



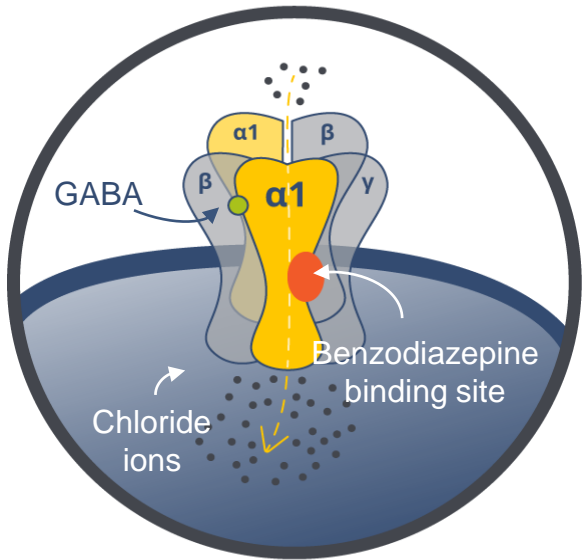
Darigabat Reduces Acute Panic and Fear Symptoms Induced by CO₂ Inhalation in Healthy Participants

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Darigabat: A Rationally Designed, α 1-Sparing GABA_A Receptor PAM for the Treatment of Anxiety



- The anxiolytic effects of BZDs are attributed to the α 2/3-containing GABA_A receptor subunits, while many unwanted side effects of BZDs are associated with the α 1 GABA_A receptor subtype^{3,4,6-8}
- Darigabat (also CVL-865, PF-06372865) selectively enhances the effect of GABA at α 2/3/5 GABA_A receptors while sparing activity at α 1⁹**

The objective of the current trial was to characterize the anxiolytic effect of darigabat in a CO₂ inhalation translational model of panic and fear in healthy participants

BZD, benzodiazepine; GABA, γ -aminobutyric acid; PAM, positive allosteric modulator.

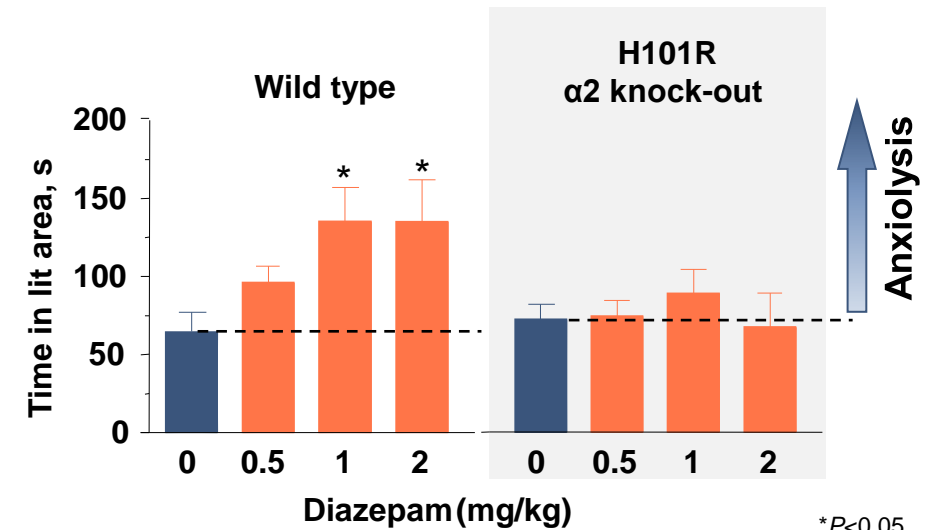
1. Ralvenius et al. *Nat Commun*. 2015;6:6803; 2. Knabl et al. *Pain*. 2009;141:233-238; 3. Löw et al. *Science*. 2000;290:131-134; 4. Dias et al. *J Neurosci*. 2005;25:10682-10688; 5. Fradley et al. *J Psychopharmacol*. 2007;21:384-391; 6. Rowlett et al. *Proc Natl Acad Sci USA*. 2005;102:915-920; 7. McKernan et al. *Nat Neurosci*. 2000;3:587-592; 8. Makaron et al. *Pharmacol Biochem Behav*. 2013;104:62-68; 9. Nickolls et al. *Br J Pharmacol*. 2018;175:708-725.

