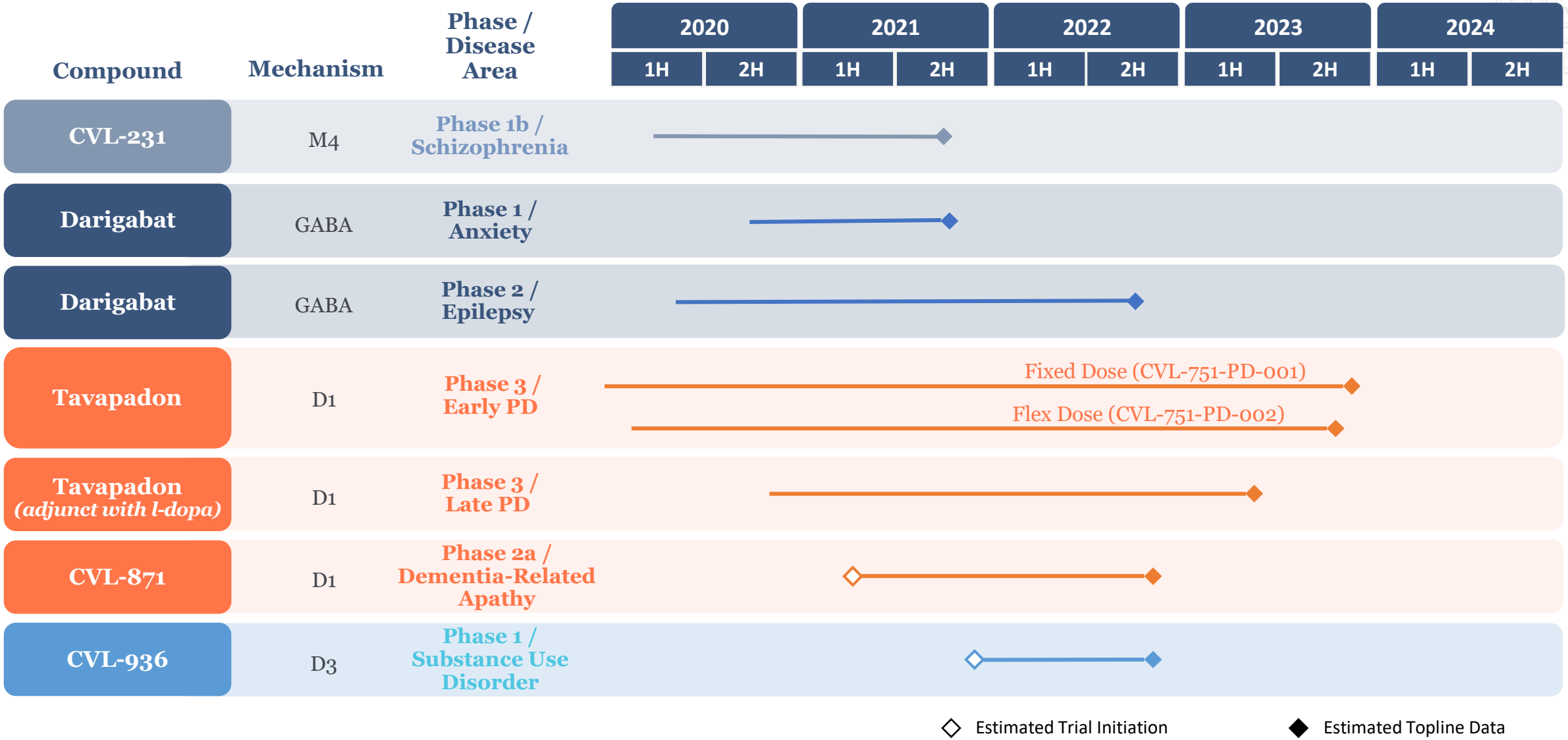
Kathleen Tregoning
Chief Corporate Affairs Officer

Yumanity Therapeutics · NPS Pharma · Vertex · Bristol-Myers Squibb · Novartis · Otsuka · Boston Scientific · Avanir pharmaceuticals · Onyx Pharmaceuticals · Biogen · Merck · Pfizer · Guidant · Imbrium Therapeutics · Purdue · Sanofi

Strong Track Record of Approvals

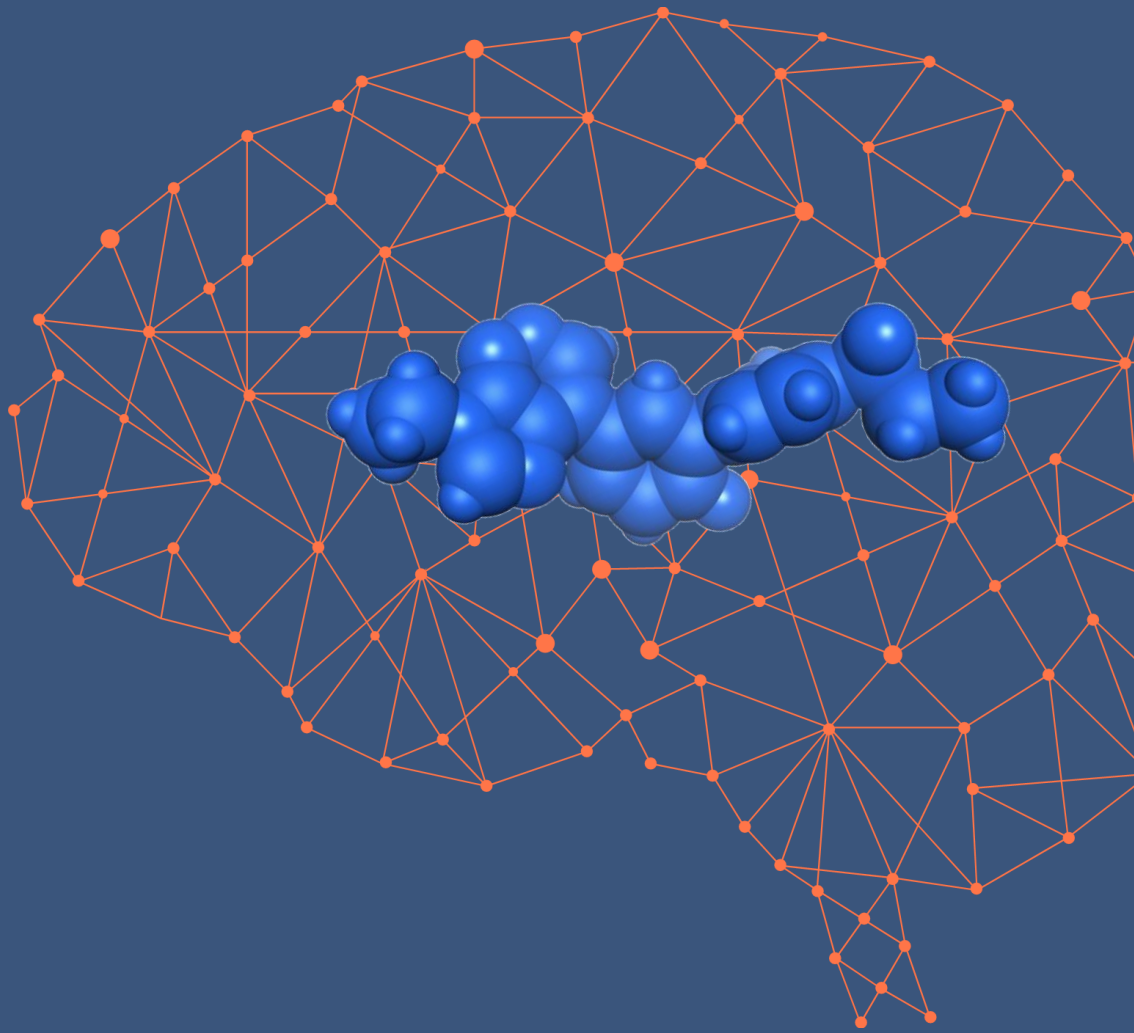
- ABILIFY® (aripiprazole)
- Abilify MyCite® (aripiprazole tablets with sensor) 2, 5, 10, 15, 20, 30 mg
- Abilify Maintena® (aripiprazole) for extended release injectable suspension
- Belsomra® (suvorexant) CIV 5, 10, 15, 20 mg tablets
- JYNARQUE® (tolvaptan) tablets
- Nexavar® (sorafenib) tablets
- Samsca® (tolvaptan)
- Kyprolis® (carfilzomib) for injection
- REXULTI® brexpiprazole
- ADHANSIA XR™ (methylphenidate HCl) CII extended-release capsules
- BLINCYTO® (blinatumomab) for injection

Expected Portfolio Timeline



Darigabat ($GABA_A$ PAM)

Selectively targeting the α-2/3/5 subunits of the $GABA_A$ receptor with the goal of enhancing anti-convulsant and anxiolytic effects without dose-limiting sedation



cerevel

Darigabat has Potential for Benzo-like Activity With Improved Side Effect Profile

Opportunity for New Treatment Option in Epilepsy & Anxiety

Across both indications, HCPs and patients are dissatisfied due to insufficient activity, side effects and poor tolerability

Darigabat

Targeted GABA α 2/3/5 Receptor Selectivity

Benzo-like Anxiolysis & Anticonvulsant Activity

Improved Tolerability

Potential for Reduced Abuse Liability

Epilepsy	~65M Patients Worldwide	30+AEDs Approved Poor Tolerability & Withdrawal	~30% of Patients Refractory to Medication
Anxiety	>280M Patients Worldwide with Anxiety Disorders	<50% Remission Rate	No new medications in over 10 years

Potential as chronic therapy with improved side effect profile and tolerability may expand use vs. traditional benzodiazepines

Sources: World Health Organization, DRG Market Research. Our World Data (ourworlddata.org). J Affect Disord. 2017 January 15; 208: 467–474.

Darigabat Speaker Bios

Rachel Gurrell
Darigabat Scientific Lead

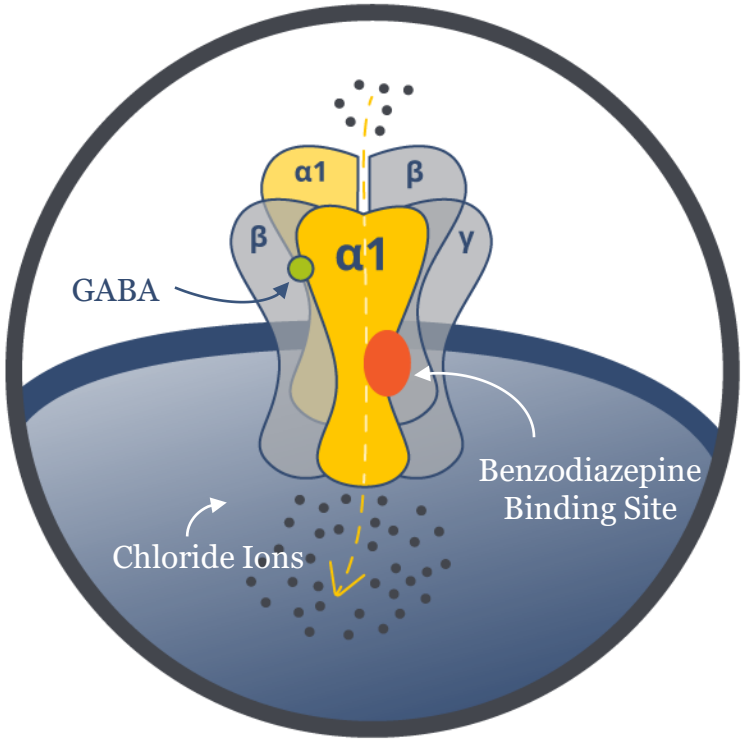
- Joined Cerevel October 2018
- Over 20 years experience in industry
- 16 years in various roles at Pfizer focusing on neuroscience and pain
- Lead Biologist, Clinical Lead and Program Lead for Darigabat
- 10 publications related to Darigabat / GABA pharmacology

Julie Jordan, M.D.
Senior Director, Global Clinical Development
Darigabat Medical Lead

- Joined Cerevel August 2019
- A.B. Harvard College and M.D. Harvard Medical School
- Internal Medicine Residency, Massachusetts General Hospital
- Former Clinical Instructor of Medicine at Harvard Medical School
- Led Clinical Development in Neuropsychiatry at Teva and Avanir

Mechanism of Action

$GABA_A$ Receptor Pharmacology 101

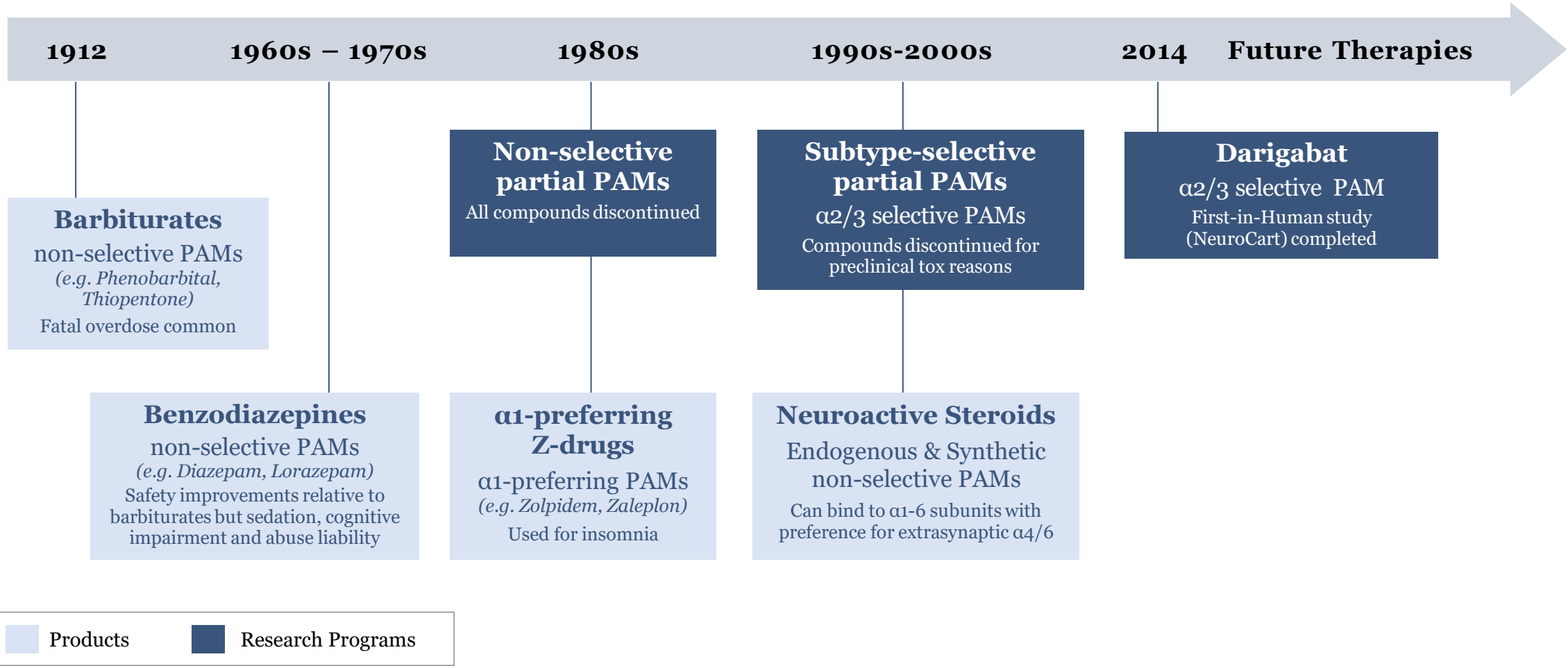


GABA-induced chloride influx hyperpolarizes neurons, preventing action potentials and dampens down excitability

- $GABA_A$ receptors are ligand-gated ion channels controlling chloride flux
- Benzodiazepine-sensitive $GABA_A$ receptors are pentameric and frequently contain:
  - Two α subunits – one of 4 subtypes (1, 2, 3, and 5)
  - Two β subunits
  - One γ subunit
- Benzodiazepines have no intrinsic effect of their own but are positive allosteric modulators (PAMs), potentiating the effects of GABA non-selectively at $GABA_A$ receptors containing α1/2/3/5 subunits
  - Used widely for anxiety, mood disorders, epilepsy, sleep, anesthesia

$GABA_A$ receptor PAMs – class innovation

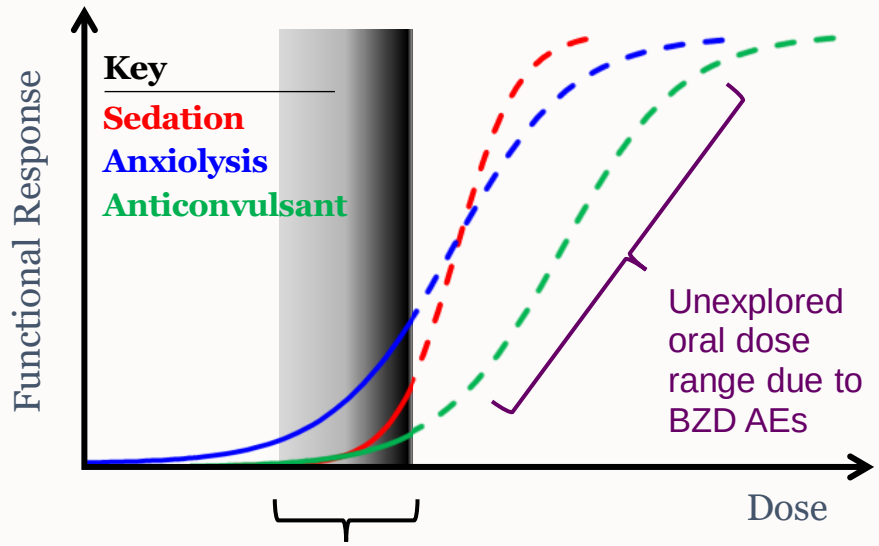
Timeline of GABA Research and Drug Development



The Problem With Benzodiazepines (abridged…)

- BZDs are efficacious in a range of indications but use and dose is limited by adverse events, even at low receptor occupancy
  - Sedation, somnolence, cognitive impairment, falls, overuse, misuse and addiction
- In general, BZDs are used acutely in epilepsy but not indicated for chronic use due to tolerance or loss of efficacy
- Darigabat has the potential to be used chronically by minimizing adverse events, risk of tolerance and abuse

Clinical experience with BZDs



Dose range for oral classical BZDs limited by sedative AEs
(<20% receptor occupancy)

Darigabat: New Mechanistic Class & Structurally Distinct from BZDs

- Pharmacology of α subtypes elucidated through knock-out mouse models ~ 20 years ago
- Development of "z-drugs" with higher α1 affinity to treat insomnia (not effective as anxiolytics)

$GABA_A$ α-2/3/5 Can Differentially Address Symptoms[1]

		Darigabat		
GABA subtype predicted effects:	α1	α2	α3	α5
Anti-convulsant	✓✓	✓✓		
Anxiolysis		✓✓	✓✓	
Analgesia		✓✓	✓	✓✓
Muscle Relaxation		✓✓	✓✓	
Sedation	✓✓			
Cognitive Impairment	✓✓	?	?	✓
Addiction	✓✓	✓		

Benzodiazepine side effects

Selectively Targeting Activity

α1-sparing PAM designed to
Enable clinical exploration at higher receptor occupancy than has been possible before
Improve side effect profile vs classical BZDs
Have broad-spectrum anticonvulsant and anxiolytic activity

Darigabat

To our knowledge, darigabat is the only GABA α-2/3/5 selective PAM in clinical trials for epilepsy or anxiety

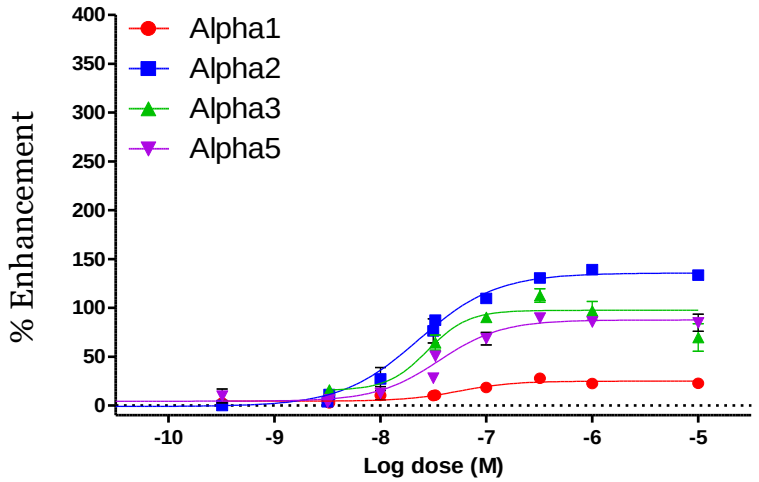
1. See appendix for relevant publications.

