

**Including Suicidal Individuals in Treatment Trials:
Treatment of Military-Related PTSD with TNX-102 SL,
a Novel Sublingual Formulation of Cyclobenzaprine Hypothesized
to Address PTSD through Improvement in Sleep Quality**

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***An AFSP/ASCP Workshop:
Inclusion of Suicidal Individuals in Treatment Trials: Now is the Time***

*Wed May 30th 2:45-4:45PM
Poinciana 1-2*

Disclosures



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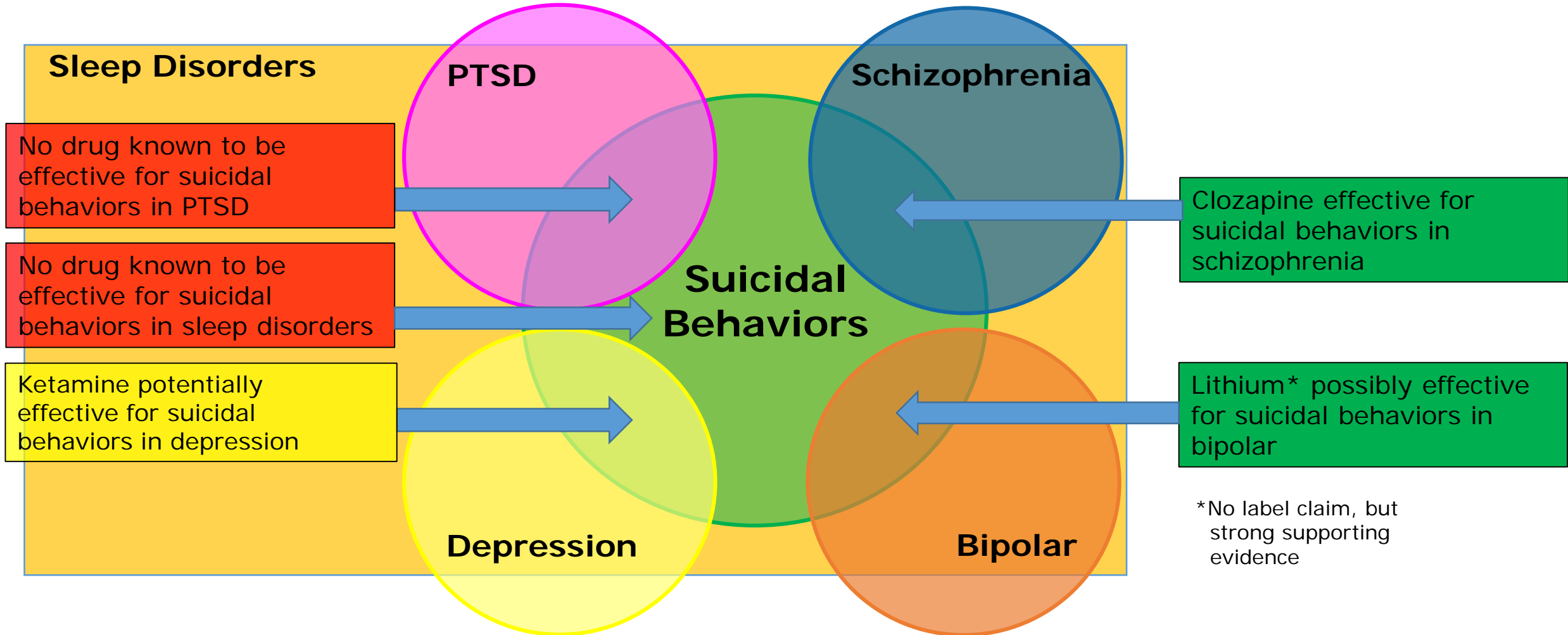
- Gregory Sullivan MD is an employee of Tonix Pharmaceuticals and owns stock and stock options in the company
- TNX-102 SL is an investigational new drug and has not been approved for any indication
- Presentation contains mention of two off-label uses of medications (lithium for reducing suicidal behaviors in bipolar disorder and ketamine for reducing suicidal behaviors in major depressive disorder)

Including Suicidal Individuals in Clinical Trials

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- Multiple psychiatric disorders are associated with increased risk of suicide
 - Examples: Major Depression, Bipolar Disorder, Schizophrenia, PTSD
- Making an impact on these suicide rates requires inclusion of this subpopulation in clinical trials
- Focusing on patient safety, outpatient trials require some degree of exclusion of those at most imminent risk who likely need more comprehensive and possibly inpatient care
- We have struck this balance in our Phase 2 trial of TNX-102 SL for military-related PTSD and this is what we have learned

Pharmacological Treatment of Underlying Disorders May Decrease Suicidal Behaviors