Effects of BZDs and GABA_A Receptor Subtypes¹⁻⁸

Effect	GABA _A receptor subtype			
	α 1	α 2	α 3	α 5
Analgesia		✓✓	✓	✓✓
Anxiolysis		✓✓	✓✓	
Anticonvulsant	✓✓	✓✓		
Muscle relaxation		✓✓	✓✓	
Sedation	✓✓			
Cognitive impairment	✓✓	? ^a	? ^a	✓
Addiction	✓✓	✓		

^aRemains uncertain due to a lack of aligned data.

Diazepam's anxiolytic effect is diminished in α 2 knock-out mice³



The Hypercapnia (CO₂ Inhalation) Model

- CO₂ inhalation challenge is a translational model providing proof of principle for anxiolytic activity in early clinical development and is well established in healthy participants and patients with panic disorder¹
 - Hypercapnia results in increased fear and panic, as measured by visual analog scales (VAS) and the Panic Symptom List (PSL)¹
- The proposed mechanism underlying the anxiety induced by the hypercapnia model is a decrease in global GABA neurotransmission and an increase in noradrenaline in the amygdala²⁻⁴
- This model can be used to assess current and emerging treatments for anxiety²



CO₂ inhalation induces fear and panic symptoms in healthy participants and patients with panic disorder¹

