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Darigabat Reduces Acute Panic and Fear Symptoms Induced by CO_2 Inhalation in Healthy Participants

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CONCLUSIONS

- Darigabat exhibited anxiolytic activity at doses of 7.5 and 25 mg BID compared with placebo in the hypercapnia model and was generally well tolerated, with no serious AEs or discontinuations
- Darigabat plasma concentrations and estimated receptor occupancies were dose related and consistent with previous trials[13]
- This study demonstrates the anxiolytic potential of darigabat and supports further evaluation of darigabat in trials of anxiety disorders

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INTRODUCTION

- Benzodiazepines (BZDs) are commonly used to treat anxiety[1]; the anxiolytic effects of BZDs are attributed to the α2/3–containing γ-aminobutyric acid A ($GABA_A$) subunits[2,3] (**Table 1**)
  - Many unwanted side effects of BZDs, including sedation, cognitive impairment, and substance dependence, are primarily associated with the α1 $GABA_A$ receptor subtype[4-6]
- Darigabat (formerly known as CVL-865 and PF06372865) was rationally designed as a $GABA_A$ positive allosteric modulator that selectively enhances the effect of GABA at α2/3/5 subunits of $GABA_A$ receptors while sparing activity at α1[7]
- The CO_2 inhalation challenge is a translational model in early clinical development providing proof of principle for anxiolytic activity and is well established in healthy volunteers and patients with panic disorder[8,9]
  - Hypercapnia results in increased fear and panic, as measured by visual analog scales (VAS) and the Panic Symptom List (PSL)[8]

OBJECTIVE

- The objective of the current study was to characterize the anxiolytic effect of darigabat in a CO_2 inhalation model of panic and fear in healthy volunteers

Table 1. Effects of BZDs and $GABA_A$ receptor subtypes[2-6,10-12]

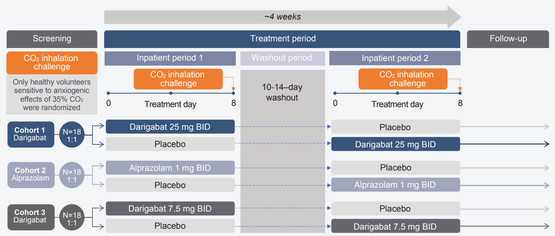
	$GABA_A$ receptor subtype			
Effect	**α1**	**α2**	**α3**	**α5**
Analgesia		✓✓	✓	✓✓
Anxiolysis		✓✓	✓✓	
Anticonvulsant	✓✓	✓✓		
Muscle relaxation		✓✓	✓✓	
Sedation	✓✓			
Cognitive impairment	✓✓	?[a]	?[a]	✓
Addiction	✓✓	✓		

[a]Remains uncertain due to a lack of aligned data. BZD, benzodiazepine; GABA, γ-aminobutyric acid.

METHODS

- This study was a randomized, double-blind, placebo- and active comparator–controlled, crossover trial comparing darigabat (25 mg twice daily [BID]), darigabat (7.5 mg BID), and alprazolam (1 mg BID) against placebo (**Figure 1**).
  - The primary endpoint was the change in the PSL-IV score from pre-CO_2 to post-CO_2; the secondary endpoint was change in the VAS Fear score from pre-CO_2 to post-CO_2
- Eligible participants were healthy adults aged 18 to 55 years who had a body mass index between 18.5 and 30.0 kg/m², a total body weight of >50 kg, and sensitivity to the anxiogenic effects of 35% CO_2 at screening
  - The PSL-IV is a questionnaire containing 13 items derived from those listed for panic disorder in the Diagnostic and Statistical Manual of Mental Disorders, version 4 (DSM-4); and uses an ordinal scale ranging from 0 (not at all) to 4 (very severe)
  - The VAS Fear consisted of a 100-mm horizontal scale, by which participants indicated their fear level from a low of 0 (no fear) to a high of 100 (the most fear possible)
- Participants were randomly assigned to 1 of 2 treatment sequences and attended the clinic for 2 inpatient periods of 9 days each for the CO_2 inhalation challenge (**Figure 2**), performed ~3 hours after administration of the last dose of treatment on Day 8
  - Darigabat doses were titrated over Days 1-4 and maintained at the target dose from Days 5-8
- The PSL-IV and VAS Fear were completed within 1 hour before and within 15 minutes after the CO_2 challenge
- Pharmacokinetic samples were collected approximately 2 and 4 hours after the morning dose on Day 8 (1 hour before and after the CO_2 challenge); plasma concentrations of darigabat were summarized using descriptive statistics, and the 2- and 4-hour concentrations were averaged
- Safety was assessed via adverse event (AE) reporting, standard clinical examinations, vital sign measurements, 12-lead electrocardiogram (ECG), and clinical laboratory assessments

Figure 1. Study design schematic.