Studying Predictors of Suicide

- Limited body of work on death from suicide, in part explained by:
 - Suicides being relatively rare events at the population level
 - Difficulty in predicting who will die by suicide even in high risk samples
 - Necessity for data collected prior to death
- Research on predictors of suicide such as suicidal ideation and suicide attempts helps fill this critical gap, although caution is warranted:
 - Major limitation: only ~15% of those surviving a suicide attempt eventually die by suicide
 - These predictors do not necessarily provide information about a direct relationship between a psychiatric disorder such as PTSD (or a symptom such as sleep disturbance) and death by suicide
- Interventional clinical trials in psychiatric disorders offer an important opportunity to learn more about predictors of suicide
- And without biomarkers specific for predicting suicide, suicidal ideation and behaviors are the most definitive endpoints to assess an intervention aimed at preventing suicide

Suicide-PTSD Link Established but Controversy Remains

Abundance of evidence suggests PTSD increases risk of death by suicide

- Consistent evidence of a strong association while accounting for pre-existing psychiatric comorbidity¹
 - Danish registry (n=208,918) study found 5.3 greater rate of death from suicide for persons with PTSD than without (adjusted for gender, age, marital status, income, pre-existing depression diagnosis)
 - Denmark study (n=22,716) found 13 times the rate with PTSD
 - US Army service members 2001-2009 who died by suicide almost 13 times more likely have received PTSD diagnosis compared to all Army service members for same time period
- Picture somewhat clouded by several studies suggesting a protective effect of PTSD from death by suicide¹
 - Some of these findings may be explained by methodological biases
 - In samples with high levels of “comorbid PTSD and depression”, statistical adjustment for depression may adjust out elements of PTSD, i.e. DSM-5 PTSD cluster D symptoms, that are most related to suicide risk
 - If depression is on a causal pathway between PTSD and suicide (PTSD->depression->suicide), adjustment for depression would obscure the relationship
 - In studies with high levels of psychopathology, such as patients discharged from inpatient psychiatric units, risk of suicide from PTSD in comparison to reference groups with very elevated risk (e.g. MDD, bipolar disorder or schizophrenia) may look relatively protective

¹ Gradus, PTSD Research Quarterly 2017 28: 1-8.

Suicides in the US Military

- Suicide rate among active duty US Army personnel was increasing since 2004¹
 - 2001: 9 per 100,000
 - 2009: 22 per 100,000
 - Surpassed comparable civilian rates in 2008
 - Suicides in US military currently account for nearly 20% of all military deaths
- Increase (2003-2008) paralleled by increase in prevalence of mental disorders across the Army
- Rate of suicide for Active Component, * all Services:² 19.9 per 100,000
- Most common methods:²
 - Firearms 68.3%
 - Hanging 24.9%
- High risk and self-destructive behaviors also increased during the Iraq and Afghanistan wars, with substantial rise in motorcycle³ and other motor vehicle deaths upon return to US

¹ Black et al. Military Psychology 2011;23: 433-451

² Department of Defense Suicide Event Report (DoDSER), Cal Yr 2014 Ann Report

³ MSMR 2011; 3: 2-5. *Non-Reserve

Rising Suicide Risk and Rates in US Veterans since 2001

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- Retrospective multivariate analysis of 3.8 million US military personnel between 2001-2011¹, with outcome of death by suicide in Cox proportional hazard models showed:
 - Hazard rate increased with first year of separation (HR 2.49)
 - Hazard rate remained elevated for those separated ≥ 6 years earlier (HR 1.63)
- In 2014², 18% of all suicides among US adults identified as veterans of the US military service
- Since 2001², the age-adjusted rate of suicide has increased among:
 - US veteran males by 30.5%
 - US veteran females by 85.2%

¹ Shen et al, Lancet Psychiatry 2016;3:10-39-48.

² VA Suicide Prevention Program, Facts about Veteran Suicide, July 2016

Disturbed Sleep and Suicide Risk

Abundance of evidence showing link between poor sleep and increased risk of suicidal ideation and behaviors

- Large epidemiological studies showing sleep disturbance as risk for suicide death^{1,2}
- Specific sleep disturbance symptoms (i.e. insomnia and nightmares) have unique relationships with suicidal ideation, attempts, and suicide³
- Suicidal ideation or attempts in individuals with PTSD criterion A-qualifying traumas higher among those with *trauma-related nightmares* (62%) than without (20%)⁴ in prior month
- Studies of veterans demonstrating link between insomnia and suicidal ideation^{5,6,7}
- Treatment study in veterans showed reduced suicidal ideation among those receiving Cognitive Behavior Therapy for insomnia (N=405)⁸

¹ Bjorngaard et al. Sleep 2011 34:1155-9; ² Fugino et al. Suicide Life Threat Behav 2005 35:227-37; ³ Pigeon et al. Sleep Med Clin 2015 10:41-8; ⁴ Littlewood et al. Journal of Clinical Sleep Medicine 2016 12:393-399; ⁵ Chkravorty et al. Addict Behav 2014 39:399-405; ⁶ Davidson et al. Suicide Life Threat Behav 2013 43:279-89; ⁷ Ribeiro et al. J Affect Disord 2012 136:743-50; ⁸ Trockel et al, Sleep 2015 38:259-65.