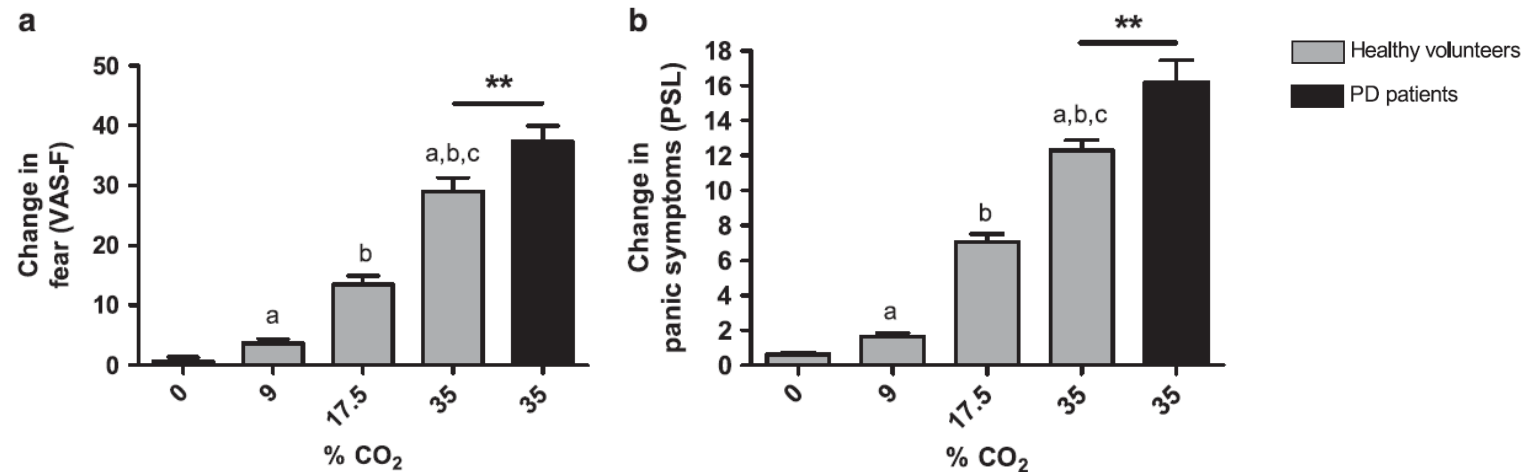


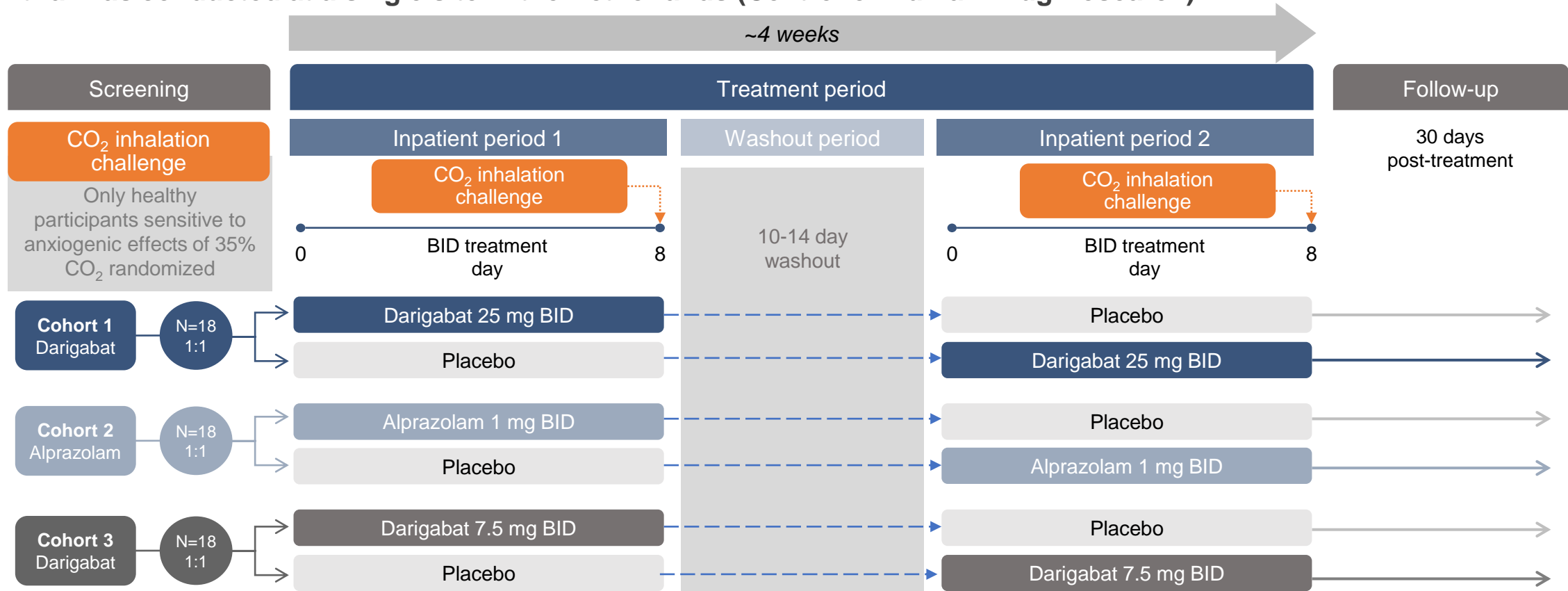
Figure. Effect of CO₂ on self-reported fear and panic symptoms in healthy participants and patients with PD. In healthy participants (gray), both fear (a) and panic symptoms (b) increased dose-dependently. Inhaling 35% CO₂ triggered a more robust response in patients (black) when compared with healthy participants. Data represent mean + standard error of the mean. (a) Compared with 0% CO₂, *P*<0.001; (b) compared with 9% CO₂, *P*<0.001; (c) compared with 17.5% CO₂, *P*<0.001. PD, panic disorder; PSL, Panic Symptom List; VAS-F, Visual Analog Scale – fear.

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1. Liebold et al. *Trans Psychiatry* 2016;6:e885; 2. Bailey et al. *J Psychopharmacol.* 2011;25:1192-1198; 3. Bailey and Nutt. *Pharmacol Biochem Behav.* 2008;90:51-7; 4. Huckstepp et al. *J Physiol.* 2011;589(Pt 23):5561-5579.

Darigabat Phase 1 Design in Acute Anxiety

Randomized, double-blind, placebo- and active-controlled crossover design with multiple doses over 8 days; the trial was conducted at a single site in the Netherlands (Centre for Human Drug Research)



Primary endpoint: Panic Symptom List-IV (PSL-IV) total score^a
Secondary endpoint: Visual analog scale - fear (VAS-F)

^aThe 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.^{1,2}
 1. Liebold et al. *Trans Psychiatry* 2016;6:e885; 2. Salvatore et al. *Transl Psychiatry*. 2020;10:308.