BID, twice daily.

Figure 2. Demonstration of the device used in the CO_2 inhalation challenge.

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RESULTS

STUDY PARTICIPANTS

- Of 241 screened participants, 56 were randomized and treated; 2 participants in the alprazolam cohort discontinued the trial during Period 2 (2 additional participants were randomized as replacements) (**Table 2**)

Table 2. Participant Disposition and Baseline Characteristics

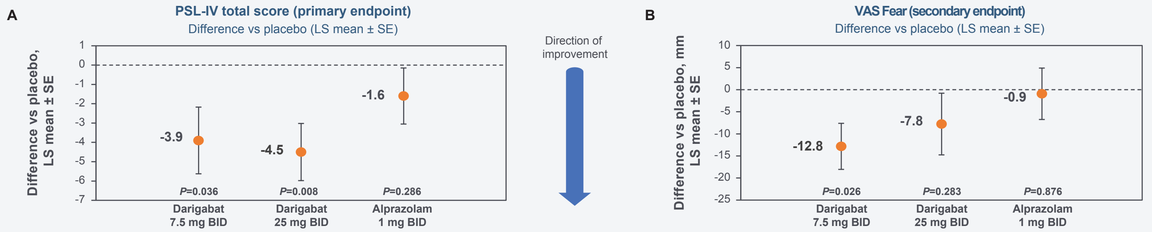
Participants, n	**Darigabat 7.5 mg BID/PBO n=18**	**Darigabat 25 mg BID/PBO n=18**	**Alprazolam 1 mg BID/PBO n=20**	**Overall N=56**
Screened				241
Randomized	18	18	20	56
Discontinued	0	0	2	2
Adverse event	0	0	1[a]	1
Withdrawal by participant	0	0	1[b]	1
Age at screening, y				
Mean ± SD	27.7 ± 8.0	26.4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

[a]Withdrew during the placebo treatment period due to adverse event of COVID-19 infection. [b]Withdrew during the placebo treatment period. [c]Racial demographics reflected the local population at the clinical site that conducted this unique translational model. BID, twice daily; PBO, placebo; SD, standard deviation.

ANXIOLYTIC EFFECTS OF DARIGABAT FOLLOWING CO_2 CHALLENGE

- Both darigabat doses demonstrated anxiolytic effect compared with placebo as assessed by the PSL-IV score following CO_2 challenge on Day 8 (**Figure 3A**)
- Additionally, the darigabat 7.5-mg BID dose attenuated fear induced by CO_2 challenge on Day 8 based on the VAS Fear score (**Figure 3B**)

Figure 3. (A) Change in PSL-IV total score and (B) change in VAS Fear relative to placebo on Day 8



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

DARIGABAT PHARMACOKINETICS AND ESTIMATED RECEPTOR OCCUPANCY

- Plasma concentrations of darigabat were dose related and corresponded with estimated α2 $GABA_A$ receptor occupancy of ~50% and 80% for the darigabat 7.5- and 25-mg BID doses, respectively (**Table 3**)

Table 3. Darigabat PK and Receptor Occupancy

Dose	**Mean (% CV) C_{AVG}, ng/mL**	**Estimated $GABA_A$ receptor occupancy**	
		Whole brain[a]	**α2[b]**
7.5 mg BID	57.3 (60)	77%	50%
25 mg BID	211.0 (43)	85%	76%

[a]RO_{MAX} = 88.4%; OCC_{50} = 8.2 ng/mL. [b]RO_{MAX} = 95.6%; OCC_{50} = 53.2 ng/mL.
C_{AVG}, average concentration; CV, coefficient of variance; OCC_{50}, 50% receptor occupancy concentration; PK, pharmacokinetics; RO_{MAX}, maximal receptor occupancy.

SAFETY AND TOLERABILITY OF DARIGABAT

- No serious AEs were reported during the trial (**Table 4**)
  - 97% of AEs reported during darigabat treatment were mild
- The most frequently reported AEs across darigabat treatment groups were dizziness (39%), somnolence (33%), bradyphrenia or slowed thought process (31%), and fatigue (28%)
- In the alprazolam treatment group, the frequencies of these same AEs were as follows: dizziness (15%), somnolence (50%), bradyphrenia (5%), and fatigue (55%)

Table 4. Summary of TEAEs

	Number of participants, %[a]			
			Darigabat	
	Placebo (combined) (N=56)	**Alprazolam 1 mg BID (N=20)**	**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)

[a]The number of participants with at least 1 AE reported. AE, adverse event; BID, twice daily; TEAE, treatment-emergent AE.