Rationale for Including Suicidal Individuals in the Clinical Trial of TNX-102 SL in PTSD

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- More representative sample of the condition for evaluating the efficacy TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 2.8 mg and 5.6 mg, as a potential treatment for military-related PTSD
- TNX-102 SL taken nightly at bedtime and absorbed sublingually (transmucosal), is hypothesized to reduce PTSD symptoms through improvement in sleep quality, potentially also addressing suicidal behaviors via upstream effects on sleep improvement
- Retrospective analyses of safety data in the Phase 2 AtEase study combined with other datasets acquired by similar methodology may provide important new information and insights leading to better prediction of, and interventions to prevent, suicides

Phase 2 AtEase Study in Military-Related PTSD

Placebo at bedtime once-daily

N= 92

TNX-102 SL at bedtime once-daily

2.8 mg

N= 90

TNX-102 SL at bedtime once-daily

5.6 mg (2 x 2.8 mg)


N= 49


12 weeks

- Randomized, double-blind, placebo-controlled trial in military-related PTSD
- Enrolled 245 participants at 24 US clinical sites
- Enrolled patients with baseline CAPS-5 score ≥ 29
- **Primary Efficacy Analysis:**
 - Difference in CAPS-5 score change from baseline between TNX-102 SL 2.8 mg and placebo at week 12
- Key Secondary Measures:
 - PROMIS Sleep Disturbance, CGI-I, SDS

CAPS-5, Clinician-Administered PTSD Scale for DSM-5; CGI-I, Clinical Global Impression – Improvement scale; SDS, Sheehan Disability Scale

Design of Phase 2 AtEase Study: Inclusions and Exclusions Based on SI /SB

- **Exclusions based on Columbia-Suicide Severity Rating Scale (C-SSRS)**
 - **Five types of Suicidal Ideation (SI)** rated as present or absent during lookback period
 - Type 1 – Wish to be Dead
 - Type 2 – Non-Specific Active Suicidal Thoughts
 - Type 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
 - Type 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
 - Type 5 – Active Suicidal Ideation with Specific Plan and Intent

Excluded if < 6 months prior to Screening
 - **Four types of Suicidal Behaviors (SB)** rated as having occurred or not during lookback period
 - Actual Attempt
 - Interrupted Attempt
 - Aborted Attempt
 - Preparatory Acts or Behavior

Excluded if < 12 months prior to Screening
- **Exclusions based on Screening MINI Module B**
 - Suicidality score of High (≥ 17) based on past month SI and lifetime suicide attempt
 - YES answer to item:
 - B10 – Intent to act on thoughts of killing self
 - B11 – Intent to die as a result of a suicidal act
 - Meets criteria for CURRENT Suicidal Behavior Disorder (Attempt <12 months prior to Screening) – same exclusion as for C-SSRS

Protocol Recommended Interventions for C-SSRS Types of Suicidal Ideation During Trial

- Type 1: Standard clinical care
- Types 2 and/or 3: Medical monitor recommended implementation of a Safety Planning Intervention (SPI) for any visit with these types of SI present
 - SPI developed by Barbara Stanley (Columbia U.) and Greg Brown (U of Penn) and adopted by US Veteran's Administration (VA)
 - SPI is a brief clinical intervention aimed at mitigating suicide risk
 - Consists of clinician- and patient-developed list of six coping strategies and sources of support that participants can refer to and utilize to alleviate a suicidal crisis
 - Training in SPI provided at IM and in form of slide deck tutorial and VA SPI manual
 - Sites could alternatively utilize an internally-developed intervention for safety if similar in scope and purpose to the VA SPI
- Types 4 and/or 5: Protocol required participant be withdrawn from the study and referred for appropriate emergency care

SAFETY PLAN: VA VERSION	
Step 1: Warning signs:	
1.	_____
2.	_____
3.	_____
Step 2: Internal coping strategies - Things I can do to take my mind off my problems without contacting another person:	
1.	_____
2.	_____
3.	_____
Step 3: People and social settings that provide distraction:	
1.	Name _____ Phone _____
2.	Name _____ Phone _____
3.	Place _____
4.	Place _____
Step 4: People whom I can ask for help:	
1.	Name _____ Phone _____
2.	Name _____ Phone _____
3.	Name _____ Phone _____
Step 5: Professionals or agencies I can contact during a crisis:	
1.	Clinician Name _____ Phone _____ Clinician Pager or Emergency Contact # _____
2.	Clinician Name _____ Phone _____ Clinician Pager or Emergency Contact # _____
3.	Local Urgent Care Services _____ Urgent Care Services Address _____ Urgent Care Services Phone _____
4.	VA Suicide Prevention Resource Coordinator Name _____ VA Suicide Prevention Resource Coordinator Contact # _____
5.	VA Suicide Prevention Hotline Phone: 1-800-273-TALK (8255), push 1 to reach a VA mental health clinician: _____ Text option (838255); Online chat at www.veteranscrisisline.net/chat
Step 6: Making the environment safe:	
1.	_____
2.	_____

Safety Plan Treatment Manual to Reduce Suicide Risk: Veteran Version (Stanley & Brown, 2008).