Participant Disposition and Baseline Characteristics

Participants, n	Cohort 1	Cohort 2	Cohort 3	Overall N=56
	Darigabat 25 mg BID/PBO N=18	Alprazolam 1 mg BID/PBO N=20	Darigabat 7.5 mg BID/PBO N=18	
Screened				241
Randomized	18	20	18	56
Discontinued	0	2	0	2
Adverse event	0	1 ^a	0	1
Withdrawal by participant	0	1 ^b	0	1
Age at screening, y				
Mean ± SD	26.4 ± 9.7	22.9 ± 4.7	27.7 ± 8.0	25.5 ± 7.8
Median	23.0	20.5	25.5	24.0
Sex, n (%)				
Male	6 (33)	6 (30)	12 (67)	24 (43)
Female	12 (67)	14 (70)	6 (33)	32 (57)
Race, n (%)^c				
Asian	0	0	1 (6)	1 (2)
Black	0	1 (5)	0	1 (2)
White	17 (94)	18 (90)	15 (83)	50 (89)
Other or multiple	1 (6)	1 (5)	2 (11)	4 (7)
Body mass index, kg/m²				
Mean ± SD	23.6 ± 3.1	22.9 ± 2.9	23.0 ± 3.1	23.1 ± 3.0
Median	23.2	22.4	22.4	22.5

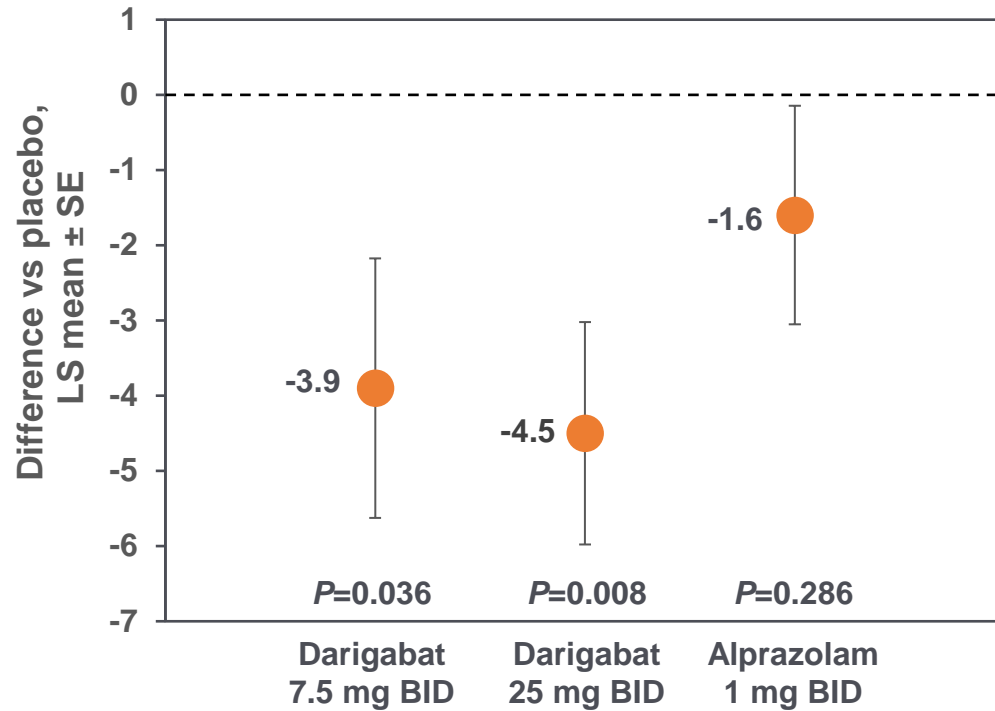
^aWithdrew during the placebo treatment period due to adverse event of COVID-19 infection; ^bWithdrew during placebo treatment period. ^cRacial demographics were reflective of the local population of the clinical site that conducted this unique translational model. BID, twice daily; PBO, placebo.



