

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): **December 19, 2019**

VistaGen Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

NEVADA

(State or other jurisdiction of incorporation)

000-54014

(Commission File Number)

20-5093315

(IRS Employer Identification Number)

343 Allerton Ave.

South San Francisco, California 94090

(Address of principal executive offices)

(650) 577-3600

(Registrant's telephone number, including area code)

Not Applicable

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

<u>Title of each class</u>	<u>Trading Symbol(s)</u>	<u>Name of each exchange on which registered</u>
Common Stock, par value \$0.001 per share	VTGN	Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR 230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR 240.12b-2)

Emerging Growth Company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act

Item 7.01. Regulation FD Disclosure.

On December 26, 2019, VistaGen Therapeutics, Inc. (the “*Company*”) began utilizing a new corporate presentation. A copy of the updated corporate presentation is attached to this Current Report on Form 8-K as Exhibit 99.1.

The information in Item 7.01 of this Current Report on Form 8-K, including the information set forth in Exhibit 99.1, is being furnished and shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the “*Exchange Act*”), nor shall Exhibit 99.1 filed herewith be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

On December 19, 2019, the Company announced successful results from a first-step, Phase 1b clinical study with healthy U.S. military Veterans, which measured NMDAR (N-methyl-D-aspartate receptor) target engagement of the Company’s investigational product candidate, AV-101, an oral NMDAR glycine site antagonist, for potential treatment of suicidal ideation in Veterans. A copy of the press release is attached to this Current Report on Form 8-K as Exhibit 99.2.

Item 9.01. Exhibits.

See Exhibit Index.

Signatures

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

VistaGen Therapeutics, Inc.

Date: December 27, 2019

By: /s/ Shawn K. Singh
Shawn K. Singh
Chief Executive Officer

EXHIBIT INDEX

<u>Exhibit Number</u>	<u>Description</u>
99.1	VistaGen Therapeutics, Inc. Corporate Presentation, dated December 2019.
99.2	Press Release issued by VistaGen Therapeutics, Inc., dated December 19, 2019.



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Therapeutics

www.vistagen.com

 Nasdaq: VTGN

Winter 2019

Forward-looking Statements



This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements concern our product candidates, our development efforts, our collaborations, our intellectual property, our financial condition, our plans and our development programs. These statements involve risks, uncertainties and assumptions, and are based on the current estimates and assumptions of the management of VistaGen Therapeutics, Inc. (Company) as of the date of this presentation and are subject to uncertainty and changes. Given these uncertainties, you should not place undue reliance on these forward-looking statements.

Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements include, among others, those set forth in our Annual Report on Form 10-K for the year ended March 31, 2019, filed with the Securities and Exchange Commission (SEC) on June 25, 2019, as well as any updates to those risk factors filed with the SEC from time to time in our periodic and current reports on Forms 8-K and 10-Q. All statements contained in this presentation are made only as of the date of this presentation, and the Company undertakes no duty to update this information unless required by law.

Looking Beyond Current Treatments for CNS Diseases and Disorders with High Unmet Need

VistaGen is developing differentiated new generation medications for large and growing mental health and neurology markets where current treatments are inadequate to meet the needs of millions of patients worldwide.



Looking beyond current therapies for CNS diseases and disorders with high unmet need

3 differentiated clinical-stage product candidates

Novel mechanisms of action

Rapid-onset

Exceptional safety

Each candidate has potential in multiple markets

Our CNS Pipeline



Product Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3
PH94B Neuroactive Nasal Spray*	Social Anxiety Disorder ^{†1}	[Progress bar: Preclinical, Phase 1, Phase 2, Phase 3]			
	Generalized Anxiety Disorder ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Peripartum Anxiety ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Preoperative Anxiety ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Panic Disorder ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
	PTSD ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
PH10 Neuroactive Nasal Spray*	Major Depressive Disorder ²	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Treatment-Resistant Depression ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Suicidal Ideation ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Peripartum Depression ³	[Progress bar: Preclinical, Phase 1, Phase 2]			
AV-101 (oral)*	Major Depressive Disorder ^{†4}	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Neuropathic Pain ^{†4}	[Progress bar: Preclinical, Phase 1, Phase 2]			
	LID associated with Parkinson's Therapy ⁴	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Suicidal Ideation ⁴	[Progress bar: Preclinical, Phase 1, Phase 2]			
	Epilepsy ⁴	[Progress bar: Preclinical, Phase 1, Phase 2]			