AtEase Study Demographics and Characteristics

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Sex distribution - 93% male / 7% female

Index traumas

98% had trauma during military service

85% combat traumas

Mean (SD) time since index trauma was 7 (3.4) yrs

Deployed an average of 2.3 times

Racial distribution

66% Caucasian

24% African American

2% American Indian or Alaskan Native

2% Asian

Ethnic distribution

81% Not Hispanic or Latino

19% Hispanic or Latino

Baseline CAPS-5¹ and MADRS² scores

Mean (SD) Baseline CAPS-5 Score 39.5 (7.85)

Mean (SD) Baseline MADRS Score 17.1 (5.83)

Family Status

29% single

46% married or living with partner

24% separated or divorced

Employment Status

62% employed

11% not able to work due to symptoms of PTSD

Education

14% High school graduate or GED

57% Some college

21% College graduate

6% Graduate degree

Substance Use

72% current alcohol users

38% current tobacco users

19% current THC/cannabinoid users

¹ CAPS-5, Clinician-Administered PTSD Scale for DSM-5

² MADRS, Montgomery-Åsberg Depression Rating Scale

Suicidal Ideation and Attempt History in AtEase Study: Screening C-SSRS Results

Suicidal Ideation (SI) and Behavior (B) at Screening (N=237)					
	Lifetime	Past 6 Months			US Army#
Any Type of Suicidal Ideation	32.1%	10.5%			13.9%
C-SSRS Type 1 SI	30.4%	10.5%			
C-SSRS Type 2 SI	20.7%	5.1%			
C-SSRS Type 3 SI	12.7%	5.1%			
C-SSRS Type 4 SI	8.4%	0.0%	(exclusionary)		
C-SSRS Type 5 SI	8.0%	0.0%	(exclusionary)		5.3%
Intensity of Ideation Score* - mean (standard deviation)	11.7 (4.86)	9.6 (3.49)			
	Lifetime	Past 12 Months			
Suicidal Behavior					
Preparatory Acts or Behaviors	2.5%	0%	(exclusionary)		
Aborted Attempt	3.0%	0%	(exclusionary)		
Interrupted Attempt	1.3%	0%	(exclusionary)		
Actual Attempt	5.5%	0%	(exclusionary)		2.4%
Non-Suicidal Self Injurious Behavior	1.3%	0%			

* Intensity of Ideation among those with any suicidal ideation in lookback period

Rates in non-deployed US Army soldiers in Army STARRS All-Army Study (AAS). Nock et al, JAMA Psychiatry 2014; 71:514-522.

Suicidal Ideation and Attempt History in AtEase Study: Screening MINI Suicidality Module B Results

MINI Module B Suicidality Rating at Screening	
Low Suicidality (score of 1-8)	15.6%
Moderate Suicidality (score of 9-16)	2.1%
High Suicidality (score of ≥ 17) (exclusionary)	0%
Lifetime Attempt on MINI Module B	8.4%

AtEase Study Screen Fails versus Inclusion in Individuals with SI/SB

- 455 individuals were screened for the AtEase study
- 210 of these were screen failed
 - 11 were screen failed due to SI/SB exclusions
 - 5 due to MINI Suicidality module score ≥ 17
 - 4 due to suicidal behavior in 12 months prior to screening
 - 2 due to increased suicide risk based on PI judgement
- 237 of 245 randomized in AtEase were in the safety population
 - 76 had experienced lifetime SI
 - 25 had experienced SI in past 6 months
 - 29 had lifetime suicidal behaviors
 - 13 of these individuals had made an actual suicide attempt
 - Firearm use in 12 of the 29 lifetime suicidal behaviors
 - 3 preparatory actions – purchasing or loading a gun with intention to kill self
 - 3 aborted attempts with firearm to head
 - 2 were interrupted when about to use firearm
 - 4 attempted suicide with firearm that failed to fire

AtEase Study Results: Safety and Tolerability

Systemic adverse events (AEs) and local administration site reactions occurring at $\geq 5\%$ rate in either TNX-102 SL group:

Systemic Adverse Events	Placebo (N=94) *	TNX-102 SL 2.8 mg (N=93) *	TNX-102 SL 5.6 mg (N=50) *
Somnolence	6.4%	11.8%	16.0%
Dry Mouth	10.6%	4.3%	16.0%
Headache	4.3%	5.4%	12.0%
Insomnia	8.5%	7.5%	6.0%
Sedation	1.1%	2.2%	12.0%
Local Administration Site Reactions			
Hypoaesthesia oral [#]	2.1%	38.7%	36.0%
Paraesthesia	3.2%	16.1%	4.0%
Glossodynia	1.1%	3.2%	6.0%

[#]Oral hypoaesthesia (tongue/mouth numbness) was most common AE, generally transient (<60 minutes), non-dose related and rated mild in 89% and moderate in 11% on TNX-102 SL; *Safety Population (Total N=237)

Trial Completion Rates[^]: 73% Placebo; 79% TNX-102 SL 2.8 mg; 84% TNX-102 SL 5.6 mg

[^] modified Intention-to-Treat Population

Approach Taken to SI /SB Adverse Event Reporting

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- Any post screening increase in C-SSRS SI over Type 1 considered an adverse event
- Any emergence of Type 4 and/or Type 5 SI post screening considered a serious adverse event (SAE)
- Any emergence of C-SSRS-defined SB considered an SAE

What was found during the AtEase study:

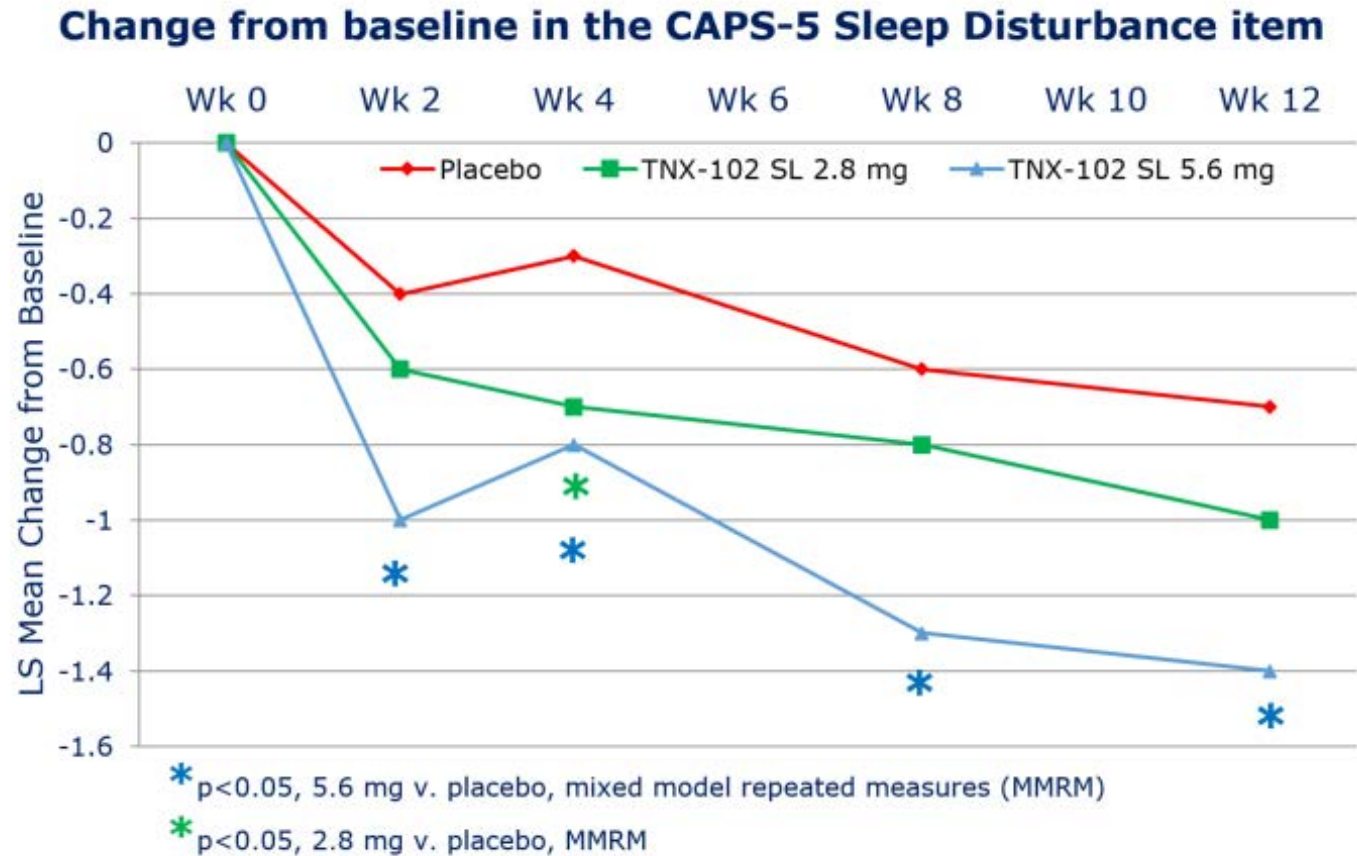
- 4 AEs of increased SI in 3 patients
 - Placebo (2); TNX-102 SL 2.8 mg (1)
- 1 SAE involving C-SSRS Type 5 SI and interrupted suicide attempt
 - Placebo patient