Robust Anxiolytic Effects of Darigabat Following CO₂ Challenge on Day 8

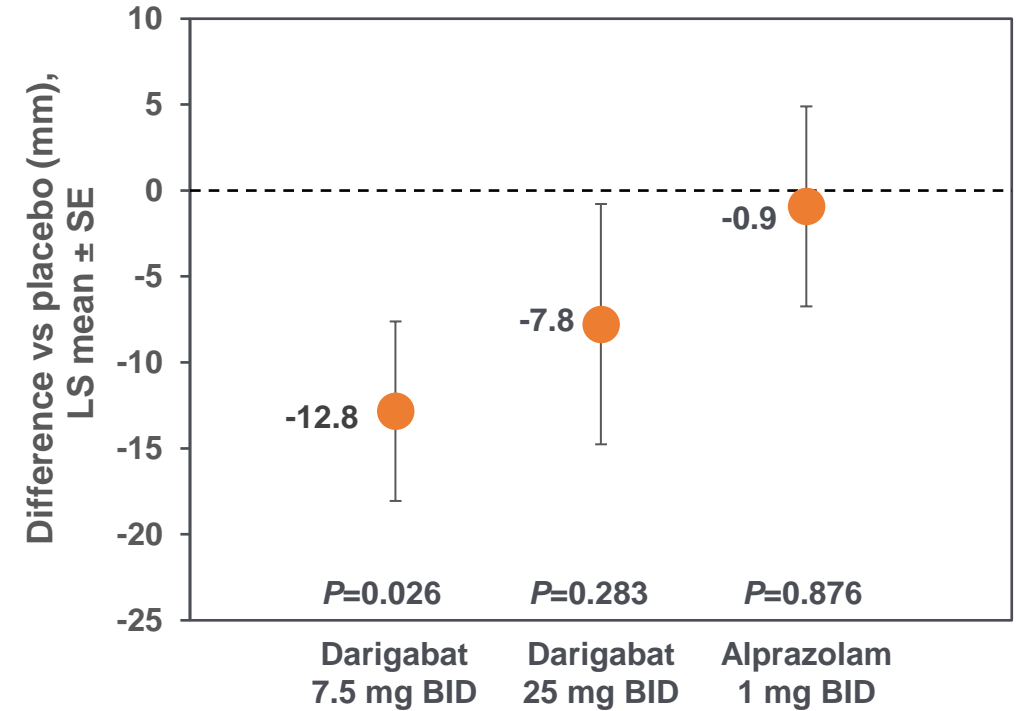
PSL-IV total score (primary endpoint)

Difference vs placebo (LS mean ± SE)



Fear VAS (secondary endpoint)

Difference vs placebo (LS mean ± SE)



Direction of improvement



- Estimated α_2 GABA_A receptor occupancy was ~50% and ~80% at darigabat doses of 7.5 mg BID and 25 mg BID, respectively

Note: P values shown should be considered nominal as no hypothesis testing was planned in the protocol. BID, twice daily; LS, least squares; PSL-IV, Panic Symptoms List IV; SE, standard error; VAS, visual analog scale.

Safety and Tolerability of Darigabat

- 97% of all AEs reported during darigabat treatment were mild
- No serious AEs were reported
- The most frequently reported AEs (>25%) in the darigabat treatment groups were dizziness (39%), somnolence (33%), bradyphrenia (slowed thought process [31%]), and fatigue (28%)
- In the alprazolam treatment group, the frequency of these same AEs were fatigue (55%), somnolence (50%), dizziness (15%), and bradyphrenia (5%)
- There were no clinically significant trends in ECGs, laboratory assessments, or vital signs

	Number of participants, % ^a			
	Placebo (combined) (N=56)	Alprazolam 1 mg BID (N=20)	Darigabat	
			7.5 mg BID (N=18)	25 mg BID (N=18)
Any TEAE, n (%)	28 (50)	18 (90)	13 (72)	17 (94)
Mild	26 (46)	18 (90)	12 (67)	16 (89)
Moderate	1 (2)	0	1 (6)	1 (6)
Severe	1 (2)	0	0	0
Serious TEAE, n (%)	0	0	0	0
TEAE leading to discontinuation	1 (2)	0	0	0
TEAE related to treatment	15 (27)	17 (85)	13 (72)	17 (94)

^aThe number of participants with at least 1 AE reported in either period.

AE, adverse event; BID, twice daily; TEAE, treatment-emergent adverse event.

Darigabat Exhibited Anxiolytic Effects Relative to Placebo in the CO₂ Inhalation Translational Model and Was Well Tolerated

Pharmacodynamics

Both darigabat 7.5 mg BID and 25 mg BID exhibited anxiolytic effect compared with placebo in the hypercapnia model

Safety and Tolerability

Darigabat was generally well tolerated, with no serious AEs and no discontinuations in the darigabat treatment groups

Pharmacokinetics

Darigabat plasma concentrations were dose related and consistent with previous trials

- This trial demonstrated the anxiolytic potential of darigabat based on reduction of acute anxiety/panic evoked by CO₂ inhalation in healthy participants
- Based on these results, darigabat is entering phase 2 testing for evaluation in panic disorder

BID, twice daily; PSL-IV, Panic Symptoms List-IV; VAS-F, visual analog scale – fear.



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