* All potential future studies are subject to securing sufficient internal and/or collaborative third-party funding

† FDA Fast Track designation granted

1. Preparing for initial U.S. Phase 3 clinical study
2. Preparing for initial U.S. Phase 2b clinical study

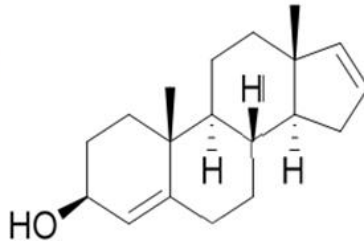
3. Assessing for potential Phase 2a POC study
4. Assessing for potential Phase 2a POC study with adjunctive probenecid

PH94B neuroactive nasal spray

(3 β)-androsta-4,16-dien-3-ol


Novel, fast-acting, non-systemic therapy for:

- Social Anxiety Disorder
- Generalized Anxiety Disorder
- Peripartum Anxiety
- Preoperative Anxiety
- Panic Disorder
- PTSD



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Therapeutics



 Nasdaq: VTGN

Social Anxiety Disorder (SAD) in the U.S.

More than Just Shyness



One of the most prevalent mental health conditions in the U.S.

Affects as many as

20 million¹
Americans



Anxiety and fear in everyday social and performance situations

meeting new people



giving a speech



eating/drinking
in front of others



making a work presentation



interviewing for a job



¹Harvard Medical School, 2007. National Comorbidity Survey (NCS). (Update - 2017, August 21); Kessler, et al, US National Comorbidity Survey Replication, 2005
<https://www.nimh.nih.gov/health/publications/social-anxiety-disorder-more-than-just-shyness/index.shtml>

Current SAD Drug Treatments Fall Short



Not FDA-Approved
*** Prescribed Off-label ***

Antidepressants (2 SSRIs, 1 SNRI)

- ✗ Slow onset, chronic administration
- ✗ May worsen anxiety initially
- ✗ Significant potential side effects
 - ❖ Nausea and vomiting
 - ❖ Weight gain
 - ❖ Sleepiness
 - ❖ Sexual problems
- ✗ Potential drug-drug interaction

Benzodiazepines & Beta Blockers

- ✗ Addiction risk
- ✗ Significant potential side effects
 - ❖ Nausea and vomiting
 - ❖ Blurred vision
 - ❖ Dizziness
 - ❖ Sedation
 - ❖ Confusion and cognitive impairment

There is no FDA-approved, fast-acting PRN treatment for SAD

The “Benzo Epidemic”

“It's not just opioids: What doctors want you to know about benzos”



“Benzodiazepines: Primary Care’s New Drug Problem”

Psychiatry Advisor

“Use of Opioids, Benzodiazepines at Same Time is Skyrocketing. Here’s Why That Matters”

FORTUNE



PH94B for SAD

- First-in-class; different from all current SAD therapies
- Successful Phase 2 completed
- Initial US Phase 3 launch in 2H 2020
- Fast-acting efficacy (10-15 minutes), exceptional safety
- Microgram dosing (3.2 μg), non-systemic
- Well-tolerated, non-sedating, non-addictive
- FDA Fast Track designation; first granted by FDA for SAD

**Potential to be the first FDA-approved
fast-acting PRN treatment for SAD**



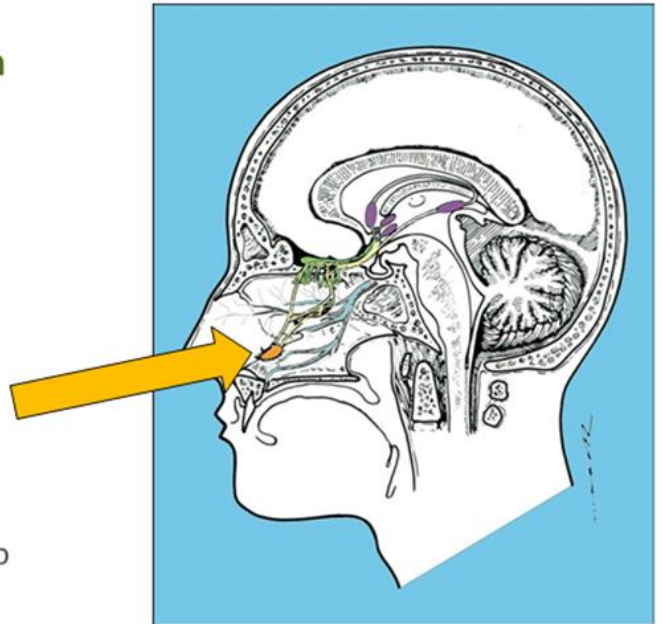
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PH94B Mechanism of Action