Darigabat In Vitro Selectivity Profile

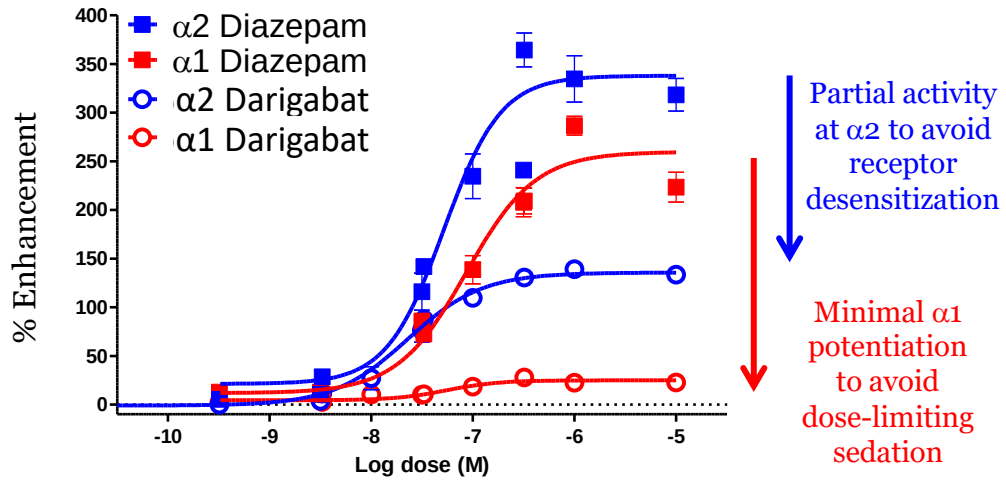
- Darigabat is structurally distinct from a classic BZD but binds to the BZD-binding site
- Darigabat is ***functionally selective*** for α2/3/5 containing $GABA_A$ receptors despite binding to all BZD-sensitive subtypes (α1/2/3/5)

$GABA_A$ Receptor Subtype	Human Binding Ki (nM)
α1β3γ2	0.16
α2β2γ2	2.47
α3β3γ2	1.06
α5β2γ2	18.04
α4β3γ2	>12500
α6β3γ2	>12500

Darigabat Demonstrates α1-sparing Activity In Vitro



Potentiation via α1 and α2 for Diazepam vs Darigabat

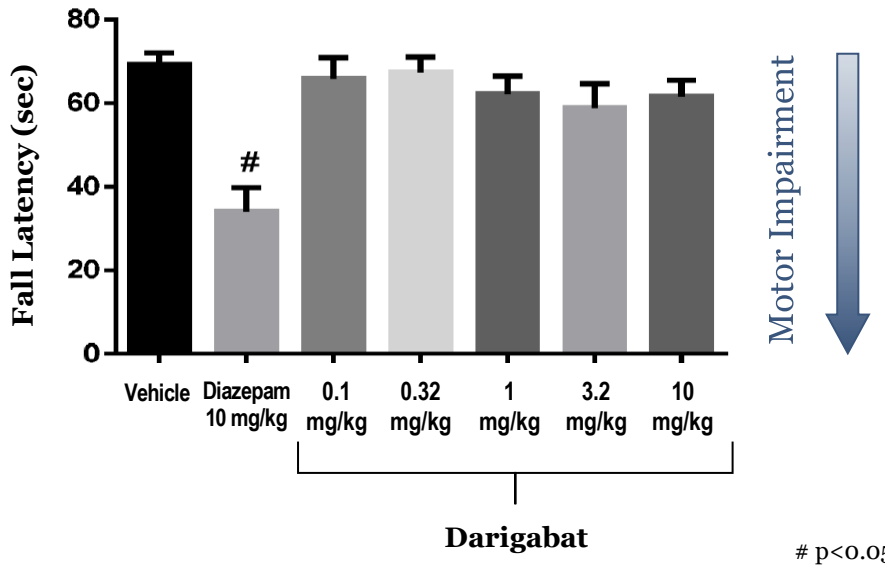


While darigabat binds to α1, it confers very low potentiation relative to α2, 3 and 5

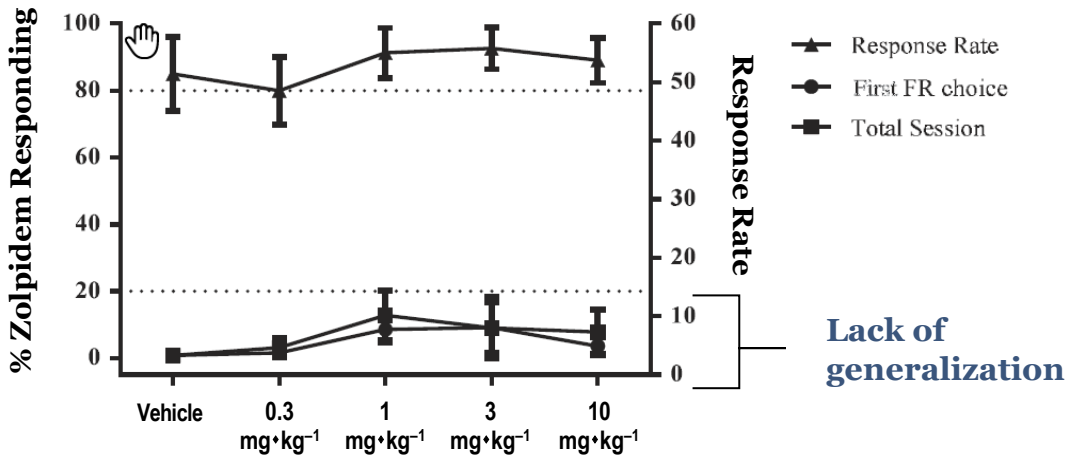
Preclinical data with Darigabat demonstrates α1-sparing activity, differentiated from a BZD

- Preclinical pharmacology and tolerability profile consistent with hypothesized effect of α2/3/5 engagement and minimal α1 pharmacology
  - No effect on mouse rotarod at >80% receptor occupancy
  - Drug discrimination: darigabat appears distinct from the α1 selective PAM zolpidem

Lack of Motor Coordination Impairment with Darigabat vs Diazepam



Darigabat-treated Rats do not Generalize to α1-selective Zolpidem, Demonstrating α1-sparing In vivo activity



α2/3/5 Subtype-selective PAMs avoided tolerance or withdrawal in preclinical models

Darigabat appears to avoid tolerance or withdrawal based on preclinical toxicity studies up to 9 months

- Chronic BZD use leads to tolerance or loss of efficacy over time
- Subtype-selective PAMs designed with "partial" activity at α subunits to reduce tolerance and withdrawal

Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective $GABA_A$ Receptor Modulators?

Christiaan H. Vinkers[1,2] and Berend Olivier[1,3]

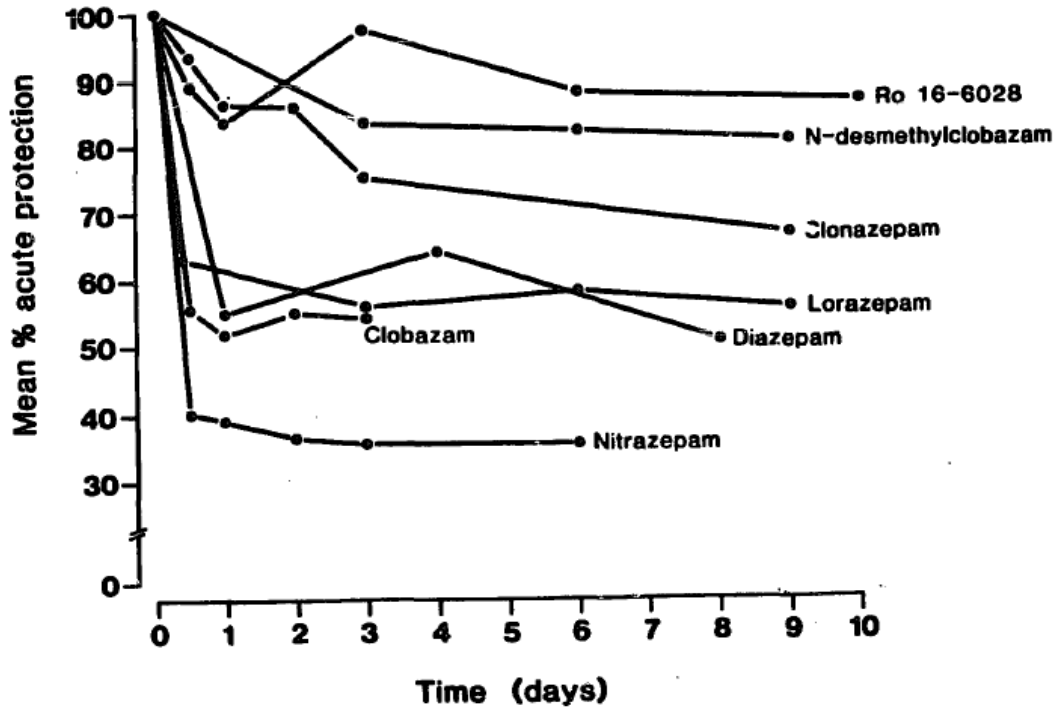
Advances in Pharmacological Sciences
Volume 2012, Article ID 416864, 19 pages
doi:10.1155/2012/416864

[1] *Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences and Rudolf Magnus Institute of Neuroscience, Utrecht University, Universiteitsweg 99, 3584CG Utrecht, The Netherlands*
[2] *Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands*
[3] *Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA*

Together, it can be concluded that so far, α2/ α 3 sub-type selective compounds have neither been found to lead to tolerance nor withdrawal symptoms

Lack of tolerance in mouse epilepsy model[1]

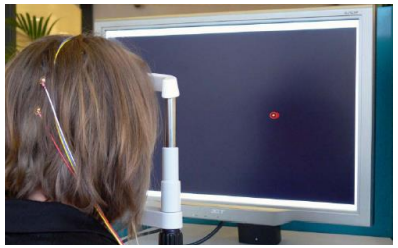
- Ro 16-6028, an α2/3/5 selective PAM, shows reduced tolerance following 10 days repeated dosing in an animal model of epilepsy
- The same dosing regimen with benzodiazepines show efficacy tolerance

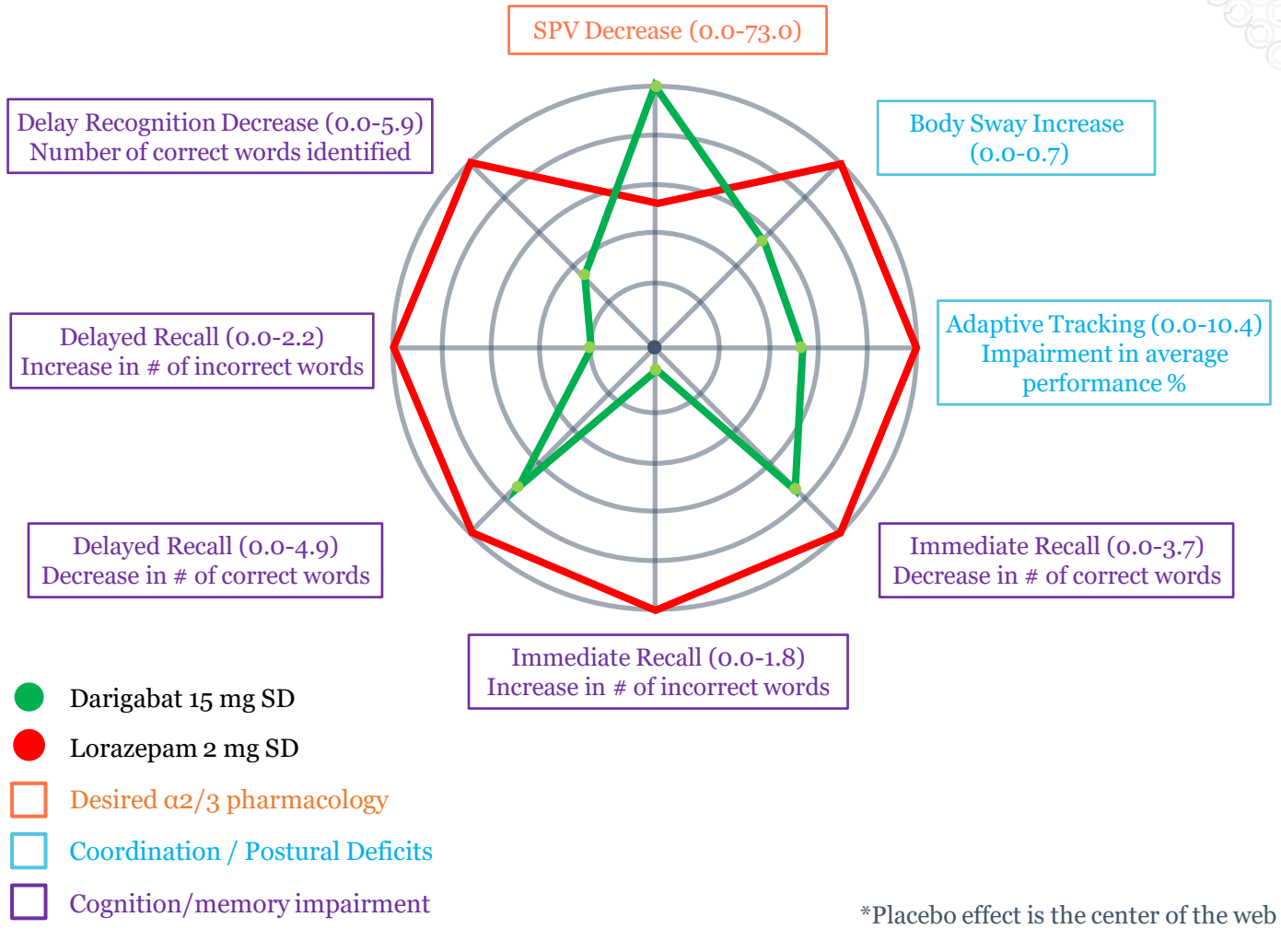


1. Haigh and Feely, TIPS – October 1988

Darigabat: Favorable Pharmacology in NeuroCart, Differentiated From a BZD

- **NeuroCart is a comprehensive battery of tests to evaluate CNS functional domains**
- **Darigabat first-in-human study tested the following brain functions based on known $GABA_A$ receptor pharmacology:**
  - Saccadic peak velocity (SPV) - desired α2/3 pharmacology
  - Body sway - undesired α1 pharmacology
  - Adaptive tracking - undesired α1 pharmacology
  - Visual-verbal learning test - undesired α1/5 pharmacology
- Relative to 2 mg lorazepam, darigabat demonstrated a larger decrease in SPV and smaller impairment on body sway, adaptive tracking and cognitive tests





*Placebo effect is the center of the web

Source: IND B7431001 - Phase 1 double-blind, randomized, placebo controlled, cross-over single dose escalation study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-06372865 in healthy subjects

Darigabat: Safety Profile

Preclinical safety

- Preclinical chronic toxicity studies with darigabat are complete (6-month rat and 9-month dog) and support long-term dosing at high receptor occupancy in the clinic
- Darigabat identified as a potential aneugen in in vitro and in vivo assays (observation of micronuclei)*
  - Pfizer self-imposed a dosing cap of 1/10 the NOAEL resulting in multiple dose clinical trials being limited to 7.5 mg BID (~60% receptor occupancy)
  - FDA Type C request to discuss the self-imposed dose cap resulted in feedback in 2017 that darigabat may be administered up to 50 mg BID (>80% receptor occupancy) in multiple dose trials
- Transgenic studies indicate $\alpha1 > \alpha2$ subtypes involved in addictive properties of BZDs
  - BZDs support self-administration (full generalization) in rodents and primate models
  - $\alpha2/\alpha3$ subtype selective compounds also support self-administration, but to a lesser extent

* aneugen is a substrate that causes a daughter cell to have an abnormal number of chromosomes. Believed to be a threshold response with no clear evidence for carcinogenicity. micronuclei are the small nuclei that form whenever a chromosome or fragment of a chromosome is not incorporated into one of the daughter nuclei during cell division.

NOAEL = no adverse effect level

Clinical Safety Across Trials

- Tested in over 300 subjects across nine completed and three ongoing trials
- Majority of side effects were mild or moderate
- Most common side effects: dizziness, drowsiness, fatigue
  - No sedation observed at any dose to date
- Side effects mitigated by titration in multi-dose studies, with no dose-dependent increases in AE severity
- Have achieved receptor occupancies >80% with only mild to moderate side effects
- To date, there have been no clinical observations reported related to aneugenicity (e.g. leukopenia)
- No evidence of withdrawal in multi-dose Phase 2 studies using the Physician's Withdrawal Checklist or on self-reported AEs in all clinical trials to date

GABA PAM Data Showed a Favorable Side Effect Profile Relative to Benzodiazepines in Phase 1 MAD Study

Multiple doses of darigabat

Phase 1 MAD Study – only mild AEs and limited somnolence up to 42.5 mg BID

Able to achieve >80% receptor occupancy without significant drowsiness observed

No evidence of withdrawal effects

No evidence of micronuclei formation

Phase 1 MAD Study

	Reaction	Week 1 (Titration)	Week 2 (Maintenance)	Week 3 (Maintenance)	Follow-up
Placebo	**No Reaction**	**4 / 4**	**4 / 4**	**3 / 4**	**4 / 4**
	Dizziness	-	-	1 / 4	-
	Drowsiness	-	-	-	-
25 mg BID (~80% RO(1))	**No Reaction**	**5 / 8**	**7 / 8**	**8 / 8**	**8 / 8**
	Dizziness	2 / 8	1 / 8	-	-
	Drowsiness	3 / 8	-	-	-
42.5 mg BID (>80% RO(1))	**No Reaction**	**4 / 7**	**6 / 7**	**6 / 7**	**6 / 7**
	Dizziness	3 / 7	1 / 7	1 / 7	1 / 7
	Drowsiness	-	-	-	-

No drowsiness observed following titration through doses of 42.5 mg BID

(1) Receptor Occupancy

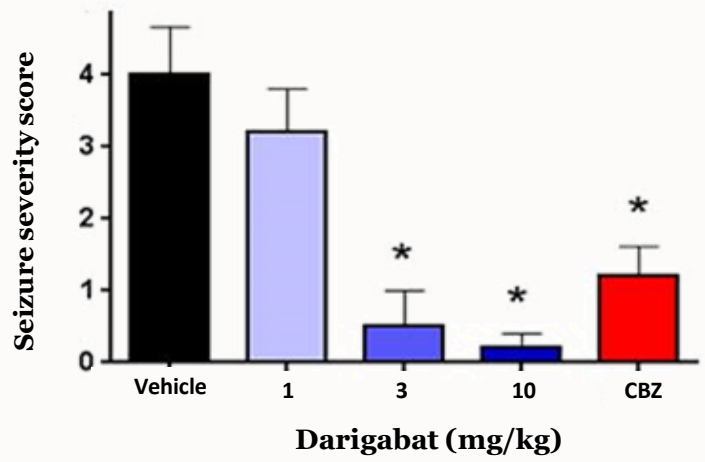
Data published in: Gurrell R, et al. Clinical Pharmacology in Drug Development, 2021.