Suicidal Ideation in the AtEase Study at Baseline and Week 12

Suicidal Ideation (SI) and Behavior (B) at Baseline and Week 12 using Since Last Visit C-SSRS						
	Baseline			Week 12		
	Placebo	TNX-2.8mg	TNX-5.6mg	Placebo	TNX-2.8mg	TNX-5.6mg
	N=94	N=93	N=50	N=68	N=72	N=41
Any Type of Suicidal Ideation, N	2	5	2	1	2	0
C-SSRS Type 1 SI, N	2	5	1	1	2	0
C-SSRS Type 2 SI, N	0	0	1	1	0	0
C-SSRS Type 3 SI, N	0	0	1	1	0	0
C-SSRS Type 4 SI, N	0	0	0	1	0	0
C-SSRS Type 5 SI, N	0	0	0	1	0	0
Intensity of Ideation Score, Mean	14.0	13.2	6.0	15.0	10.0	NA
Suicidal Behavior						
Preparatory Acts or Behaviors, N	0	0	0	0	0	0
Aborted Attempt, N	0	0	0	0	0	0
Interrupted Attempt, N	0	0	0	1	0	0
Actual Attempt, N	0	0	0	0	0	0
Non-Suicidal Self Injurious Behavior (NSSIB), N	1	0	1	0	0	0
Cumulative NSSIB, N				1	1	1

TNX-102 SL 5.6 mg Provided Significant Improvement in Sleep Disturbance in the AtEase Study

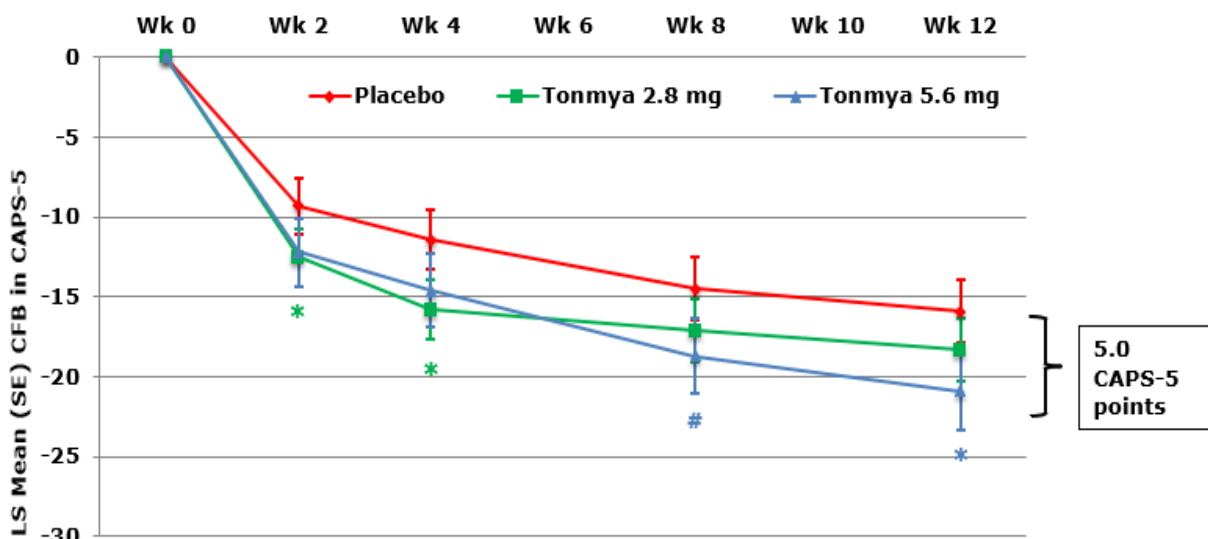
- Mechanism of action of TNX-102 SL is hypothesized to be through improvement in sleep quality
- Sleep responded early in treatment with TNX-102 SL, by Week 2 on CAPS-5 sleep disturbance item



CAPS-5 Treatment Response in Modified Intention-to-Treat Population and in Retrospective Analysis for Subgroup with Entry CAPS-5 ≥ 33