- **Engages nasal chemosensory receptors, which activate neural circuits in the brain that suppress fear and anxiety**
 - Engages nasal chemosensory receptors, which activate olfactory bulb (OB) neurons that project to the limbic amygdala
 - Modulates activity of the limbic-hypothalamic autonomic nervous system, which is involved in the pathophysiology of SAD and multiple other anxiety and mood disorders
 - Does not require systemic uptake and distribution to produce pharmacological effects

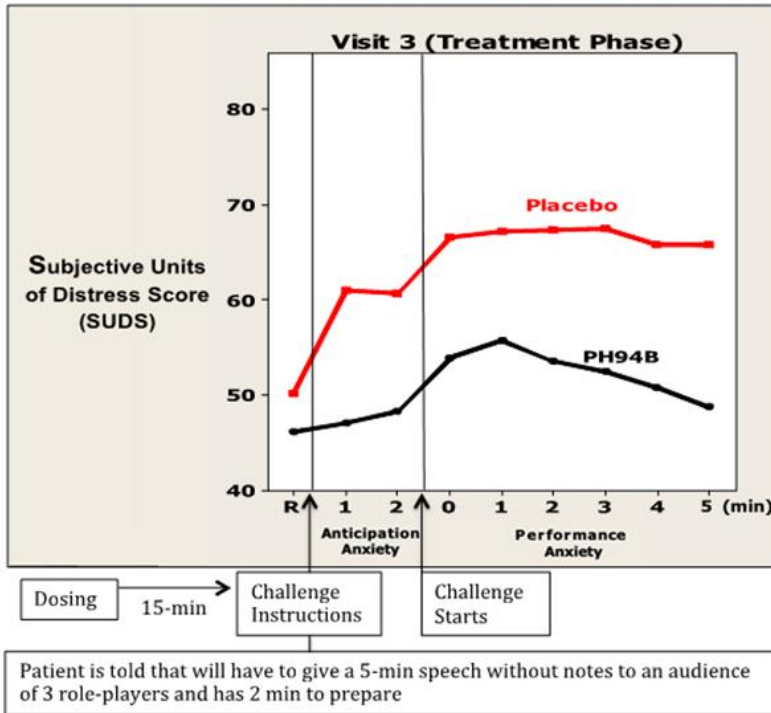


PH94B Reduced Social Anxiety Produced by Public Speaking and Social Interaction Challenges

- Multi-center, randomized, double-blind, placebo-controlled, parallel design laboratory study
- 91 female patients ages 19-60 with social anxiety disorder (SAD)
- 1.6 µg of PH94B or placebo given intranasally 15 min before each challenge
- Placebo-like safety and tolerability
- Primary Endpoint: Change in Subjective Units of Distress Scale (SUDS) from baseline compared to placebo
- PH94B significantly reduced anxiety using the SUDS compared to placebo ($p < 0.01$)

PH94B reduced anxiety in SAD patients in 10-15 minutes

Published PH94B Phase 2 Study – Public Speaking (n = 91)



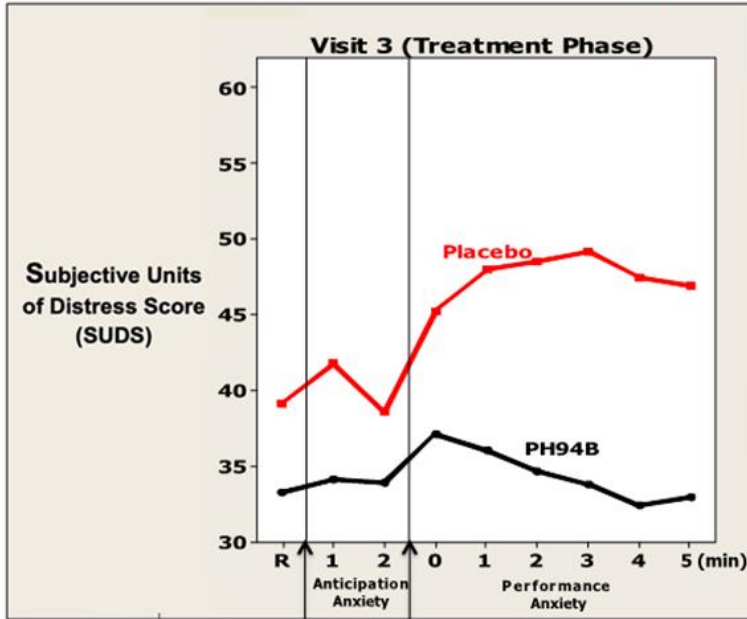
PH94B Rapidly Reduced Anxiety in Response to Public Speaking Challenge