Darigabat in Epilepsy

Darigabat is Anticonvulsant in a Range of Preclinical Models

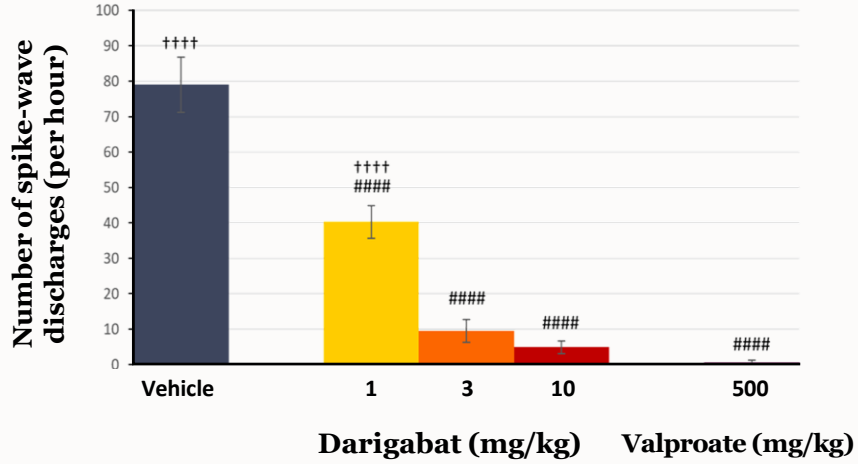
- Strong correlation of animal models of seizures translating to clinical activity across mechanism
- Darigabat demonstrated broad spectrum activity at ~>50% receptor occupancy
  - Darigabat is active in pentylenetetrazol-induced seizures
  - Amygdala kindling is a validated model for predicting activity in focal seizures
  - Genetic absence epilepsy rat model predictive of activity in absence (generalized) seizures

Amygdala Kindled Seizures in Rats: Focal Seizures



* p<0.05

Genetic Absence Epilepsy in Rats: Generalized Seizures



†††† p<0.0001 vs. valproate; #### p<0.0001 vs. vehicle

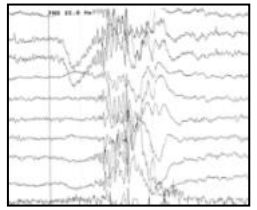
Darigabat demonstrated broad spectrum preclinical anticonvulsant activity, potentially through high receptor occupancy at α2 subunits

Duveau et al., CNS Neurosci Ther 2019; Owen et al., J Med Chem 2019

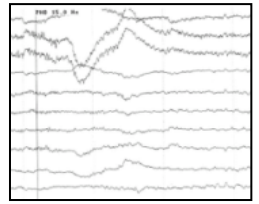
Identifying an Early Signal of Anticonvulsant Activity in the Photosensitive Epilepsy Model

- Population that translates well (efficacy and dose)
- Subjects exposed to bursts of light with different flash frequencies
- Epileptiform activity (photoparoxysmal response; PPR) observed on EEG
- Effective AEDs reduce/block the Standardized Photosensitive Range (SPR) at clinically relevant doses
  - Including levetiracetam and, more recently, cenobamate
  - Sedatives that are not anticonvulsant do not impact SPR indicating it is a selective effect

PPR recorded on EEG



Prevention of PPR recorded on EEG



Flash frqcy (Hz)	2	5	8	10	13	15	18	20	23	25	30	40	50	60
Subject X	-	-	-	+	←		SPR = 8			→	+	-	-	-

Table 2
Anti-epileptic drugs investigated in photosensitive POP trials and the comparisons to minimally efficacious doses in epilepsy.

AED	Doses investigated in POP trial (mg)	ED_{50-100} (mg)	MED (type of seizure indicated)[a]	Ratio MED:ED_{50-100}[b]
Diazepam	5	5	2 mg (adjunct in convulsive disorders)	0.4
Sodium valproate	600, 900	600	600 mg (partial)	1
Mephenytoin	400	400	200 mg (generalised)	0.5
Progabide	1200–1800, 2700	1200–1800	1800 mg[c] (partial + generalised)	1.2
Ethosuximide	400	400	500 mg (generalised)	1.3
Primidone	500	500	750 mg (generalised)	1.5
Lamotrigine	120, 240	240	225 mg (partial + generalised)	0.9
Nafimidone	200, 400	400	600 mg[d] (partial)	1.5
Carbamazepine	400	400	800 mg (partial + generalised)	2
Loreclezole	100–110, 150	100	12.5 mg[e] (partial)	0.13
Levetiracetam	250, 500, 750, 1000	500–1000	1000 mg (partial)	1.3
Carisbamate	500, 750, 1000	500–1000	350 mg[f] (partial)	0.4
Brivaracetam	10, 20, 40, 80	10	5 mg[g] (partial)	0.5

French et al., 2016; Yuen & Sims, 2014; Kasteleijn-Nolst Trenite et al., 2019

Photosensitive Epilepsy Model Study Design

- Randomized, double-blind, placebo- and active-controlled single dose cross-over study
- Up to 8 subjects to be randomized to one of four active-treatment cross-over sequence groups, where:
  - A = placebo
  - B = darigabat 17.5 mg (~ 60% receptor occupancy)
  - C = darigabat 52.5 mg (~ 80% receptor occupancy)
  - D = lorazepam 2 mg

Sequence	Treatment period 1	Treatment period 2	Treatment period 3	Treatment period 4
1 (n=2)	A	B	C	D
2 (n=2)	B	D	A	C
3 (n=2)	C	A	D	B
4 (n=2)	D	C	B	A

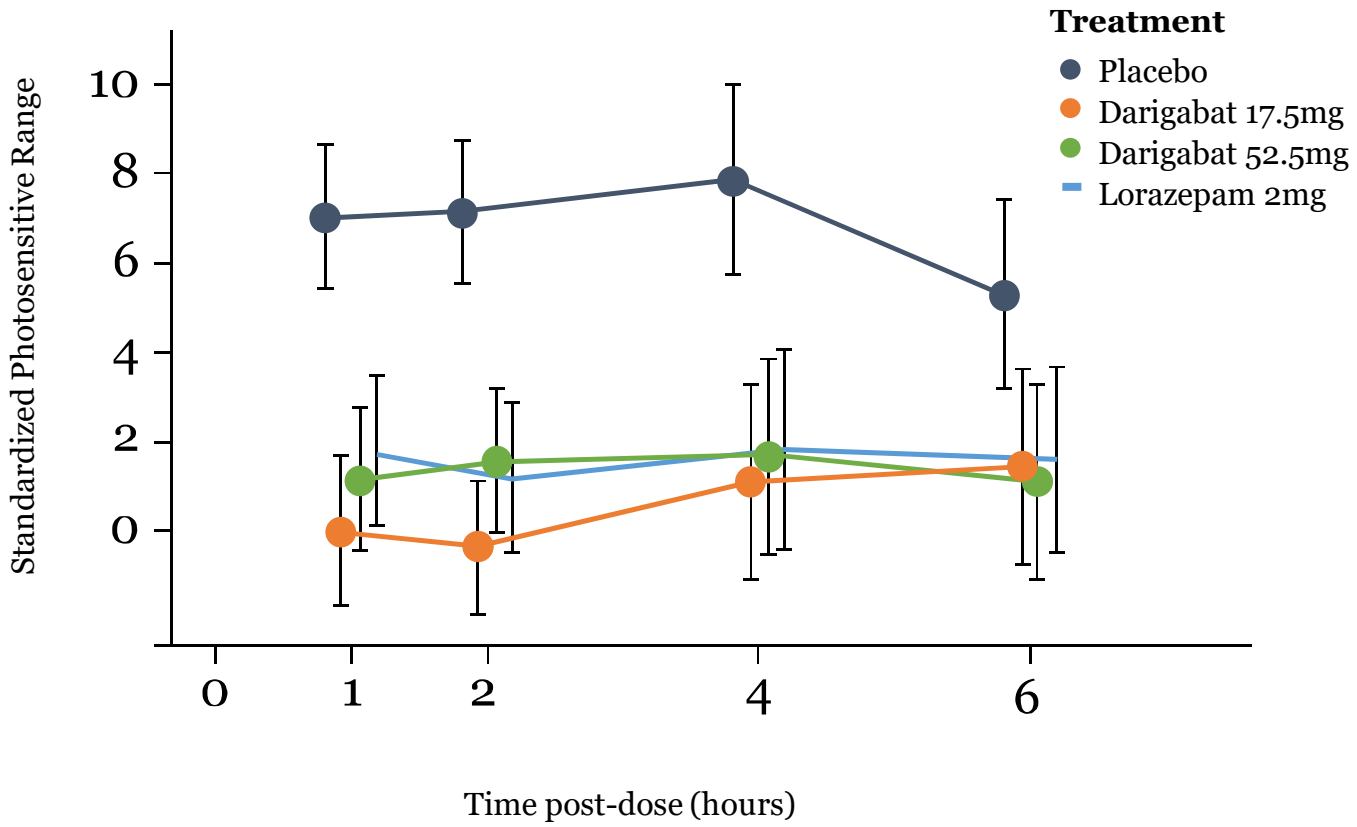
Washout 1-3 weeks between treatment periods

- Primary endpoint: reduction of standardized photosensitivity range (SPR)
  - SPR was measured pre-dose, then at 1, 2, 4 and 6 hours post-dose
- Secondary endpoint: proportion of subjects with complete suppression, partial suppression and no response

Gurrell et al., Neurology 2019

Darigabat Phase 2 Data Showed Benzo-like Anticonvulsant Activity in Photosensitive Epilepsy(1)

Darigabat in Single-Dose Photosensitive Epilepsy Study



Darigabat Results

Anticonvulsant activity comparable to lorazepam at both doses (achieving ~60 and 80% receptor occupancy)

Complete suppression in 6 of 7 subjects

Majority of AEDs developed for epilepsy that demonstrated positive published photoepilepsy results were approved(2)

Source: (1) IND B7431005: Phase 2 double-blind, randomized, cross-over study using lorazepam as a positive control; n=7 photoepilepsy subjects per arm; Gurrell et al., Neurology 2019; (2) Yuen and Sims. Seizure 23 (2014) 490–493

Darigabat Phase 2 Design in Focal Epilepsy: Data Expected 2H22

Darigabat Phase 2 Program In Epilepsy

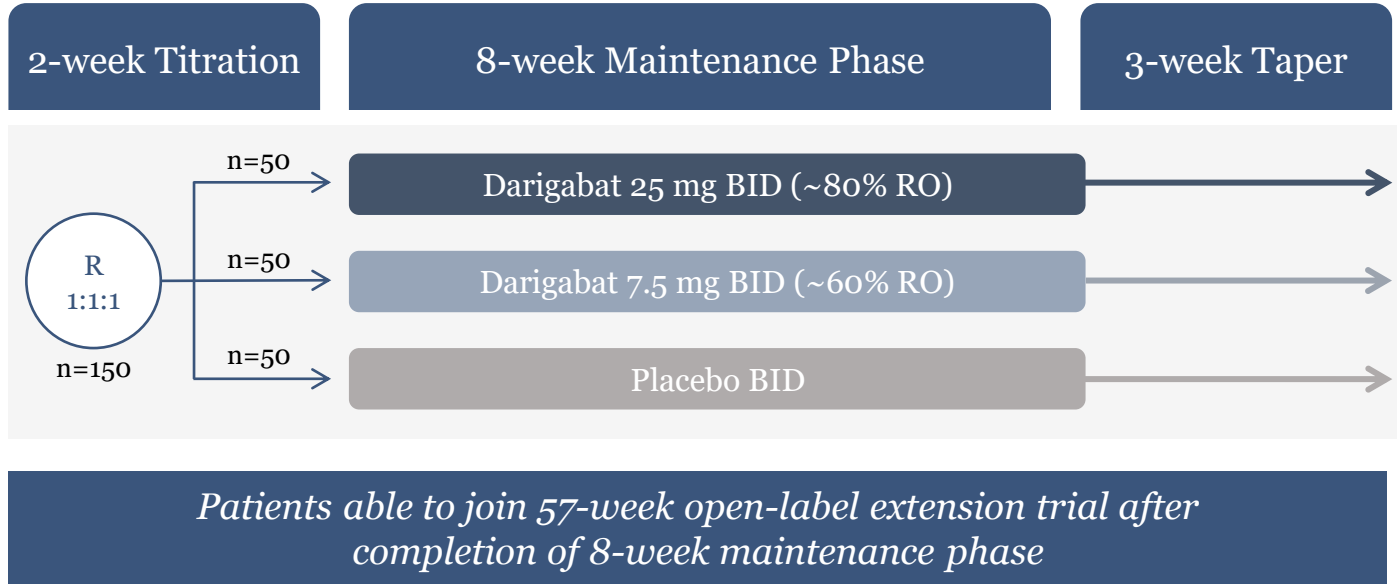
Targeting ~60 sites in 3 countries

Inclusion criteria

- Adults (18-75) with drug-resistant focal onset seizures
- History of 4+ seizures per month for at least 3 months
- 1-3 stable background AEDs allowed

Primary endpoint

- Reduction in focal onset seizure frequency



Focal epilepsy intended to establish proof of concept and side effect profile to support development in broader epilepsy indications

Epilepsy Treatment Landscape

Darigabat has Potential for Benzodiazepine-like Activity, Improved Side Effects and Chronic Dosing in Epilepsy

Darigabat

Potential to become first-line and adjunct therapy

Targeted GABA α 2/3/5 Receptor Selectivity

Benzodiazepine-like Activity

Improved Tolerability

Potential for Reduced Abuse Liability

Opportunity for New Treatment Option in Epilepsy

HCPs and patients are dissatisfied due to insufficient activity, side effects and poor tolerability

Large Patient Need

- ~65M Patients Worldwide
- >$6B G7 Revenues in 2018
- ~6% per year Branded AED[1] Market Growth through 2025

Benzos are highly efficacious, but…

- Poor Tolerability
- Desensitization & Loss of Efficacy
- Potential for Abuse
- Withdrawal

Potential as chronic therapy with improved side effect profile and tolerability may expand use vs. traditional benzodiazepines

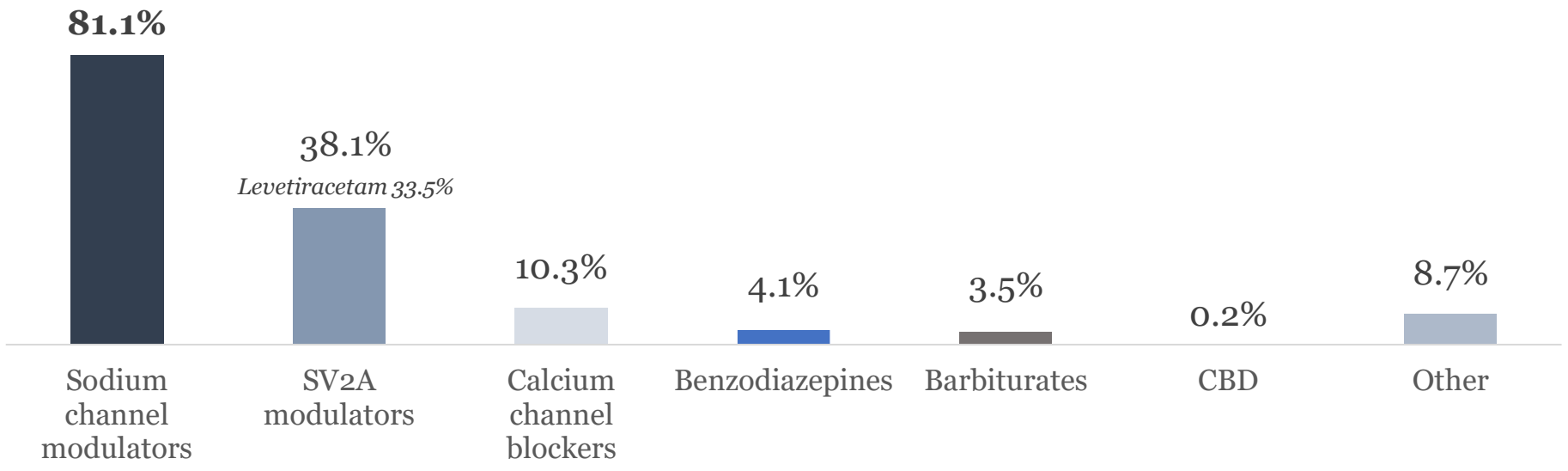
Source: World Health Organization, DRG Market Research

1. AED: Anti-Epileptic Drug

Treatment Options Dominated by Sodium Channel Modulators

Total Epilepsy Patient Share

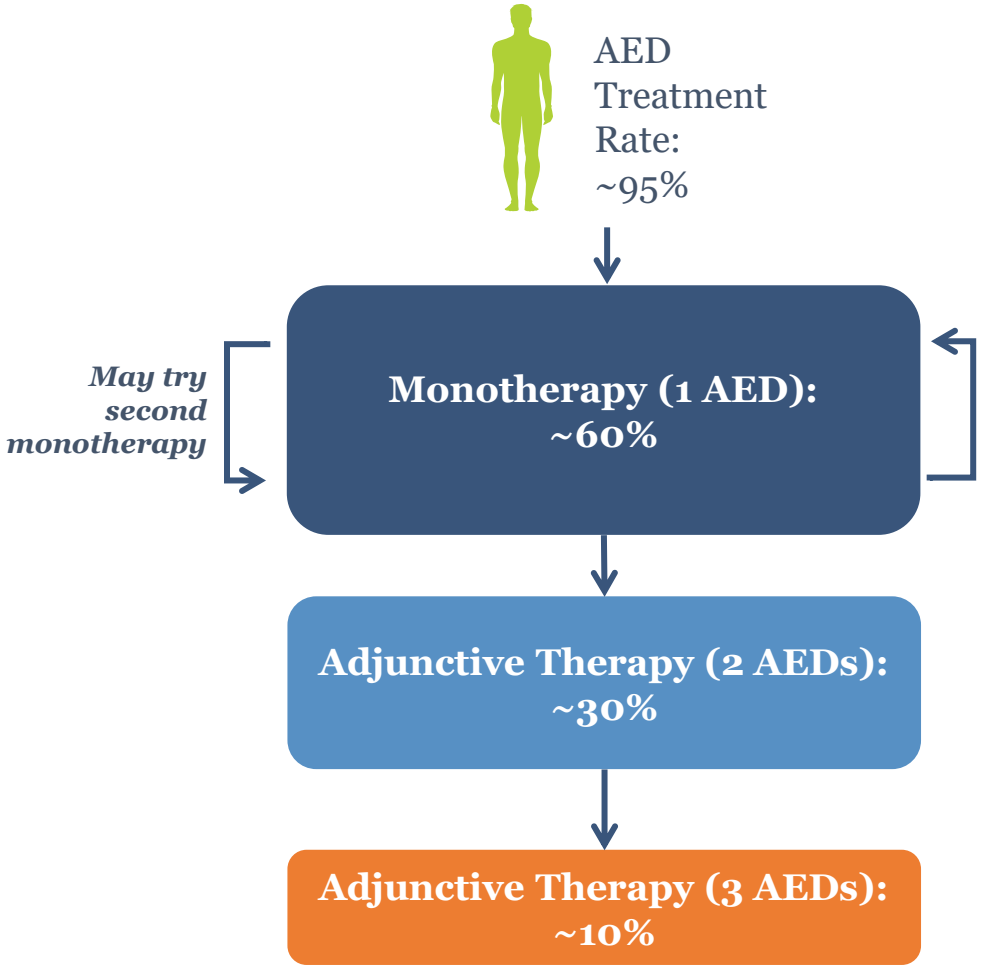
Note: Numbers sum to >100% due to significant polypharmacy