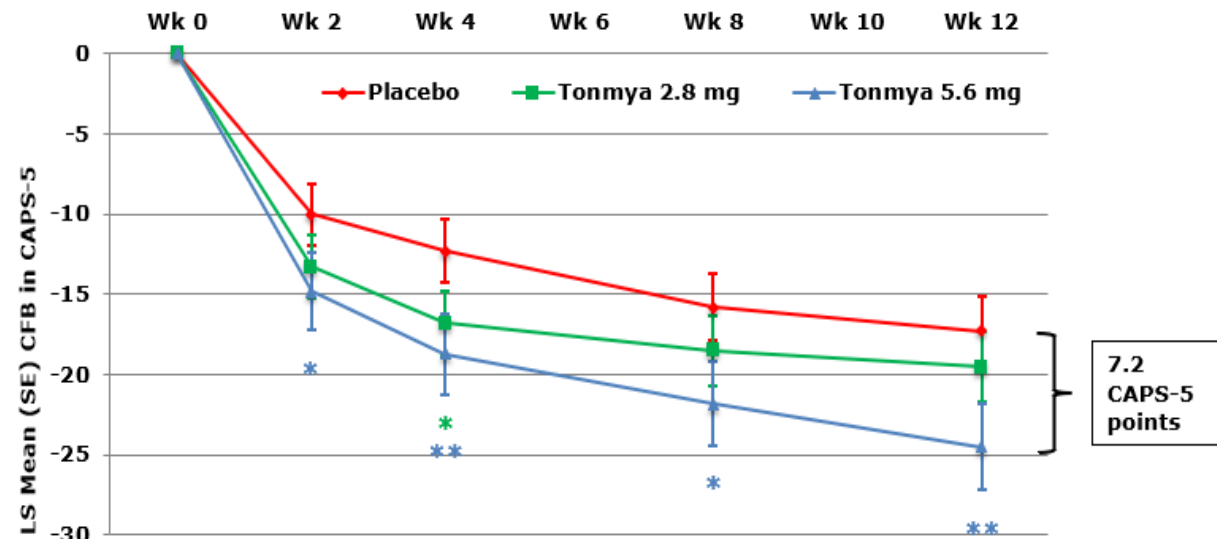
CAPS-5 LS Total Score Mean Change from Baseline (CFB)

Modified Intention-to-Treat Population



*p=0.031, #p=0.063, Tonmya 5.6 mg compared with placebo; *p<0.05, Tonmya 2.8 mg compared with placebo; analysis is mixed-effect model repeated measures (MMRM) with multiple imputation (MI); CAPS-5, Clinician-Administered PTSD Scale for DSM-5; LS, least squares; SE, standard error.

Subgroup with entry CAPS-5 ≥ 33



**p<0.01, *p<0.025, Tonmya 5.6 mg compared with placebo; *p=0.018, Tonmya 2.8 mg compared with placebo; analysis is MMRM with MI; LS, least squares; SE, standard error.

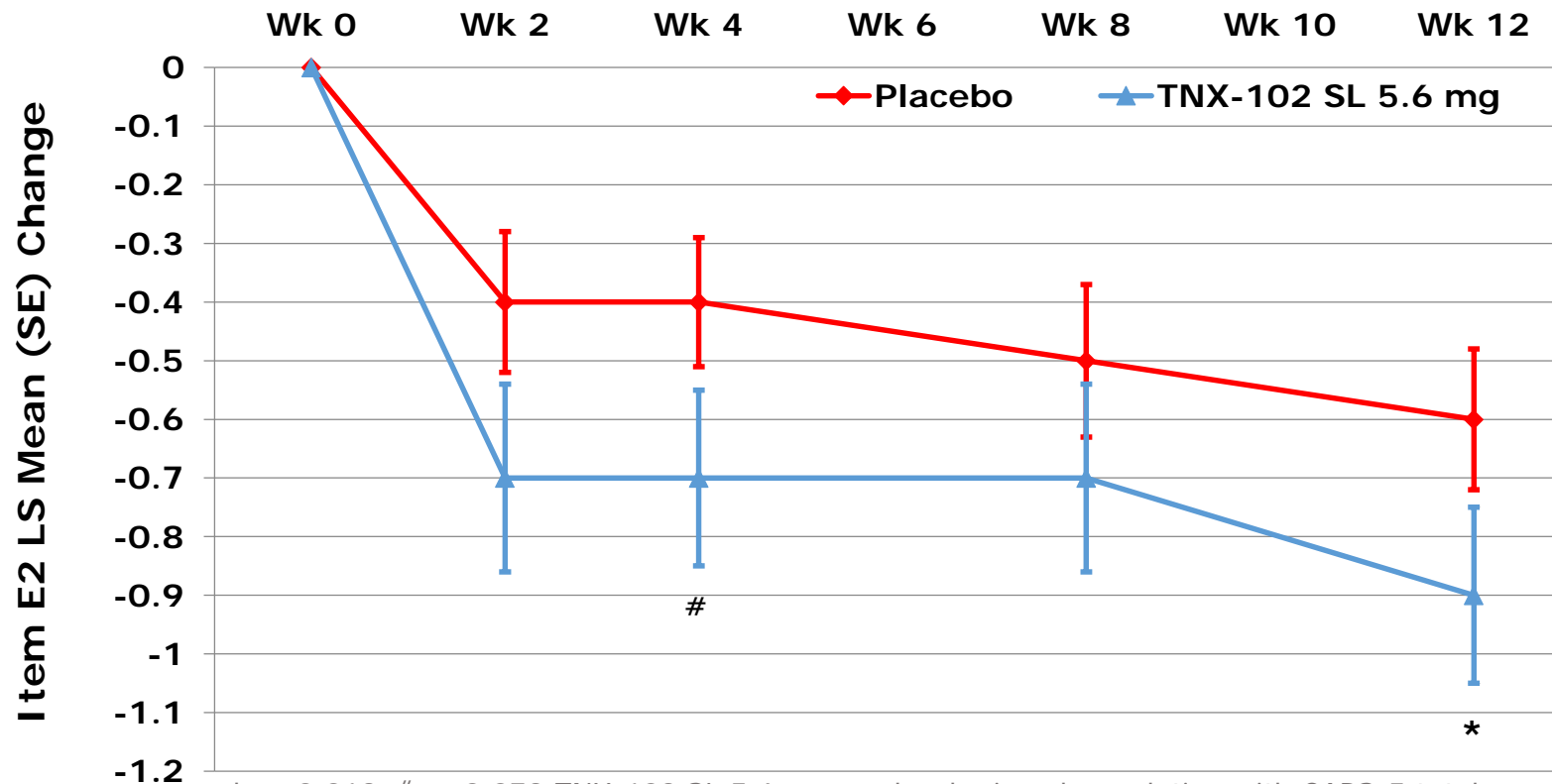
A baseline CAPS-5 score ≥ 33 was set as entry criterion in ongoing Phase 3 HONOR study