Active Group:	Placebo Group:
Mean Difference = 26.7	Mean Difference = 14.0
Standard Deviation = 21.6	Standard Deviation = 16.3
Number of Subjects = 45	Number of subjects = 46

t = 3.16	p = 0.002	Cohen's d (Effect Size)
		.72

Liebowitz, MR, Salman, E, Nicolini, H, Rosenthal, N, Hanover, R, Monti, L (2014). Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder. *Am. J. Psychiatry* 171:675-682.

Published PH94B Phase 2 Study – Social Interaction (n = 91)



PH94B Rapidly Reduced Anxiety in Response to Social Interaction Challenge

Active Group:	Placebo Group:
Mean Difference = 18.3	Mean Difference = 6.6
Standard Deviation = 17.4	Standard Deviation = 23.6
Number of Subjects = 45	Number of Subjects = 46

t = 2.67	p = 0.009	Cohen's d (Effect size)
		.56



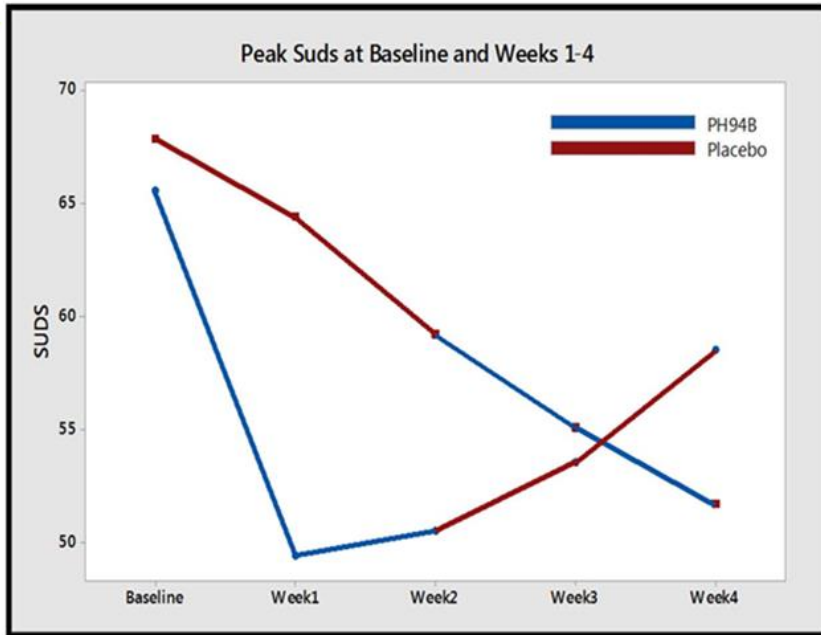
Liebowitz, MR, Salman, E, Nicollini, H, Rosenthal, N, Hanover, R, Monti, L (2014). Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder. *Am. J. Psychiatry* 171:675-682.