Significant need for a safe and well tolerated agent with a new mechanism

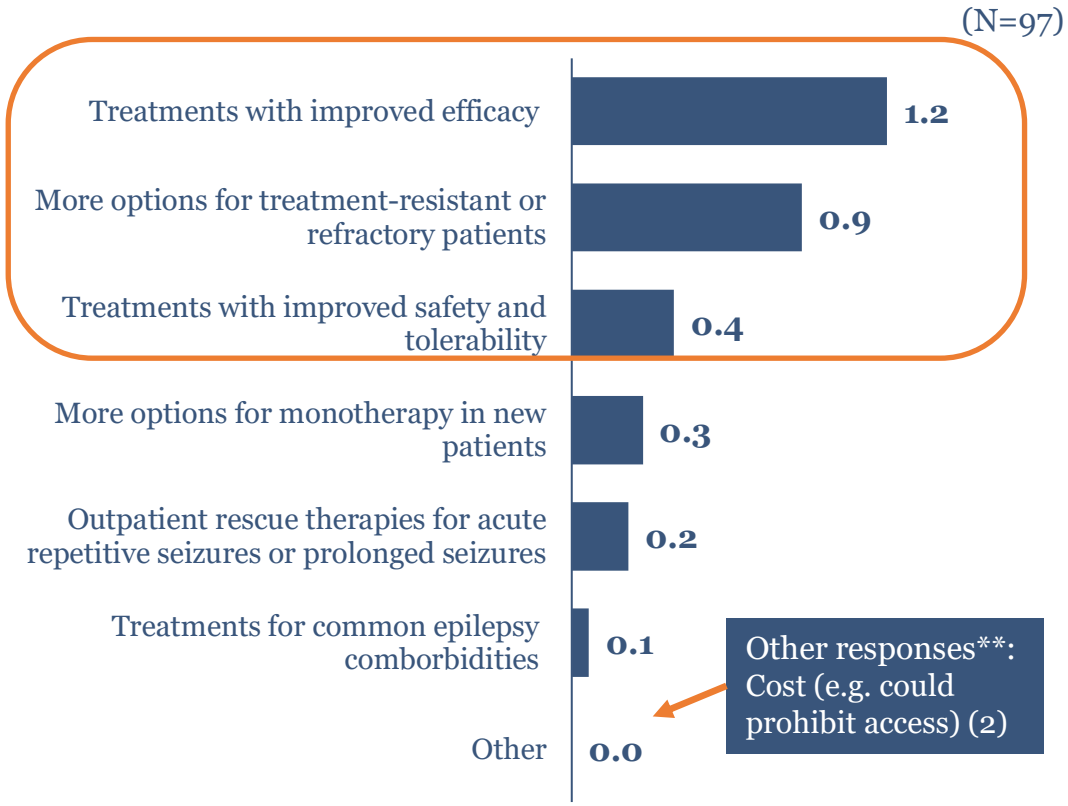
Sources: Decision Resources Epilepsy Disease Market and Forecast (08/2019), Thurman et al., Epilepsia 2011 and Zack et al., MMWR Morb Mortal Wkly Rep 2017

AEDs: Efficacy Still a Top Priority for Physicians, Followed by Safety



Top Drivers of Unmet Need

*Average Weighted Ranking**



Question 7: What are the top 3 drivers of unmet need among adult, focal epilepsy patients? Please rank the top 3 drivers.

* Average Weighted Ranking scale is designed such that higher numbers represent a higher rank as selected by more physicians.

** Parentheses signify number of physicians that selected this option

Source: Huron Primary Research (11/2019-12/2019)

Darigabat: Potential for Benzodiazepine-like Anticonvulsant Activity for *Chronic* Treatment

Darigabat Summary

- Novel mechanism
- Potential for better activity than chronic treatment alternatives
- Potentially favorable side effect profile
- Significant unmet patient need (focal & generalized epilepsy)

Pricing & Launch

- High branded market share despite many generics
- Slow erosion to generics
- Branded US price analogs >$10K/year

Darigabat in Anxiety

Darigabat has Potential for Benzodiazepine-like Activity, Improved Side Effect Profile and Chronic Dosing

Darigabat

Potential to become first-line and adjunct therapy

Targeted $GABA_A$ α 2/3/5 Receptor Selectivity

Benzodiazepine-like Activity

Improved Tolerability

Potential for Reduced Abuse Liability

Opportunity for New Treatment Option in Anxiety

HCPs and patients are dissatisfied due to insufficient activity, side effects and poor tolerability

High Unmet Need

- >280M[1] Patients Worldwide with Anxiety Disorders
- <50% Remission Rate[2]
- No new medications in over 10 years

Benzos are highly efficacious, but…

- Indicated for short-term use
- Poor Tolerability
- Potential for Abuse
- Withdrawal

Potential as chronic therapy with improved side effect profile and tolerability may expand use vs. traditional benzodiazepines

cerevel

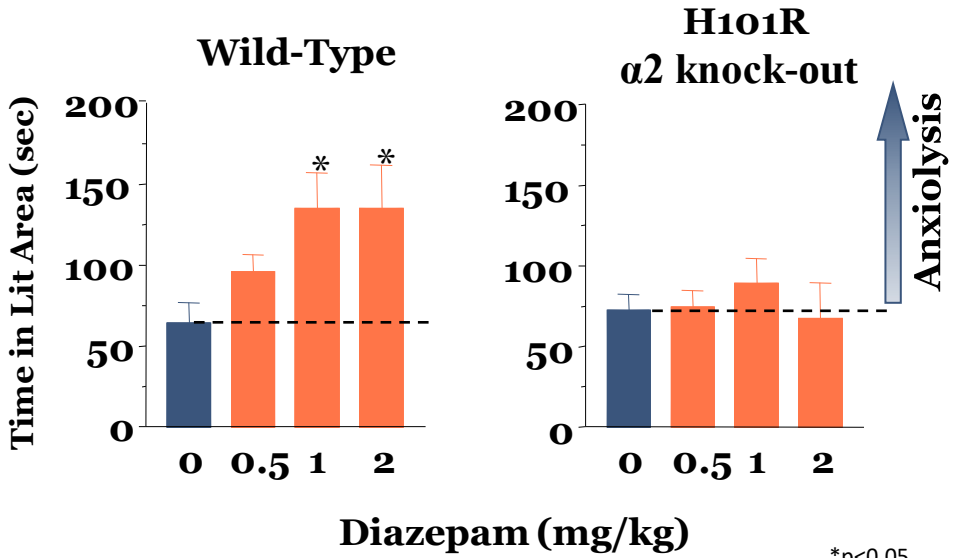
Source: 1. 2017 per ourworldindata.org 2. Kelly & Mezuk J Affect Disord 2017.

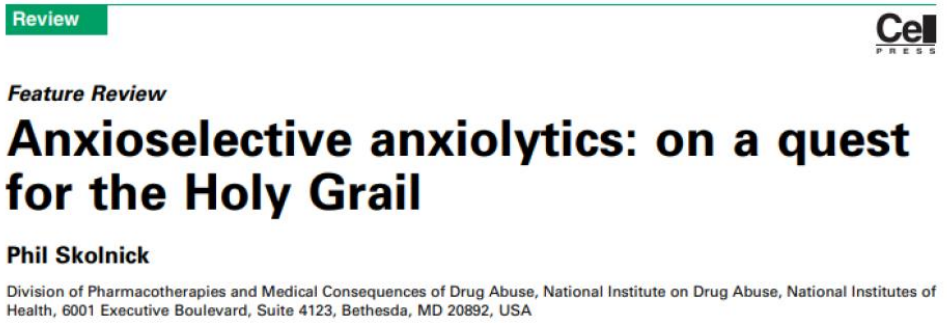
Identification of α2/3 Subunits as Targets for Anxiolysis

α2/3-subunits are responsible for the preclinical anxiolytic activity of BZDs

- The $GABA_A$ receptor is a precedented clinical target for anxiety disorders
- Functional knockout studies in mice have attributed the anxiolytic effects of BZDs to α2/3-containing $GABA_A$ subunits
- Exploiting α2/3-subunit pharmacology to exert anxiolytic benefits is "The Holy Grail"

Diazepam's anxiolytic effect eliminated in α2 knock-out mice




Review

Feature Review

Anxioselective anxiolytics: on a quest for the Holy Grail

Phil Skolnick

Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, National Institutes of Health, 6001 Executive Boulevard, Suite 4123, Bethesda, MD 20892, USA

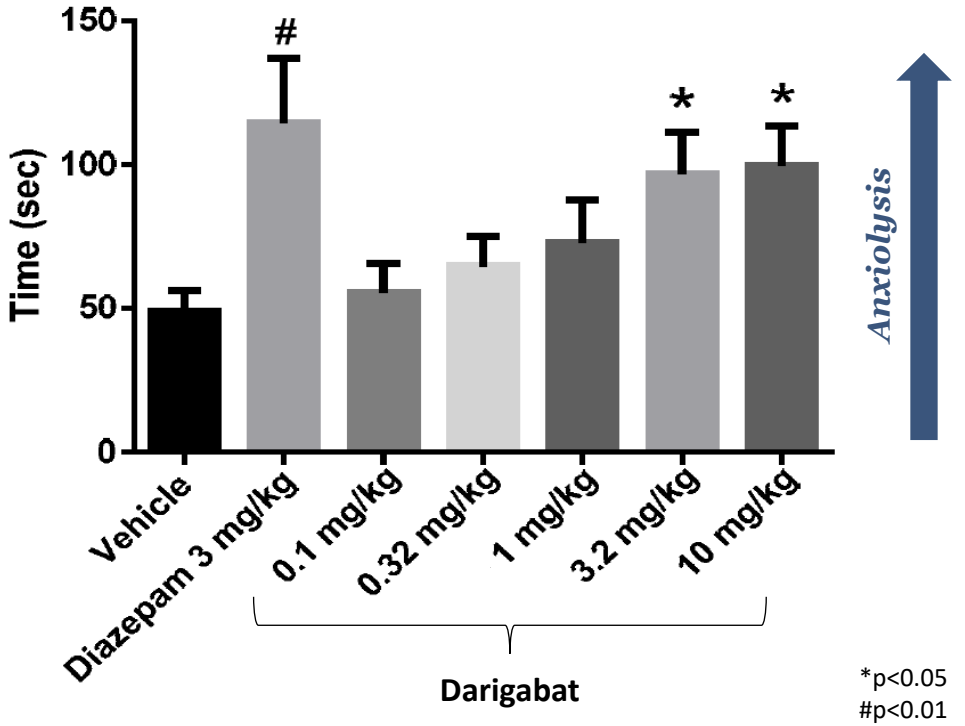
Low et al., Science 2000; Skolnick P. Trends Pharmacol Sci 2012.

Darigabat Demonstrated Activity in Preclinical Model of Anxiety

- Darigabat demonstrated anxiolytic activity in preclinical model of anxiety at ~ 70% receptor occupancy
- Model is sensitive to anxiolytics such as benzodiazepines and SSRIs

Darigabat retained preclinical anxiolysis, potentially by driving activity through high receptor occupancy at α2

Elevated plus maze in mice:
Increased time spent in open arms indicates anxiolytic effect



*p<0.05
#p<0.01

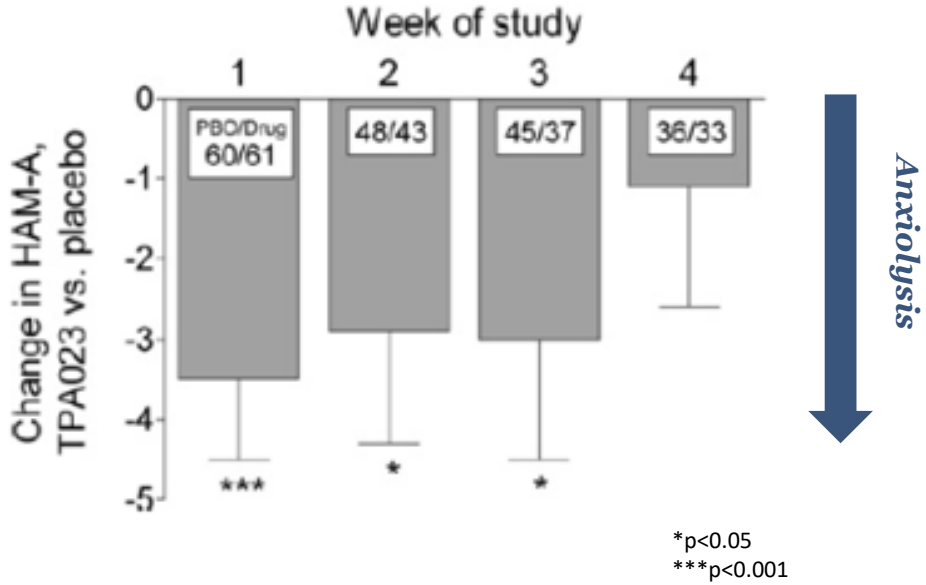
Source: Pfizer internal

Selective α2/3-Subunit Potentiation is Anxiolytic in Patients with GAD

Anxiolytic potential of α2/3-subunits has been demonstrated in the clinic

- TPA023 (lower α2 functional activity than darigabat) was anxiolytic in generalized anxiety disorder trials (3 combined Ph2 trials) at ~70% RO
  - Primary endpoint: Hamilton Anxiety Inventory (HAM-A)
  - TPA023 terminated due to compound-specific preclinical toxicity
- AZD7325 (significantly lower α2 functional activity than darigabat) was futile in a GAD trial at ~ 70% RO

α2/3-selective TPA023 in Ph2 GAD trial[1]



*p<0.05
***p<0.001

There is a clear reduction in anxiety at earlier time points with TPA023. However, limited patient numbers makes data interpretation challenging at week 4

Source: 1.Atack Adv Pharmacol 2009; Nickolls et al., BJP 2018

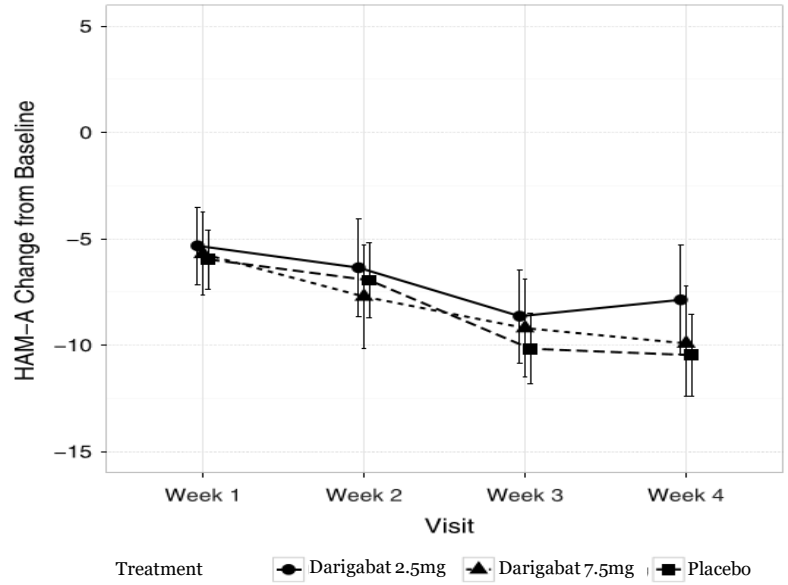
Prior Clinical Study of Darigabat in Anxiety

Use of subtherapeutic doses believed to account for lack of activity in prior trial

Phase 2: Generalized Anxiety Disorder

- Adjunctive therapy trial: enrolled patients with treatment-resistance – persistent anxiety symptoms despite standard-of-care therapy (minimum HAM-A score at entry ≥22)
- Sequential parallel comparison design
- Primary endpoint: HAM-A
- 4 weeks on treatment: 2.5 mg BID darigabat, 7.5 mg BID darigabat, placebo
  - Max receptor occupancy achieved ~ 60%
- Study stopped early for project prioritization - 90 enrolled of planned 384

Darigabat not differentiated from placebo on HAM-A



> 60% receptor occupancy remains unexplored in anxiety

Source: Simen et al J Clin Psychopharmacology 2019

The Hypercapnia (CO_2 Inhalation) Model

- CO_2 inhalation challenge is translational model providing proof-of-principle for anxiolytic activity in early clinical development
- Well-established in both healthy volunteers and in patients with panic disorder
  - Hypercapnia results in increased fear and panic, as measured by Visual Analogue Scales (VAS) and the Panic Symptom List (PSL)[1]
- The proposed mechanism of the anxiety induced by hypercapnia model is decreased GABA and increased noradrenaline[2]
- The model is sensitive to drugs used to treat anxiety disorders (including benzodiazepines & SSRIs) and emerging new treatments with novel mechanisms

CO_2 inhalation induces fear and panic symptoms in healthy volunteers and panic disorder patients

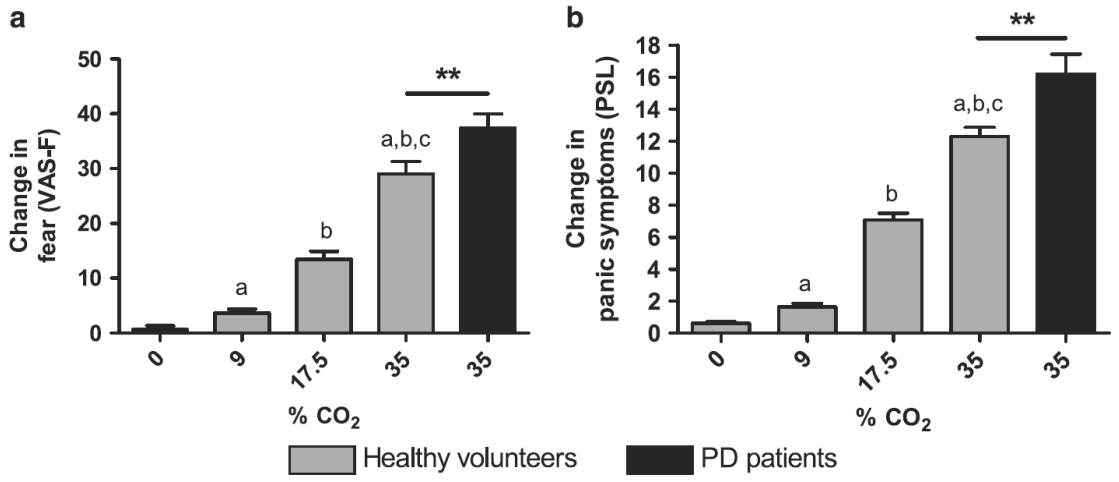


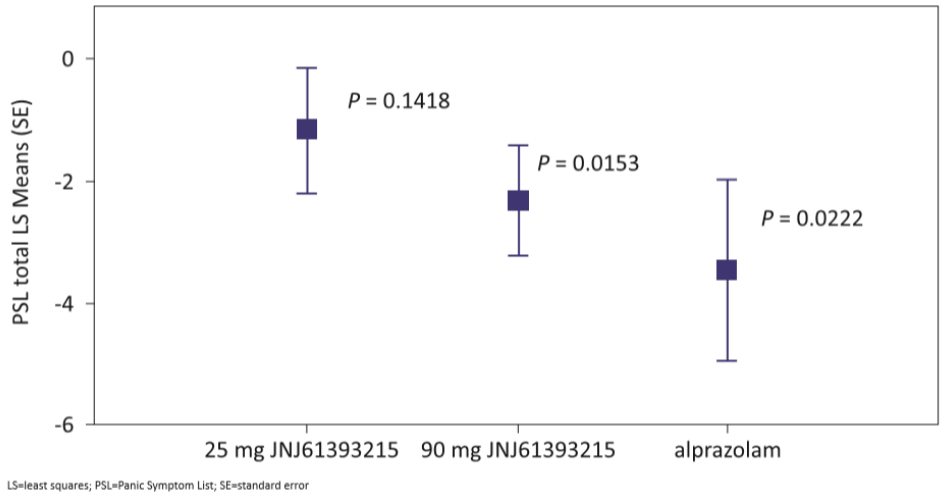
Figure 2. Effect of CO_2 on self-reported fear and panic symptoms in healthy volunteers and PD patients. In healthy volunteers (gray), both fear (**a**) and panic symptoms (**b**) increased dose-dependently. Inhaling 35% CO_2 triggered a more robust response in patients (black) when compared with healthy volunteers. Data represent mean+s.e.m. (**a**) Compared with 0% CO_2, $P < 0.001$; (**b**) compared with 9% CO_2, $P < 0.001$; (**c**) compared with 17.5% CO_2, $P < 0.001$; $^{**}P < 0.01$. PD, panic disorder; PSL, Panic Symptom List; VAS-F, Visual Analog Scale for fear.