CAPS-5 Item 16 (E2) – New to DSM-5/CAPS-5

- Reckless or self-destructive behavior
 - Risk
 - “In the past month/week, have there been times when you were taking more risks or doing things that might have caused you harm?”
 - Can you give me some examples?
 - How much risk do you take? (How dangerous are these behaviors? Were you injured or harmed in some way?)”
 - Frequency
 - How often have you taken these kinds of risks in the past month/week? (# of times)
 - Trauma-relatedness
 - Did this behavior start or get worse after (index trauma)?
- As per DSM-5, intended for behaviors such as dangerous driving, excessive alcohol or drug use, and self-injurious or suicidal behavior
- Due to exclusion of SB in past year and very low rates of any non-suicidal self injurious behavior or SB *during* trial, item appeared to be *primarily indexing dangerous, high risk activities in prior week that had developed or got worse after index trauma(s)*

Reduction in Reckless or Self-Destructive Behavior Item Compared with Placebo Over 12 Weeks in Subjects with More Severe PTSD (Baseline CAPS-5 total ≥ 33)

CAPS-5 Item E2: Reckless or self-destructive behavior



- Placebo N=77
 - For subgroup with baseline E2>0:
 - N = 25 of 77
 - Change from Baseline in subjects with E2>0, mean (SD): -1.8 (1.34)
- TNX-102 SL 5.6 mg N=38
 - For subgroup with baseline E2>0:
 - N = 9 of 38
 - Change from baseline in subjects with E2>0, mean (SD): -2.9 (0.64)

* p=0.012, # p=0.073, TNX-102 SL 5.6 mg v. placebo in subpopulation with CAPS-5 total baseline score of ≥ 33 ; LS, least squares; MMRM, mixed-effects model repeated measures; SE, standard error

Conclusions about Including Suicidal Individuals in Phase 2 Trial of Military-Related PTSD

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- AtEase military-related PTSD sample had higher lifetime rates of SI/B compared with non-deployed Army sample
- Rates of since-last-visit SI and SB during study were extremely low, such that meaningful statistical inferences are not possible
- Employing Safety Planning Intervention (SPI) for C-SSRS Types 2 and/or 3 helpful for ensuring intensive clinical management for safety
- High risk behaviors were reduced with treatment in more severe subpopulation
- Non-exclusion of PTSD participants with history of SI/B greatly strengthens generalizability of any treatment findings for this population
 - Future outpatient studies could reduce SI/SB exclusions further, such as no C-SSRS Types 4 or 5 in past month and no SB in past 3 months
- Inclusion of individuals with SI/B in pharmacotherapy trials such as AtEase provides critical data for meta-analyses aimed at better understanding of the predictors of suicide, reducing the risk, and facilitating the development of drug candidates for the prevention of death by suicide

Thank you...!

To our research participants for their collaboration in the AtEase study!

To our site PIs and Staff!

To Tonix personnel responsible for AtEase:

➤ Seth Lederman, Judy Gendreau, Ashild Peters, Perry Peters, Gregory Sullivan

And to key consultants:

➤ Pauliana Hall, R. Michael Gendreau, Amy Schaberg, Frank Weathers, Jonathan Davidson