PH94B Reduced Anxiety in a Pilot Phase 3 “Real World” SAD Cross-over Study

- Randomized, double-blind, 4 week (two 2-week periods), cross-over study
- 22 male and female patients ages 18-65 with social anxiety disorder (SAD)
- Before a potentially stressful social situation, females self-administered 1.6 µg of PH94B or placebo and males self-administered 3.2 µg of PH94B or placebo, up to 4X/day
- PH94B significantly reduced anxiety on SUDS compared to placebo (p<0.01)
- Strong trend for improvement on LSAS during first period before cross-over
- Carryover effects of PH94B after cross-over support using a parallel design in Phase 3

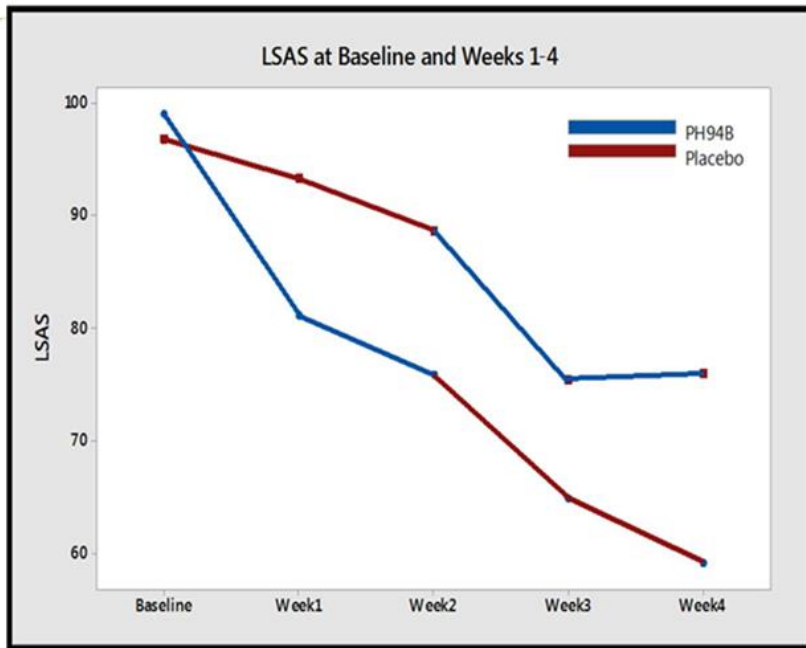
PH94B reduced anxiety in SAD patients in the “real world”
Phase 3 will employ a standard parallel design

PH94B Pilot Phase 3 Cross-over Study



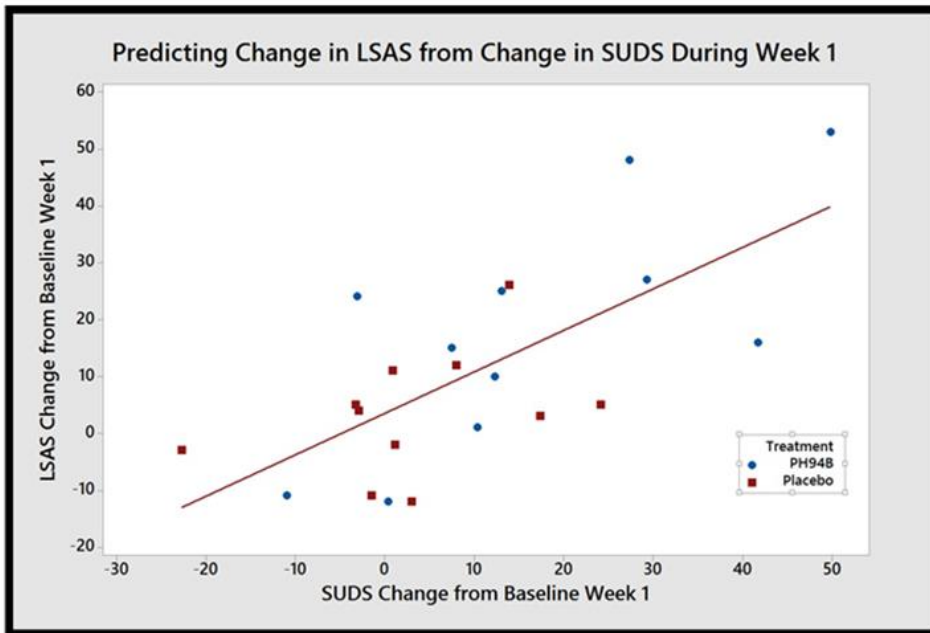
- Early suggestions of drug/placebo differences were seen in week 1 and week 2 SUDS scores: average change in SUDS at week 1 was 16.1 for PH94B vs. 3.4 for placebo ($t=1.86$, $p=.078$, ES .79); at week 2, the average change was 15.9 for PH94B and 6.9 for placebo ($t= 1.35$, $p=0.192$, ES .576)
- Peak SUDS score for the PH94B group increased after cross-over to placebo, though not back to the baseline, due to increased confidence from PH94B treatment prior to the cross-over to placebo