1. Leibold et al., Trans Psychiatry 2016 2. Bailey et al., J Psychopharm 2011
*PD patients = Panic Disorder patients

Hypercapnia Case Study: Orexin-1 Inhibitor JNJ-61393215

- Randomized, placebo and active-comparator (alprazolam)-controlled, partial cross-over study in healthy volunteers. Study drugs were administered for 7 days.
  - Study performed at the Centre for Human Drug Research (CHDR), Netherlands

Anxiety symptoms induced by the 35% CO_2 challenge: LS Means differences between active treatments and placebo



LS=least squares; PSL=Panic Symptom List; SE=standard error

Individual PSL-IV anxiety items scores in each treatment group

	PBO	JNJ-61393215 25 mg	PBO	JNJ-61393215 90 mg	PBO	ALPRAZOLAM 1mg
Dizziness	1.9	1.3	2.3	**1.8**	2.1	1.7
Choking/Gasping for breath	1.8	1.9	2.5	**1.8**	2.1	1.9
Hot flashes/Cold shiver	0.3	0.3	0.9	**0.5**	0.8	0.2
Nausea	0.4	0.2	0.7	**0.5**	0.8	0.2
Palipitations	1.9	1.3	1.8	1.8	1.9	1.3
Sweating	0.7	0.8	1.3	**0.9**	1.3	1.0
Shortness of breath	1.6	1.8	2.3	**2.1**	2.2	1.9
Numb/tingling	0.8	0.7	1.5	**1.2**	0.9	0.7
Depersonalization/ derealization	0.5	0.6	1.2	1.2	1.1	0.8
Fear of dying	0.1	0.1	0.3	0.4	0.3	0.1
Fear of losing contract	0.3	0.3	0.4	0.4	0.3	0.4
Chest pain discomfort	0.3	0.2	0.8	**0.7**	0.1	0
Trembling/shaking	1.3	1.3	1.6	**1.4**	1.1	1.2

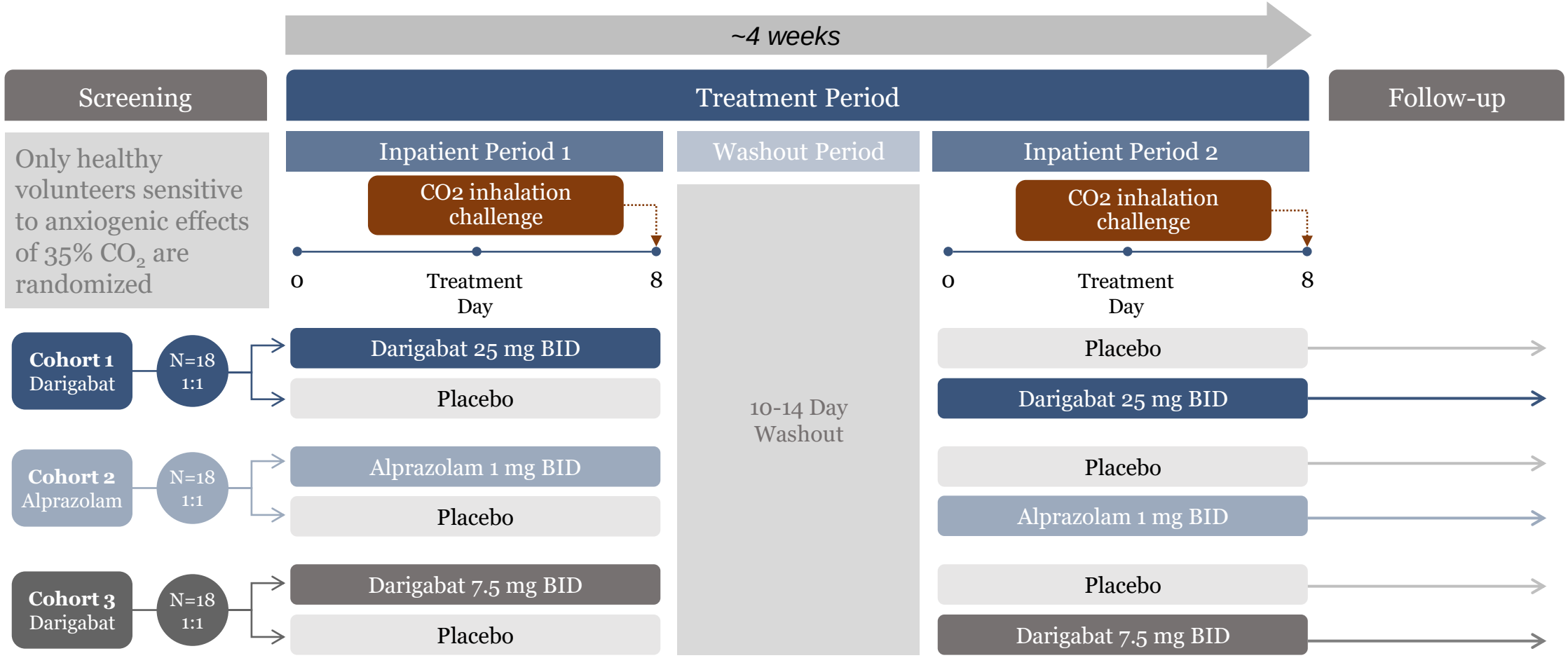
PBO=placebo; PSL=Panic Symptom List

- Significant anxiolytic effect of alprazolam at a therapeutic dose (1 mg BID)
- Anxiolytic effect of JNJ-61393215 (90 mg BID) present in most participants → *POC in subjects with major depressive disorder and anxious distress underway (NCT04080752)*

Source: Salvadore et al., 2020 Translational Psychiatry

Darigabat Phase 1 Design in Acute Anxiety - Data Expected 2H21

Randomized, double-blind, placebo- and active-controlled crossover design with multiple doses over 8 days. Primary endpoint: Panic symptoms list[1]. Doses selected to achieve ~60 and 80% receptor occupancy



1. The Panic Symptom List (PSL) includes 13 symptoms scored across a range of 0 (absent) to 4 (very intense) that is used to assess panic anxiety. Liebold et al. Trans Psychiatry. 2016.; Bailey et al. J Psychopharm. 2011.; Malizia et al. Arch Gen Psychiatry. 1998.; Salvatore et al. Translational Psychiatry 2020.

RO = Receptor Occupancy

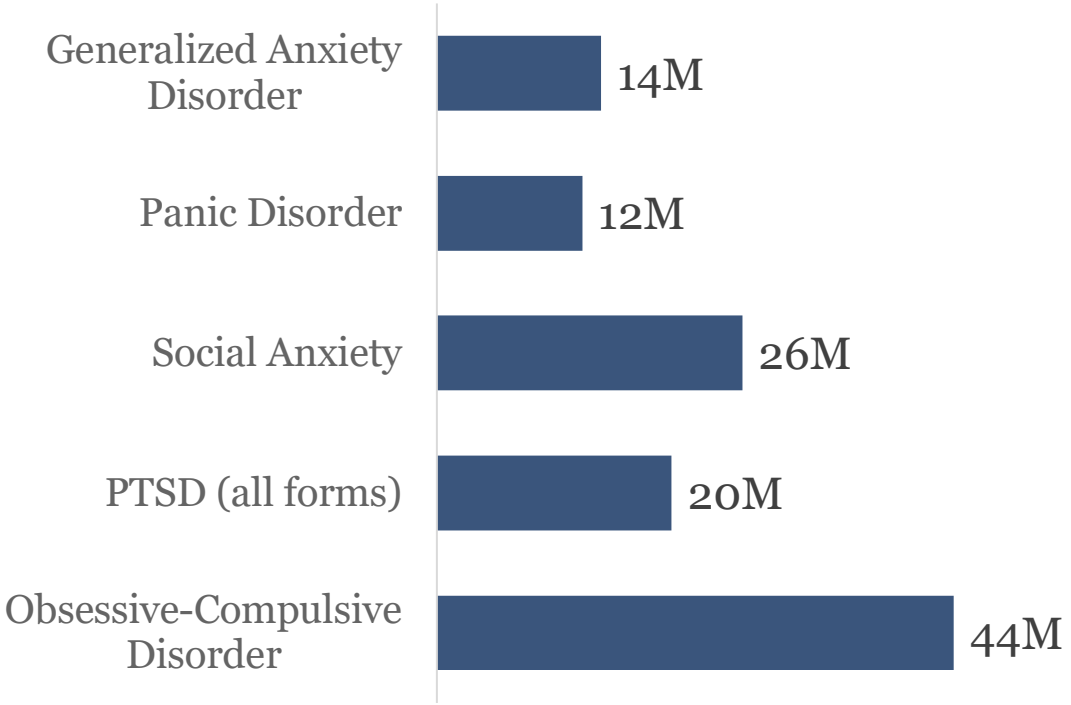
Anxiety Treatment Landscape

>100M people in the 8 Large Countries and >280M WW Suffer from an Anxiety Disorder[1,2,4]

- Prevalence of anxiety disorders worldwide ranges from 2.5 to 7% depending on country
- Anxiety disorders are the most common form of mental illness in the US, affecting >45M adults or ~15% of the population each year
- Females are disproportionally impacted by anxiety disorders by over 3:2 compared to males
- GAD will increase by 8% over the next 20 years from 14M to over 15M[3]
- ~40M U.S. prescriptions for alprazolam in 2018[5]

Estimated 2020 12-Month Total Prevalent Cases[1-4]

8 Large Countries, All Ages >18 Years

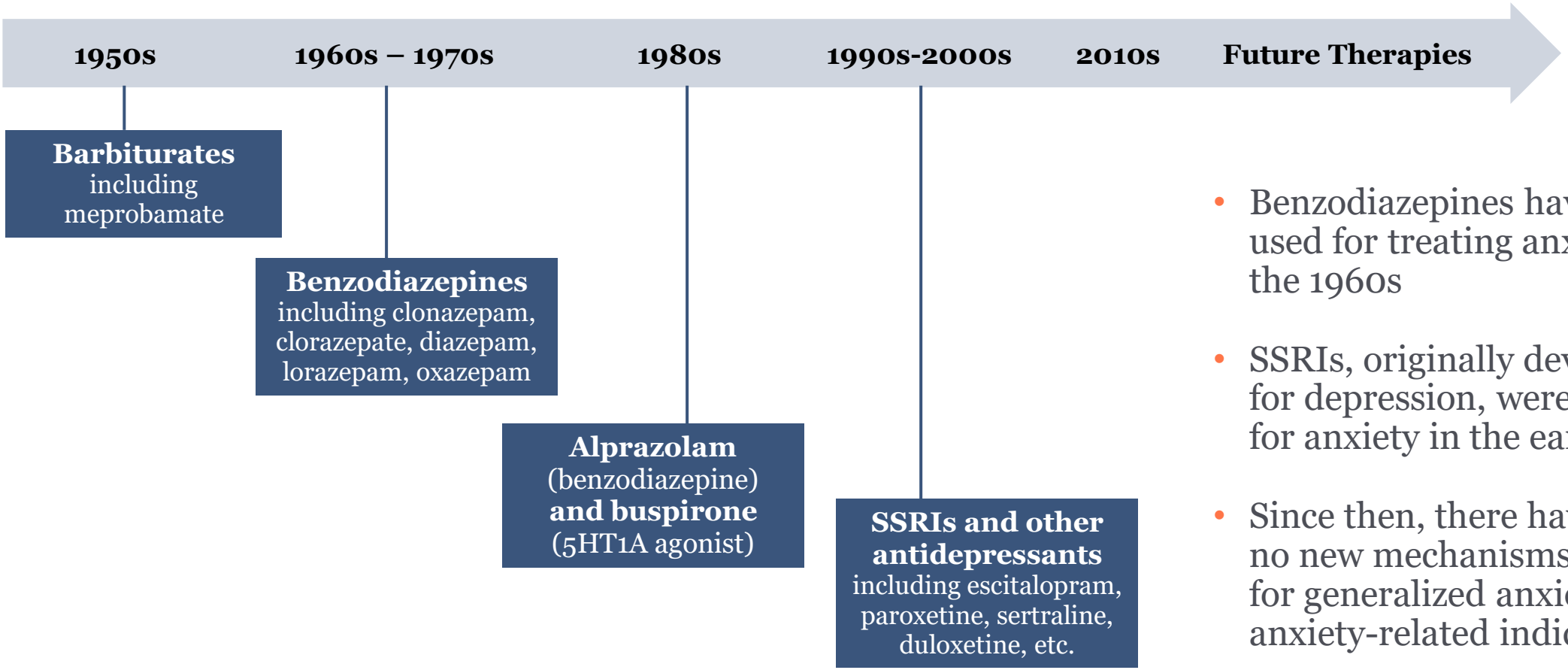


Sources: 1. GlobalData (accessed Dec 2020), 2. 2017 per ourworldindata.org/mental-health, 3. Decision Resources General Anxiety Disorder Epidemiology (2018), 4. Sasson et al. J Clin Psychiatry, 5. https://psychcentral.com/blog/top-25-psychiatric-medications-for-2018 (sourced from IQVIA)

8 Large Countries = US, 5EU, Japan and China

No New Medications in Anxiety in Over a Decade

Timeline of Medications Approved for Anxiety and Anxiety-Related Disorders[1]



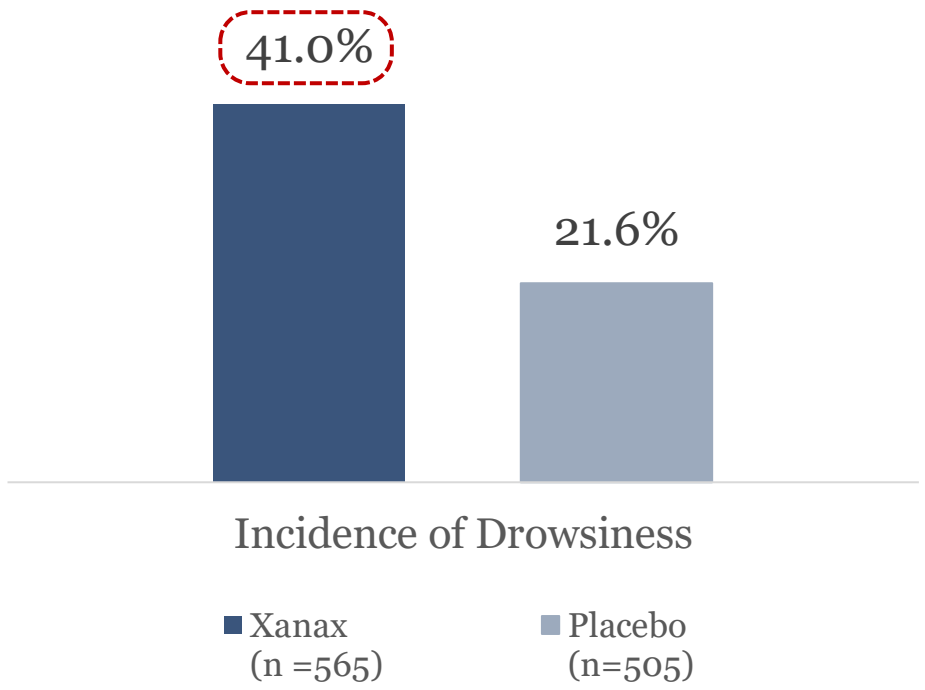
- Benzodiazepines have been used for treating anxiety since the 1960s
- SSRIs, originally developed for depression, were approved for anxiety in the early 2000s
- Since then, there have been no new mechanisms approved for generalized anxiety or any anxiety-related indication

1. Adapted from Santori, Singewold; Pharmacology & Therapeutics 204 (2019) 107402

Patient Journey and Standard of Care for Anxiety

- Benzodiazepines used to treat anxiety disorders for > 60 years and remain in widespread use
- Adoption of SSRIs as first-line therapy has been due to safety concerns with long term use of benzodiazepines
- Onset of symptom relief is slow with SSRIs; patients wait up to 4+ weeks before symptom relief
- By contrast, benzodiazepines have much faster speed of onset and, at least initially, greater efficacy
- Patients prescribed an SSRI may experience an initial increase in anxiety symptoms, and benzodiazepines are often prescribed during this "cover" period
- Successful treatment requires tailoring options to individuals and may often include a combination of modalities

Xanax Label: TEAE Incidence (Drowsiness)*



Sedation is a persistent side effect with benzodiazepines at anxiolytic doses

Source: Locke et al. AFP 2015
*Xanax FDA Label, fda.gov. TEAE = Treatment-Emergent Adverse Events

Darigabat in Anxiety: A Novel Mechanism with Benzodiazepine-like Anxiolysis for *Chronic* Treatment

Darigabat in Anxiety Summary

- Novel mechanism
- Potential for better activity with faster onset than chronic treatment alternatives (e.g. SSRIs)
- Potentially favorable side effect profile (including reduced sedation and abuse liability)
- Potential to replace need for benzodiazepines as “induction” therapy
- Millions of patients with high unmet need

Darigabat: Summary Highlights

High Unmet Need

- 30% of epilepsy patients fail to achieve seizure control despite treatment
- >280 million patients living with anxiety disorders; no new treatments in >10 years

α2/3/5 selective Mechanism of Action

- Benzodiazepines are limited to acute use
- Potential for benzodiazepine-like efficacy with minimal side effects and ability to dose chronically

Clinical Data Demonstrating…

- α2/3/5 pharmacology
- Anti-epileptic potential
- Favorable tolerability profile relative to benzodiazepines

Three Ongoing Studies

- Phase 2 in Focal Epilepsy + OLE: **data expected in 2H 2022**
- Phase 1 in Acute Anxiety: **data expected in 2H 2021**