PH94B Pilot Phase 3 Cross-over Study



- In the sample as a whole, drop in LSAS scores after treatment did not differ between groups because subjects receiving PH94B before receiving placebo continued to improve when crossed over to placebo
- After the first 2 weeks of treatment, subjects who received PH94B dropped an average of 23.2 points on the LSAS, while those who received placebo dropped only 8.2 points, showing a strong trend for improvement on LSAS ($t=1.9$, $p=.07$) with a large effect size of .812
- Similar trend differences on total LSAS scores were seen after 1 week of treatment, where the PH94B group showed a 17.8 point drop compared to a 3.5 point drop with placebo ($t=2.02$, $p=.057$, ES .86) 17

PH94B Pilot Phase 3 Cross-over Study



Changes in total LSAS scores were closely associated with change in SUDS peak anxiety scores at week 1 (R-sq (adj) 45.2%) and at week 2 (R-sq (adj) 34.95%). Looking at LSAS subscales, the strongest associations for SUDS peak anxiety scores were with the LSAS avoidance subscale at week 1 (R-sq (adj) 58.78%) and week 2 (R-sq (adj) 42.74%), and LSAS performance at week 1 (R-sq (adj) 50.33%).

PH94B Phase 3 Development Plan for SAD

Initial U.S. Phase 3 Study

Principal Investigator: Dr. Michael Liebowitz, Columbia University, New York

- Randomized, double-blind, placebo-controlled, parallel design monotherapy study
- 3.2 µg of PH94B or placebo for 4 weeks
- Multi-center, ca. 15 sites in North America
- Target enrollment, n = ca. 200 - 250
- Target launch, 2H 2020
- Target completion, 2H 2021

Primary Endpoints: Change in LSAS and SUDS from baseline compared to placebo

PH94B Commercial Opportunity – U.S. SAD Market

SUBSTANTIAL UNMET NEED

Though SAD is highly prevalent with a significant impact on quality of life recognition, diagnosis and treatment remain low. Few novel medications in development to address high unmet needs.

UNIQUE MOA

While some clinicians are skeptical that PH94B is not habit-forming, most are cautiously optimistic due to its novel, differentiated MOA and non-systemic administration.



STRONG INTENT TO PRESCRIBE

Motivated by safety/tolerability, efficacy and PRN use, most clinicians intend to offer PH94B to a majority of their patients with SAD. Additionally, most patients are interested in trying PH94B and would be motivated to discuss with an HCP after seeing an advertisement.

EASE OF USE

Given similar efficacy, patients and clinicians will likely prefer PH94B's faster onset vs. antidepressants and may prefer a convenient, non-systemic, non-addictive as-needed nasal spray administration over a daily pill.

PH94B Beyond SAD



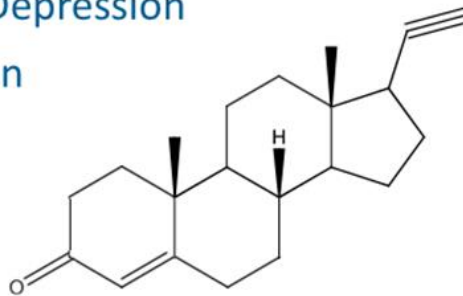
**Potential Next Steps:
Phase 2a POC studies**

PH10 neuroactive nasal spray

Pregn-4-en-20-yne-3-one

Novel, safe, fast-acting therapy for:

- Major Depressive Disorder
- Treatment-Resistant Depression
- Peripartum Depression
- Suicidal Ideation



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Major Depressive Disorder in the U.S.

1 in 4 women



1 in 6 men



1 in 8



diagnosed with depressive disorders

age 12 and over takes an antidepressant¹

LARGE ADDRESSABLE MARKET WITH HIGH UNMET NEED^{2,3}

11.6M

Drug-treated patients with Major Depressive Disorder

7.3M

Inadequate response to 1st antidepressant

5.1M

Treatment-resistant after 2nd antidepressant

1. CDC – NCHS – National Center for Health Statistics, August 2017; 2. Rush AJ, et al. Am J. Psychiatry. 2006, 163(11): 1905-1917 (STAR*D Study); 3. Decision Resources 2016.