Early Discovery Initiatives

Cerevel's Differentiated Approach to CNS Disease

Leveraging Expertise in Neurocircuitry

Differentiated Understanding of Neurocircuitry

→

Receptor Binding/Modulation

→

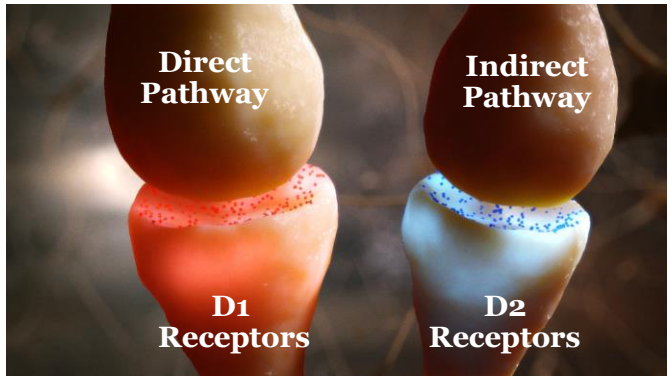
Highly Selective Small Molecules in Clinical Studies

Pipeline Uniquely Based on

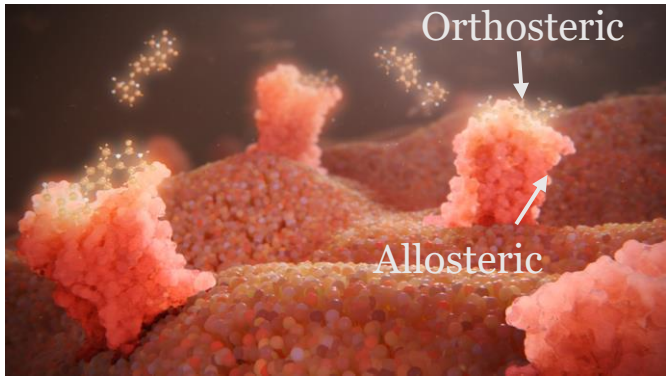
- Targeted Receptor Subtype Selectivity
- Optimized Receptor Pharmacology
- Robust Data Packages

Cerevel's Neurocircuitry Approach to Treating Neuroscience Diseases

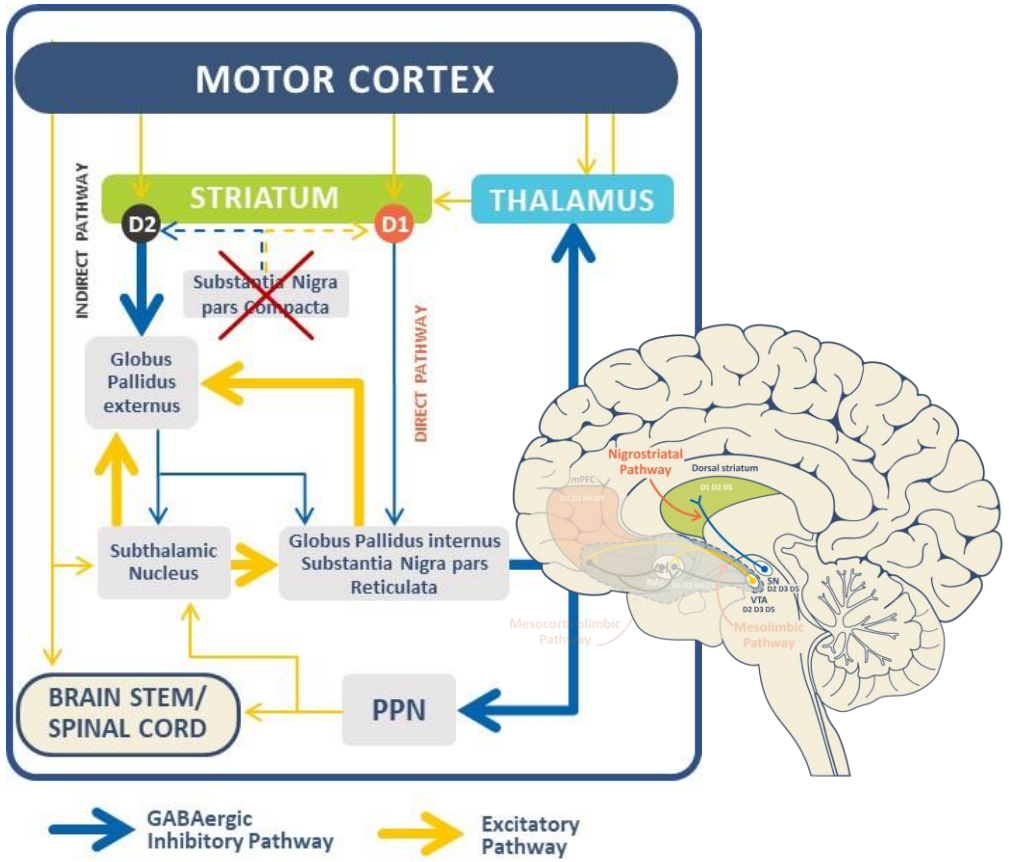
Receptor Selectivity



Receptor Binding / Modulation



Differentiated Understanding of Neurocircuitry

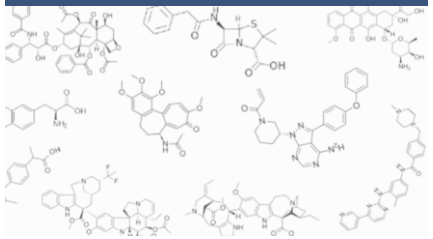


Building Discovery and Translational Capabilities

Target ID | Target Validation | Lead ID | Lead Opt | Clinical Enabling | Phase 1 | Phase 2 | Phase 3

Genetics

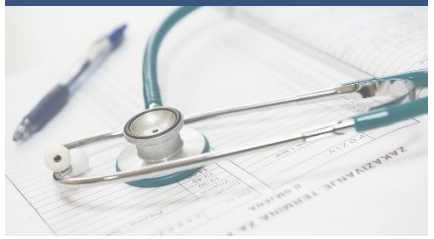
Chemical Libraries



in vitro

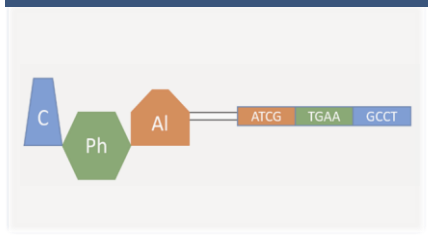
Toxicology

Clinical Trials



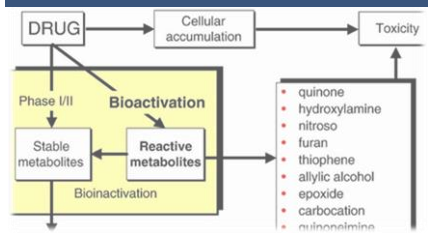
CRISPR Screens

DNA-Encoded Libraries



in vivo

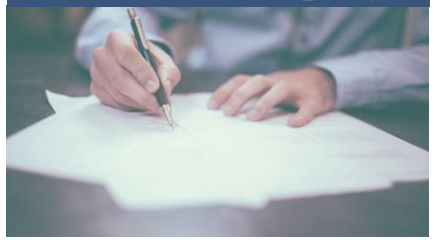
DMPK



Electrophysiology

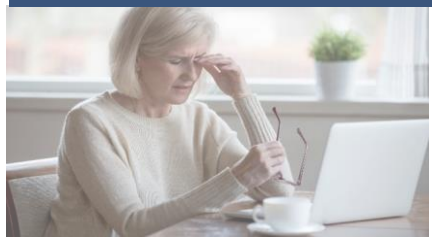
Artificial Intelligence

Intellectual Property



Behavioral Neurobiology

Patient Stratification



Imaging

Cerevel New Home: 222 Jacobs St, Cambridge

- Cerevel's new facility is ~60,000 sq ft
- 15,500 sq ft dedicated to laboratories
- Located in new Cambridge Crossing development
- Anticipated move: 1Q 2021

Cerevel Preclinical Portfolio: The Next Chapter

Compound	Mechanism	Disease Area	Upcoming Milestone	
CVL-354	KOR Antagonist	MDD / Substance Use Disorder	IND Filing – 1H 2021	★
Lead Optimization	M4 Agonist	PD-LID	Candidate Selection	
Lead Optimization	PDE4B	Schizophrenia / MDD	IND Filing – YE 2021	★
Lead Optimization	LRRK2	Parkinson's	Candidate Selection	
Lead Generation	Undisclosed	Neurodegeneration	Lead Generation	
Lead Generation	Undisclosed	Parkinson's	Lead Generation	

PDE4 & KORA Speaker Bios

Phil Iredale, Ph.D.
Vice President, Head of Biology

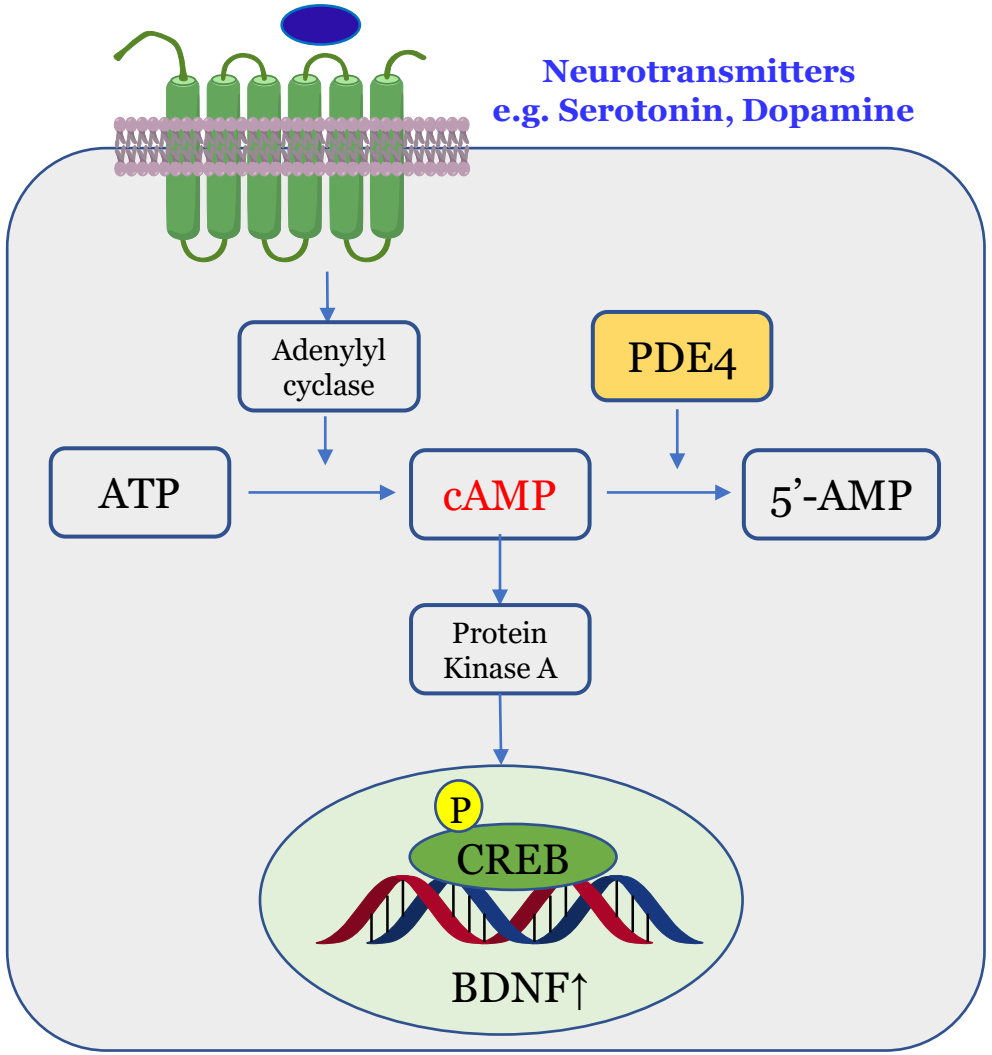
- Joined Cerevel October 2018
- >20 years in various neuroscience roles at Pfizer
- Roles included Research Portfolio Lead for multiple CNS projects, head of Neurodegeneration group, head of External Opportunities Group
- Expertise in both psychiatry and neurodegenerative diseases

Georgette Suidan, Ph.D.
Head, In Vivo Pharmacology
KORA Scientific Lead

- Joined Cerevel in July 2019
- Prior experience at Biogen & Pfizer
- >10 years experience in psychiatric and neurological disorders
- Expertise in neurodegeneration and behavioral modeling of disease

- Targeting selective PDE4 inhibition (PDE4D-sparing) for MDD, Schizophrenia and Inflammation in CNS

Targeting PDE4 inhibition for Major Depression, Schizophrenia and Inflammation in CNS



- Phosphodiesterases (PDEs) are a diverse family of enzymes that hydrolyze cyclic nucleotides and thus influence cell signaling
- PDE4 is made up of 4 closely related subtypes (A,B,C,D) all of which are expressed in the brain
- Clinical data from the non-selective PDE4 inhibitor, rolipram, suggests activity in major depression but with dose-limiting nausea and emesis
- **PDE4D is believed to be the primary isozyme driving the emetic side-effect**
- Cerevel is developing more selective inhibitors to improve the overall therapeutic potential of PDE4 inhibitors to treat CNS diseases
- We are planning to file an IND for one of our lead candidates in 2021

PDE4 is a Well-Established Target

Approved & Clinically Validated PDE4 Inhibitors

Compound	Brand(s)	Approval	Indication(s)	Selectivity	Brain-Penetrant?
Roflumilast	Daxas™	2011	Chronic Obstructive Pulmonary Disease (COPD)	Non-selective PDE4 inhibitor	No, oral but brain-impaired
Apremilast	Otezla™	2014	Psoriasis, psoriatic arthritis	Non-selective PDE4 inhibitor	No, oral but brain-impaired
Crisaborole	Eucrisa™	2016	Atopic dermatitis	Non-selective PDE4 inhibitor	No, topical
Ibudilast	Eyevinal™, Ketas™, Pinatos™	Only in Asia	Asthma, Cerebrovascular disorders, Allergic conjunctivitis, Headaches	Modestly PDE4D sparing	Yes
Rolipram	None	Not Approved	Literature standard brain penetrant PDE4 inhibitor	Non-selective PDE4 inhibitor	Yes

- There are several PDE4 inhibitors approved on the market
- PDE4 inhibitors have proven effective in inflammatory conditions including **arthritis, atopic dermatitis, asthma and COPD**
- Lack of PDE4 isoform selectivity has impaired development for CNS indications due to the occurrence of dose-limiting side-effects

Subtype Selective PDE4 Inhibitors: Broad CNS Therapeutic Potential with Reduced Side Effects

Avoiding PDE4D should improve side-effect profile

	PDE Isozyme			
Associated Effect/Side-Effect	A	B	C	D
Antidepressant	✓	✓	?	✓
Antipsychotic	✓	✓	?	✓
Anti-inflammatory		✓✓	?	
Pro-cognitive		✓	?	✓✓
Nausea/Vomiting			?	✓✓

- Rolipram targets all PDE4 subtypes
- Nausea, vomiting and other GI side effects are believed to be driven by PDE4D inhibition
- CVL-047, one of our program lead candidates, is brain-penetrant and selectively targets PDE4A, B and C subtypes (avoiding PDE4D)

Rolipram dose-limiting side effects

To our knowledge, there are no other brain-penetrant PDE4D-sparing inhibitor programs in development for schizophrenia, depression or neuroinflammatory conditions

Rolipram Clinical Data: Observed Activity in Major Depression

- Rolipram demonstrated anti-depressant activity in several small trials (total 200+ patients)
- Comparable effect observed to tricyclic antidepressants (TCAs), desipramine and imipramine
- Rolipram produced fewer adverse effects attributable to cholinergic blockade than the tricyclics **but more nausea**
- **Further clinical development was limited by its tolerability (hypothesized to be PDE4D activity)**
- **Current Cerevel PDE4 inhibitors are more selective than Rolipram**

Double-Blind Comparative Study with Rolipram (N=32)

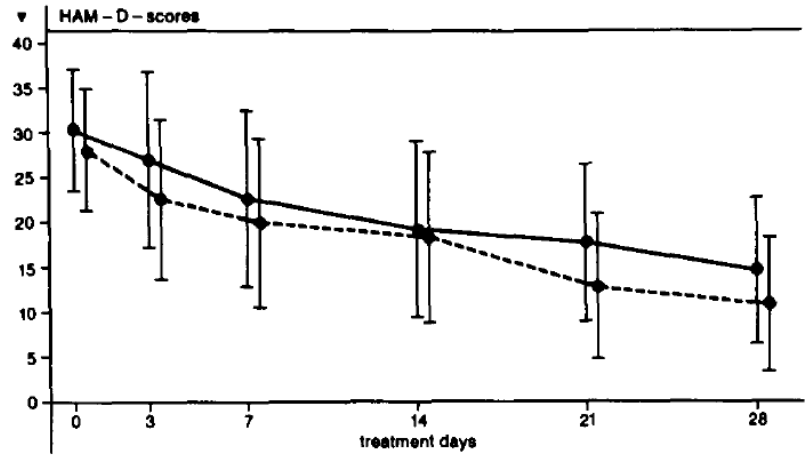


Fig. 1 Mean HAM-D-scores over time with respect to rolipram (0.75 mg t.i.d.) and imipramine (50 mg t.i.d) treatment.

--- imipramine (50 mg t.i.d.) —— rolipram (0.75 mg t.i.d.)

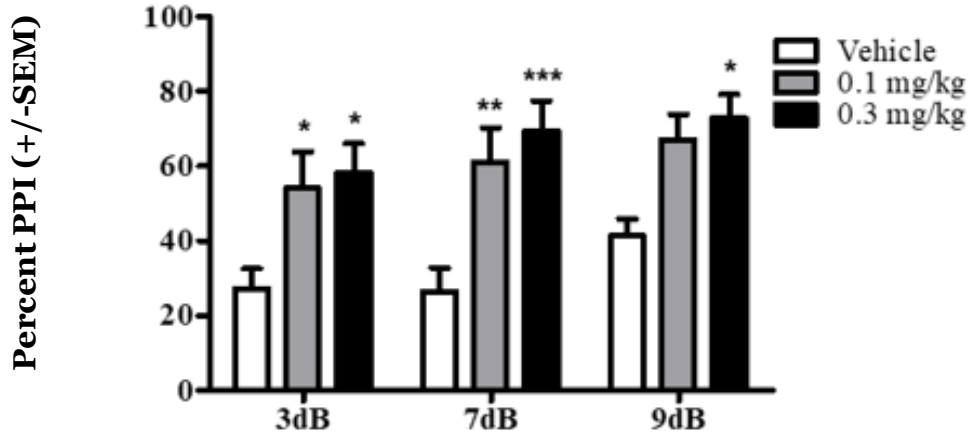
--- imipramine (50 mg t.i.d.)

—— rolipram (0.75 mg t.i.d.)

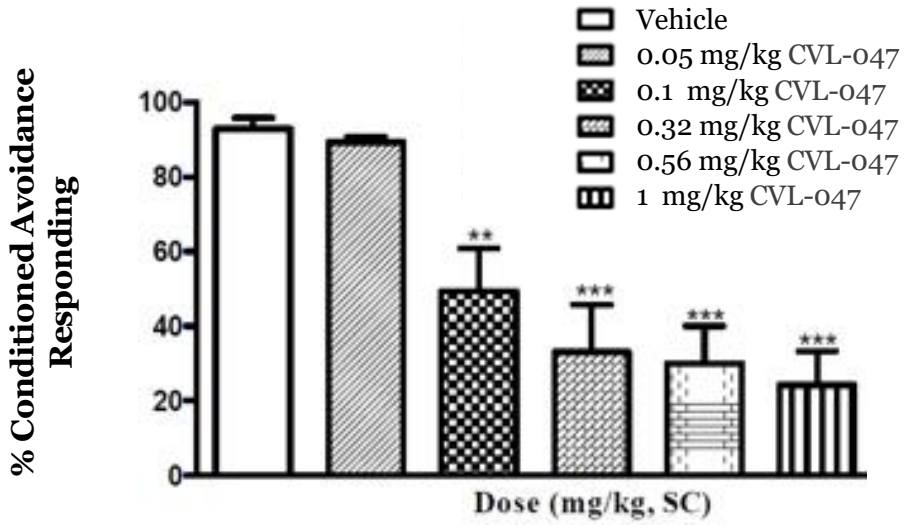
Source: Pharmacopsychiatry, 1989, 22, 156-160

A Cerevel Lead PDE4 Inhibitor also Demonstrated Potential in Treating Schizophrenia

CVL-047 in Pre-Pulse Inhibition model



CVL-047 in Conditioned Avoidance Responding model



*p<0.05; **p<0.01; ***p<0.001 vs vehicle

CVL-047 showed robust activity in animal models predictive of an antipsychotic effect

PDE4 Subtype Selective Program: Potential In Numerous Indications

- **PDE4 subtype selective inhibitors may enable us to achieve therapeutic benefits while minimizing side effects**
- Has potential in depression, schizophrenia and neuroinflammatory conditions

Potential to Develop in Multiple Indications

Depression	>260M Patients[1]
Schizophrenia	~22M Patients
Neuroinflammation in Alzheimer's Disease	>30M Patients[2]
Juvenile Batten's	2-4 of 100,000 Births[3]

We expect to file an IND for the PDE4D-sparing inhibitor program in the second half of 2021.

cerevel

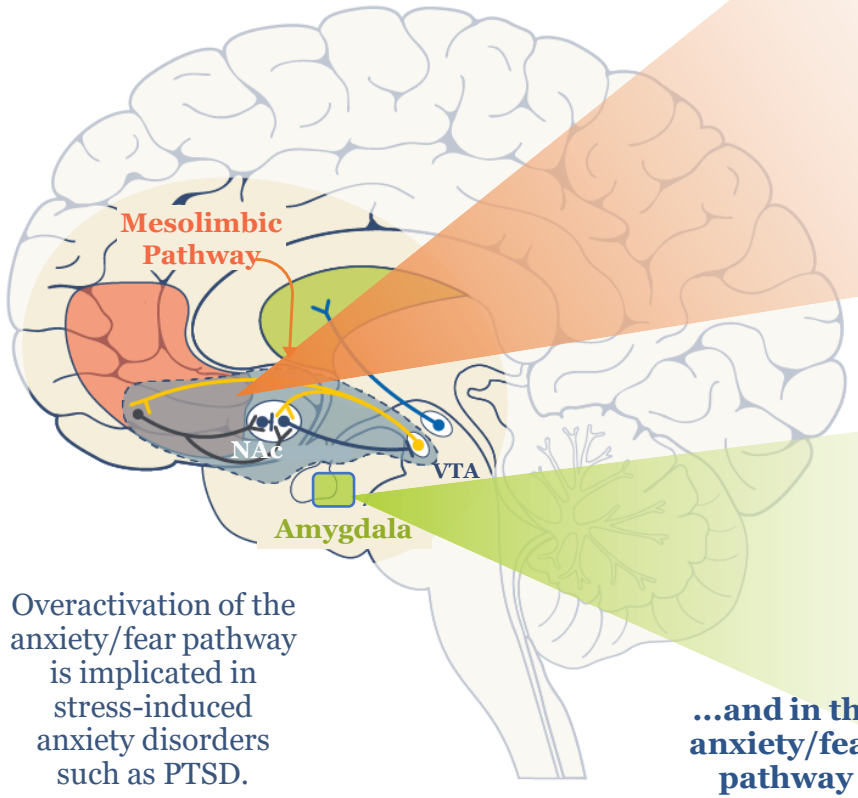
Anxiety & Depression Association of America: Depression | Anxiety and Depression Association of America, ADAA
1.World Health Organization: Dementia (who.int)
2.NIH Batten Fact Sheet: Batten Disease Fact Sheet | National Institute of Neurological Disorders and Stroke (nih.gov)

CVL-354:
Kappa Opioid Receptor Antagonist (KORA)

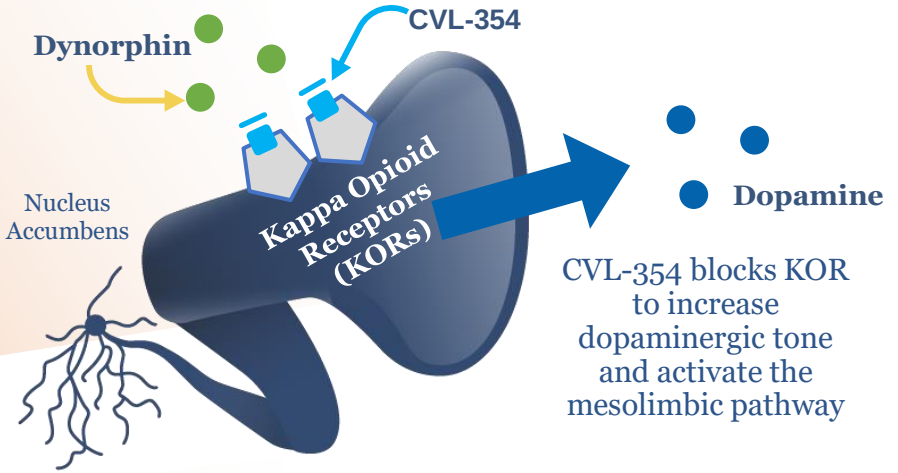
Kappa Opioid Receptor Antagonism (KORA) for Psychiatric Diseases

Reduced activity in the reward and motivation pathway (mesolimbic system) is implicated in anhedonia/depression.

External stressors cause increased dynorphin production leading to activation of KORs in the mesolimbic pathway…

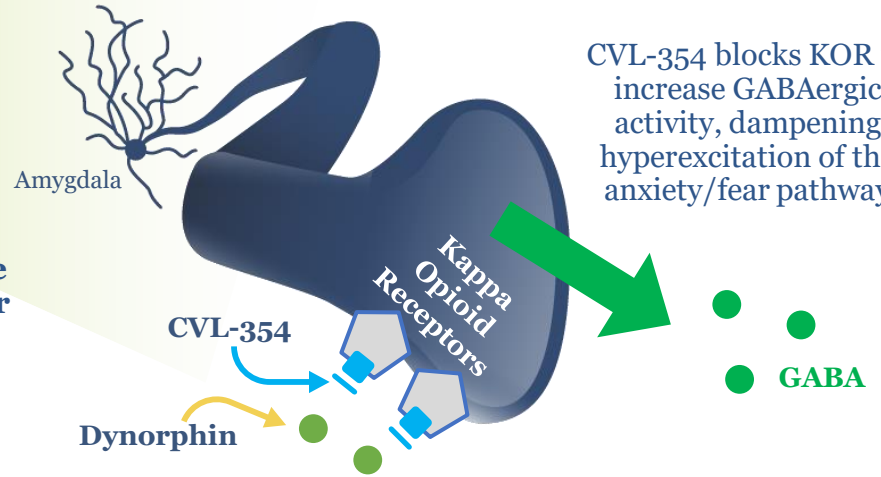


Overactivation of the anxiety/fear pathway is implicated in stress-induced anxiety disorders such as PTSD.



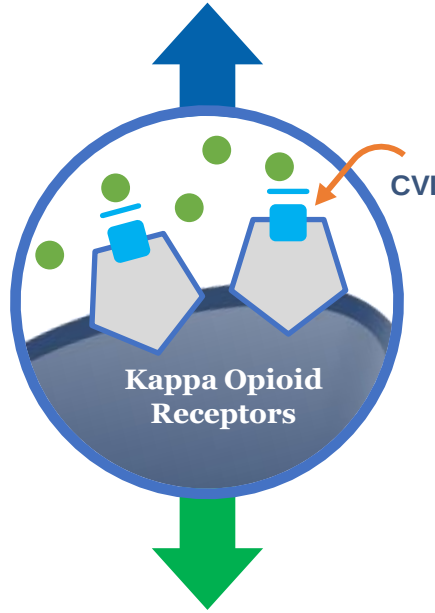
CVL-354 blocks KOR to increase dopaminergic tone and activate the mesolimbic pathway

…and in the anxiety/fear pathway



CVL-354 blocks KOR to increase GABAergic activity, dampening hyperexcitation of the anxiety/fear pathway

Inhibiting KOR can restore balance in the mesolimbic pathway to address depression disorders

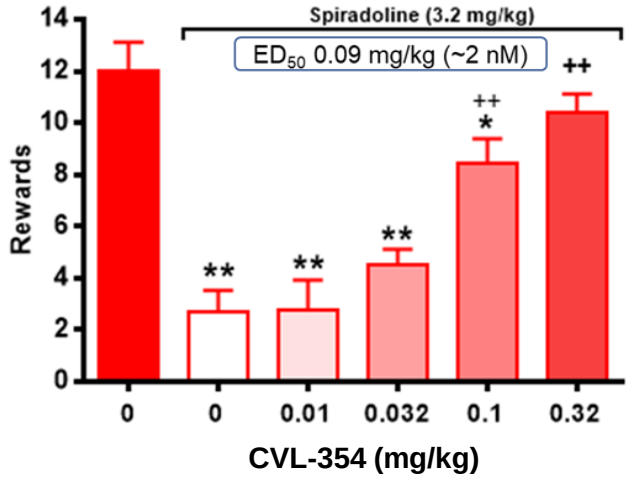


Inhibiting KOR can restore balance in the fear/motivation pathway to address anxiety disorders

Kappa Opioid Receptor Antagonism Showed Activity in Preclinical Models of Addiction and Psychiatric Disorders

Progressive ratio (Anhedonia)

Pfizer internal

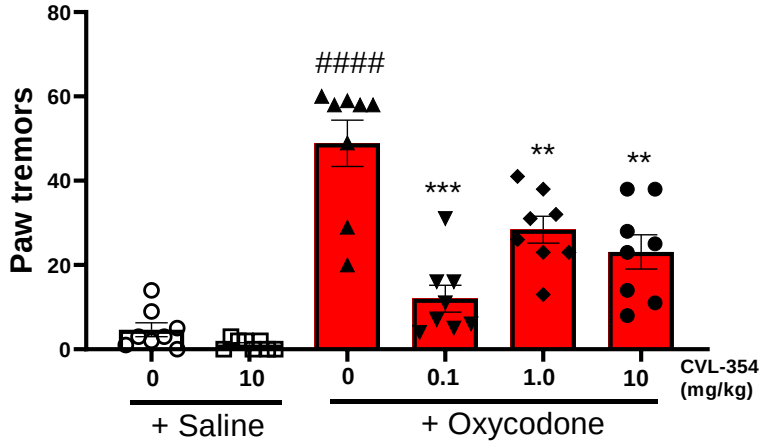


Increased motivation

Opioid withdrawal syndrome

(Somatic signs of acute oxycodone withdrawal)

Data generated in collaboration with the National Institute on Drug Abuse

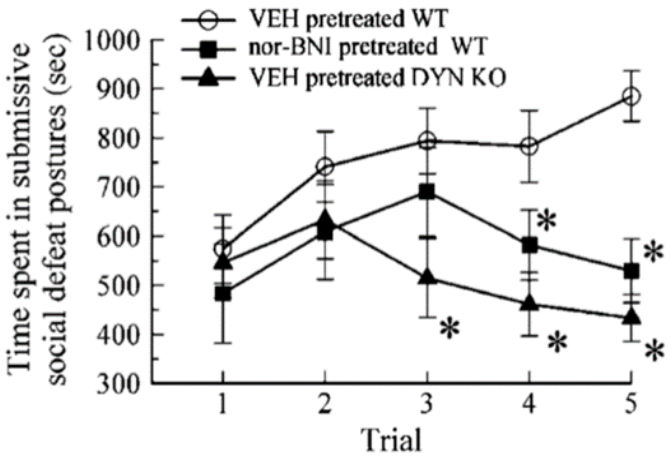


Reduced symptoms

Social defeat stress

(hypothesized to reflect aspects of PTSD)

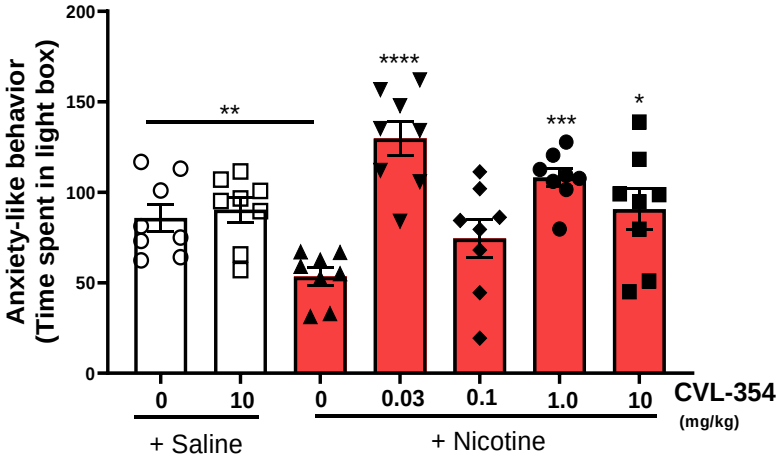
McLaughlin et al 2006



Reduced defeat behavior

Withdrawal-induced anxiety

Data generated in collaboration with the National Institute on Drug Abuse



Less anxious

Social defeat stress: *p<0.05; Progressive ratio: *p<0.05, **p<0.01 vs vehicle ; ++p<0.01 vs spiradoline

Opioid withdrawal & anxiety models: #### p<0.0001 vs. saline; ****p<0.0001; *** p<0.001; **p<0.01; *p<0.05

Positive Proof-of-Mechanism Clinical Study Utilizing JNJ-964

"Fast-fail" trial: Ph 2a double-blind, parallel group, placebo-controlled POM. 8 weeks.

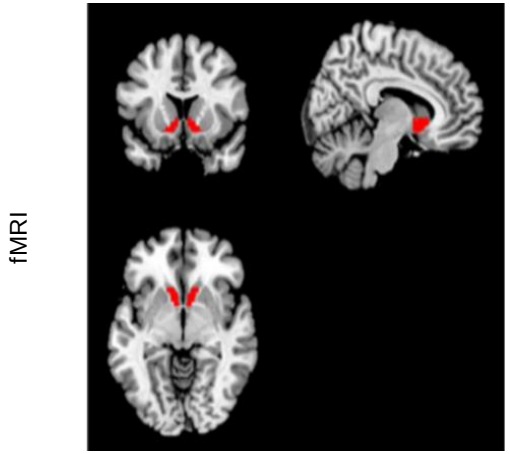
Patient group	Dosing and Receptor Occupancy	Primary endpoints	Secondary
Individuals with anhedonia and a mood or anxiety disorder	10 mg QD >90% peak at Kappa (reported) / ~35% at Mu (projected)	Mean fMRI readout in anticipation of reward	SHAPS, PRT

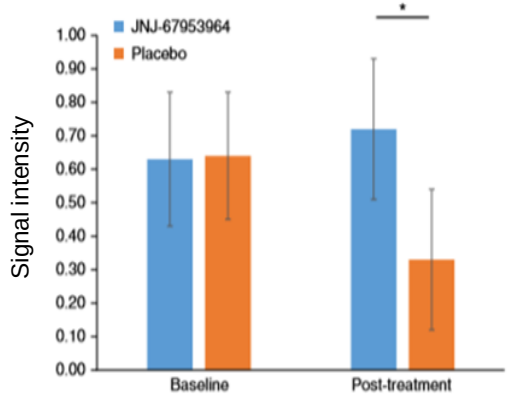
Preclinical data informed on the study design

KOR activation ⊣ Dopamine release in Nucleus Accumbens → Negative Mood state

Reward-related DA release (PET) → BOLD fMRI activation in ventral striatum

Carlezon et al. 2006; Knutson & Gibbs 2007; Schott et al. 2008





Krystal et al 2020, Nat Med

JNJ-964 (Aticaprant)	Phase 2a MDD + SSRI. Completed: 5/2020[1]. Data not yet disclosed.
BTRX-140	Phase 2a in MDD enriched for anxiety and anhedonia. Estimated completion date: 12/2020[1]. Data not yet disclosed.
Subutex/vivitrol	Phase 2 in PTSD + AUD. Estimated completion date: 9/2021[1].

1. Per clinicaltrials.gov

CVL-354: Cerevel's KOR-selective Antagonist

Excellent Pharmacological Properties

- 30x selectivity for human Kappa Opioid Receptor (KOR) over human Mu Opioid Receptor (MOR).
- Selective and potent antagonist at KOR and has no agonist activity at KOR or MOR.
- Preclinical safety package supports dosing up to 90 days in humans. 20x margins over predicted efficacious exposures.
- Preclinical activity in models of anhedonia, withdrawal-induced anxiety and physical signs of opioid withdrawal.

Potential to Develop in Multiple Indications

Major Depressive Disorder	>260M	Patients (WW)
Anxiety Disorders	>280M	Patients (WW)
Substance Use Disorder	~20M	Patients (US)[1]

We expect to file an IND for CVL-354 in the first half of 2021

cerevel

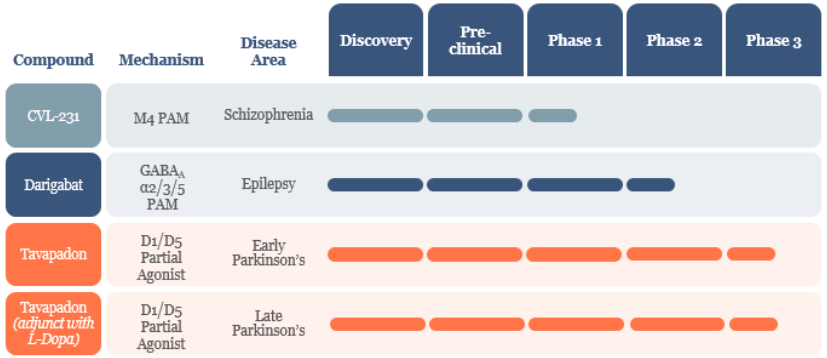
1. National Center for Drug Abuse Statistics: NCDAS: Substance Abuse and Addiction Statistics [2020] (drugabusestatistics.org)

Cerevel is Transforming Possibilities for Tomorrow

Multiple Programs Aimed at Providing New Options for Millions of Patients

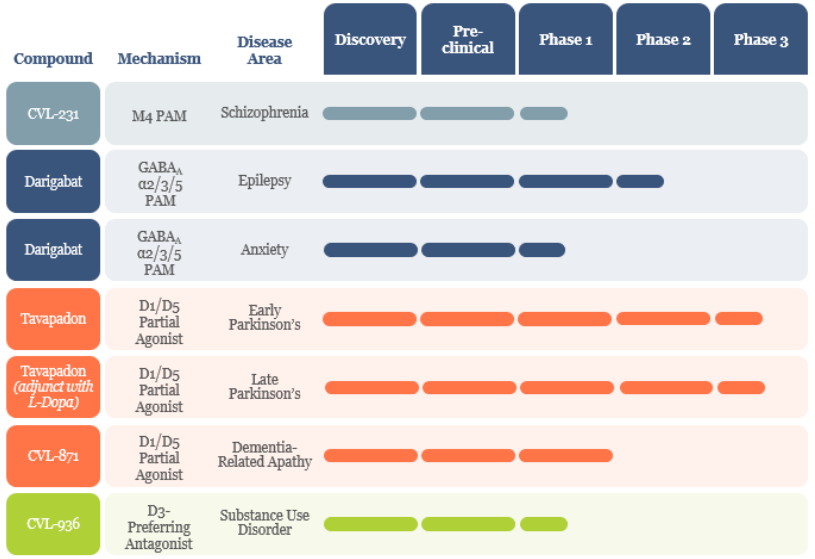
Tangible near-term value creation

- Schizophrenia
- Epilepsy
- Parkinson's



Expansion to other diseases

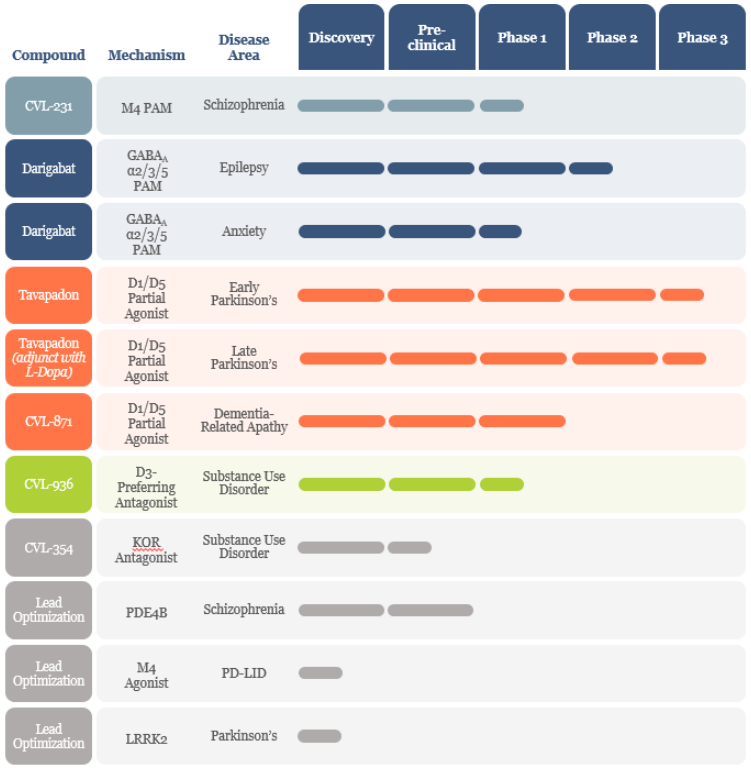
- Alzheimer's Psychosis
- Anxiety
- Apathy
- Substance Abuse Disorder



Long-term discovery efforts

Disease-modifying therapies based on human genetics and novel targets addressing:

- Neuronal loss
- Synaptic health



50M+ Patients WW ⊕ 100M+ Patients WW → Premier Neuroscience Company

Questions & Answers

Appendix

Bibliography: Subtype Selective $GABA_A$ Publications

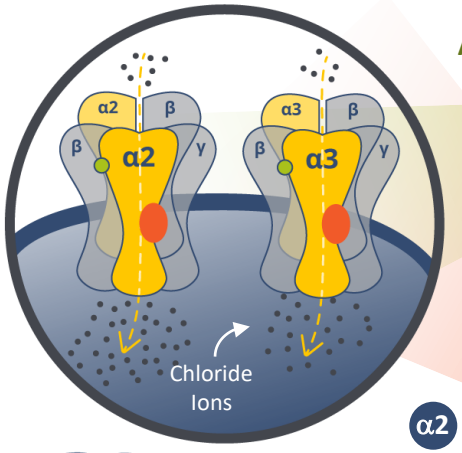
- McKernan RM, Whiting PJ. Which GABAA-receptor subtypes really occur in the brain? Trends in Neurosci 1996;19(4):139–143.
- Rudolph Y, Crestani F, Benke D, Benson JA, Fritschy JM et al., Benzodiazepine actions mediated by specific γ-aminobutyric acidA receptor subtypes. Nature 1999; 401:796-800.
- McKernan RM, Rosahl TW, Reynolds DS, et al. Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype. Nature Neurosci 2000;3:587-592.
- Fradley RL, Guscott MR, Bull S et al. Differential contribution of GABAA receptor subtypes to the anticonvulsant efficacy of benzodiazepine site ligands. Psychopharm 2007;21(4):384-391.
- Knabl J, Witschi R, Hösl K, et al. Reversal of pathological pain through specific spinal GABAA receptor subtypes. Nature 2008;451(7176):330–334.
- Atack JR. Development of subtype-selective GABAA receptor compounds for the treatment of anxiety, sleep disorders and epilepsy. In: Monti J, Pandi-Purumal S, Mohler H (eds). GABA and Sleep, Springer, Basel, 2010.
- Knabl J, Zeilhofer UB, Crestani F et al. Genuine antihyperalgesia by systemic diazepam revealed by experiments in GABAA receptor point-mutated mice. Pain 2009;141(3):233-8.
- Ralvenius WT, Benke D, Acuna MA et al. Analgesia and unwanted benzodiazepine effects in point-mutated mice expressing only one benzodiazepine-sensitive GABAA receptor subtype. Nature Comm 2015; 6:6803.
- Vinkers CH, Olivier B. Mechanisms underlying tolerance after long-term benzodiazepine use: a future for subtype-selective GABAA receptor modulators. Adv Pharmacol Sci 2012:2012:416864. doi:10.1155/2012/416864.
- Rowlett JK, Platt DM, Lelas S et al. Different GABAA receptor subtypes mediate the anxiolytic, abuse-related, and motor effects of benzodiazepine-like drugs in primates. PNAS 2005;102(3):915-920.
- Vinkers CH, van Oorschot R, Nielsen EO et al. GABAA receptor α subunits differentially contribute to diazepam tolerance after chronic treatment. PLOS One 2012;7(8):e43054.
- Kohut SJ, Ator NA. Novel discriminative stimulus effects of TPA023B, subtype-selective γ-aminobutyric-acidA/benzodiazepine modulator. Comparisons with zolpidem, lorazepam, and TPA023. Pharmacol Biochem Behav 2008;90-65-73.
- Ator NA, Atack JR, Hargreaves RJ, et al. Reducing abuse liability of GABAA/benzodiazepine ligands via selective partial agonist efficacy at α1 and α2/3 subtypes. J Pharmacol Exp Ther 2010;332:4-16.

Bibliography: Darigabat (CVL-865) Publications

- Nickolls SA, Gurrell R, et al. Pharmacology in translation: the preclinical and early clinical profile of the novel α2/3 functionally selective GABAA receptor positive allosteric modulator PF-06372865. Br J Pharmacol. 2018;175(4):708-725. Erratum in: Br J Pharmacol. 2019 Jan;176(1):127
- Owen RM, Blakemore D, Cao L, Flanagan N, Fish R, Gibson KR, Gurrell R, et al. Design and Identification of a Novel, Functionally Subtype Selective GABAA Positive Allosteric Modulator (PF-06372865). J Med Chem. 2019;62(12):5773-5796.
- Van Amerongen G, Siebenga PS, Gurrell R, et al. Analgesic potential of PF-06372865, an α2/α3/α5 subtype-selective GABAA partial agonist, in humans. Br J Anaesth. 2019;123(2):e194-e203.
- Gurrell R, Dua P, Feng G, Sudworth M, Whitlock M, Reynolds DS, Butt RP. A randomised, placebo-controlled clinical trial with the α2/3/5 subunit selective GABAA positive allosteric modulator PF-06372865 in patients with chronic low back pain. Pain. 2018;159(9):1742-1751.
- Duveau V, Buhl DL, Evrard A, Ruggiero C, Mandé-Niedergang B, Roucard C, Gurrell R. Pronounced antiepileptic activity of the subtype-selective GABAA -positive allosteric modulator PF-06372865 in the GAERS absence epilepsy model. CNS Neurosci Ther. 2019;25(2):255-260.
- Gurrell R, et al. Photosensitive epilepsy: Robust clinical efficacy of a selective GABA potentiator. Neurology. 2019;92(15):e1786-e1795.
- Bialer M, Johannessen S, Koepp M, Levy R, Perucca E, Perucca P, Tomson T, White H. Progress report on new antiepileptic drugs: A summary of the Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV). I. Drugs in preclinical and early clinical development. Epilepsia. 10.1111/epi.16725, 61, 11, (2340-2364), (2020).
- Gurrell R, Whitlock M, Wei H, Shen Z, Ogden A. Safety, tolerability, and pharmacokinetics of multiple repeated oral doses of the α2/3/5-subtype selective GABAA positive allosteric modulator PF-06372865 in healthy volunteers. Clinical Pharmacology in Drug Development 2021; 00(0): 1 -9.

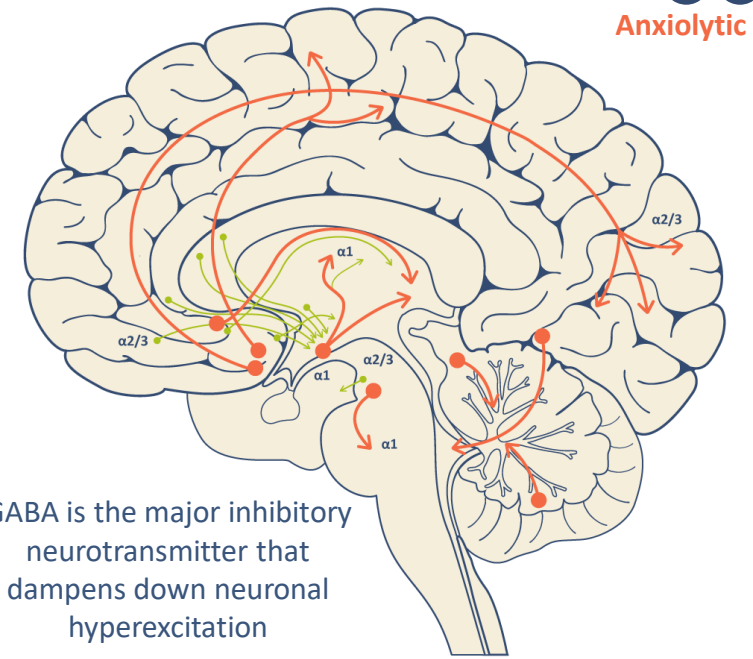
Darigabat Mechanism: Selective α2/3/5 $GABA_A$ Receptor PAM

α2 α3 α5 Darigabat is designed to selectively enhance $GABA_A$ receptor activity at α2/3/5 subunits

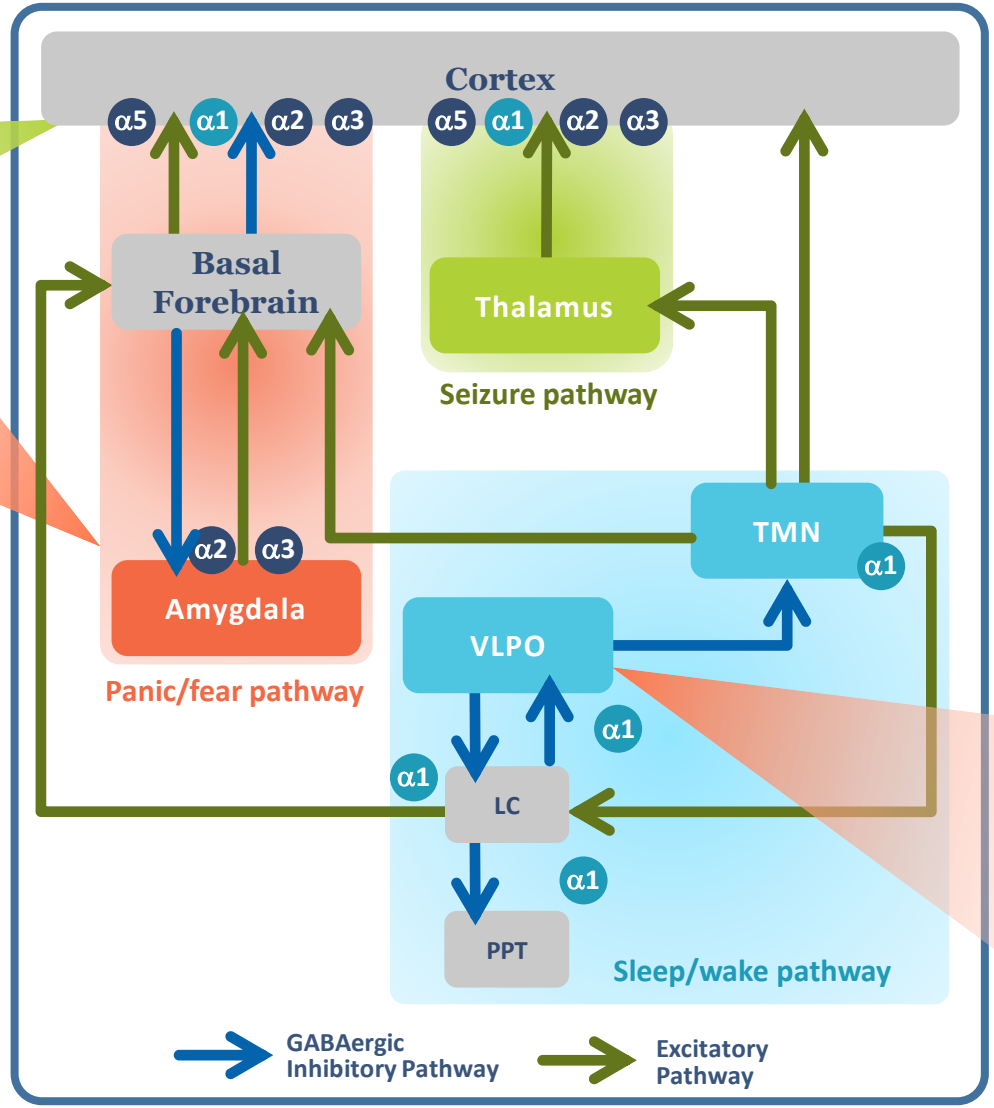


α1 α2 Anticonvulsant effect

α2 α3 Anxiolytic effect



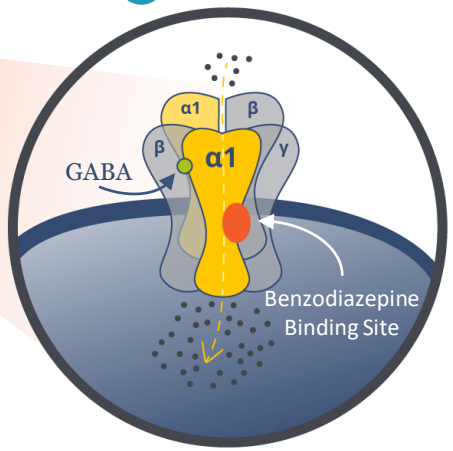
GABA is the major inhibitory neurotransmitter that dampens down neuronal hyperexcitation



α1 Benzodiazepines ***non-selectively*** enhance $GABA_A$ receptor activity, which can cause side effects primarily driven by α1 subunit activation

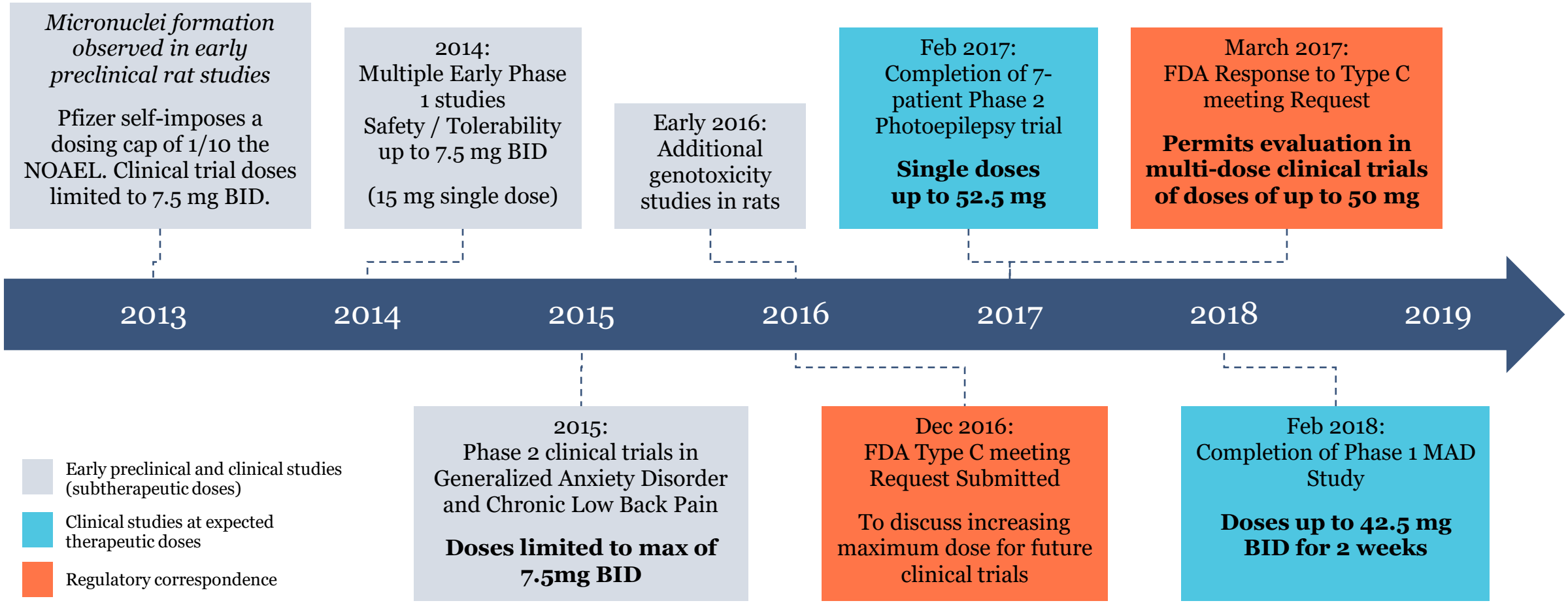
- Sedation
- Cognitive impairment
- Addiction

α1 Sedative effect



History of Darigabat Development

- Results of early clinical trials were believed to be limited by Pfizer's self-imposed dosing cap



Darigabat Favorable Side Effect & Tolerability Profile Across Completed Trials

Darigabat has been tested in 289 subjects in 9 completed trials and was generally well-tolerated. There have been no clinically significant side effect observations from physical examination, vital sign measurements, laboratory safety assessments, or ECG parameters and no reports of sedation across single and multiple dose trials

I. Across Phase 1 trials:
- 81 healthy subjects received single doses of darigabat (0.04 to 100 mg); 55 healthy subjects received multiple doses of CVL-865 (2.5 to 42.5 mg BID)
- Most common AEs: dizziness, somnolence, and fatigue. All AEs across trials have been mild or moderate in severity
- No drug-related SAEs in Phase 1 trials
- Titration in multiple dose healthy volunteer studies appeared to reduce the incidence of somnolence and dizziness

II. Across Phase 2 trials:
- 146 subjects received multiple doses of darigabat (2.5 to 7.5 mg BID); 7 subjects with documented photosensitive epilepsy received single doses of 17.5 mg and 52.5 mg in a crossover trial
- Most common AEs: dizziness and somnolence; the majority of AEs were mild or moderate
- In Study B7431007, there was limited increase in sleepiness as measured by the Epworth Sleepiness Score with either darigabat 7.5 mg, darigabat 2.5 mg or placebo at Week 2 and Week 4
- In Study B7431006, one patient experienced an SAE (transient ischemic attack) that was considered related to darigabat by the investigator. The patient had a history of high cholesterol levels and high blood pressure and was diagnosed with diabetes mellitus after the onset of TIA
- Use of titration in multi-dose Phase 2 trials appeared to mitigate CNS effects, including somnolence, over time

III. Other considerations:
- No evidence to date of withdrawal effects
- GABAergic pharmacology observed in clinical trials up to 4-weeks administration
- No evidence of the bone marrow effects seen in preclinical studies
- Reproductive effects are being addressed for all trials with requirements for contraception and standard warnings