FDA-Approved MDD Treatments Fall Short

Current Oral Antidepressants

- **Often do not work; slow to work**
 - Initial ADT effective in 1 of 3 patients
 - May take 4 to 6 weeks or more for antidepressant effects
- **Significant potential side effects**
 - Anxiety, sexual dysfunction, insomnia, dizziness, nausea and vomiting, headache, sweating

Atypical Antipsychotics

- **Often do not work**
 - Only ca. 20% of patients respond to augmentation
- **Significant potential side effects**
 - Weight gain, stomach pain, tiredness, dizziness, tardive dyskinesia, headache, nervousness, restlessness

Ketamine Therapy for Treatment-Resistant Depression

Intravenous ketamine



“Ketamine offers lifeline for people with severe depression, suicidal thoughts”



Intranasal ketamine



“J&J’s new ketamine-like depression drug Spravato off to ‘very, very strong start,’ company says”

Ketamine-based therapy offers new hope to millions, but is it a safe, convenient and cost-effective long-term solution?

“In the clinical trials, the most common side effects of SPRAVATO™ when used along with an antidepressant taken by mouth included: dissociation, dizziness, nausea, sedation, spinning sensation, reduced sense of touch and sensation, anxiety, lack of energy, increased blood pressure, vomiting, and feeling drunk.”¹

Janssen Pharmaceuticals, Inc.
Press Release, March 5, 2019

- Side Effects?
- Inconvenience?
- Safety Concerns?
- Compliance?
- High Cost?
- Durability?

1. Johnson & Johnson Press Release. Janssen Announces U.S. FDA Approval of SPRAVATO™ (esketamine) CIII Nasal Spray for Adults with Treatment-Resistant Depression (TRD) Who Have Cycled Through Multiple Treatments Without Relief. Available at: <https://www.jnj.com/janssen-announces-u-s-fda-approval-of-spravatotm-esketamine-ciii-nasal-spray-for-adults-with-treatment-resistant-depression-trd-who-have-cycled-through-multiple-treatments-without-relief>

PH10 for MDD

- First-in-class
- Fundamentally different MOA from all antidepressants
- Successful Phase 2a completed
- Rapid-onset antidepressant effects
- Microgram dosing, non-systemic
- Well-tolerated, minimal side effects
- Preparing for U.S. Phase 2b

Potential stand-alone and adjunctive at-home therapy with fast-acting, esketamine-like antidepressant effects, without side effects and safety concerns of ketamine-based therapy



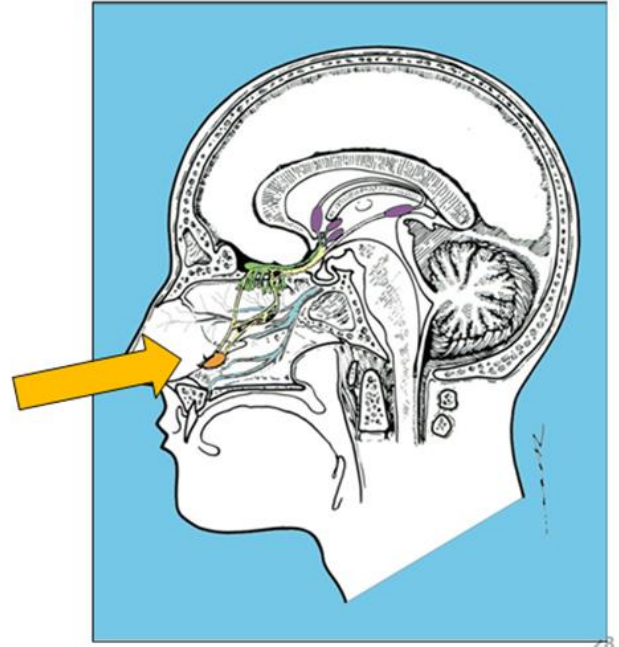
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PH10 Mechanism of Action

- **Engages nasal chemosensory receptors, which activate neural circuits in the brain leading to antidepressant effects**
 - Engages nasal chemosensory receptors, which activate olfactory bulb (OB) neurons that project to the limbic amygdala
 - OB neurons stimulate neurons in the limbic amygdala that release norepinephrine and increase activity of the limbic-hypothalamic sympathetic nervous system
 - Does not require systemic uptake and distribution to produce pharmacological effects

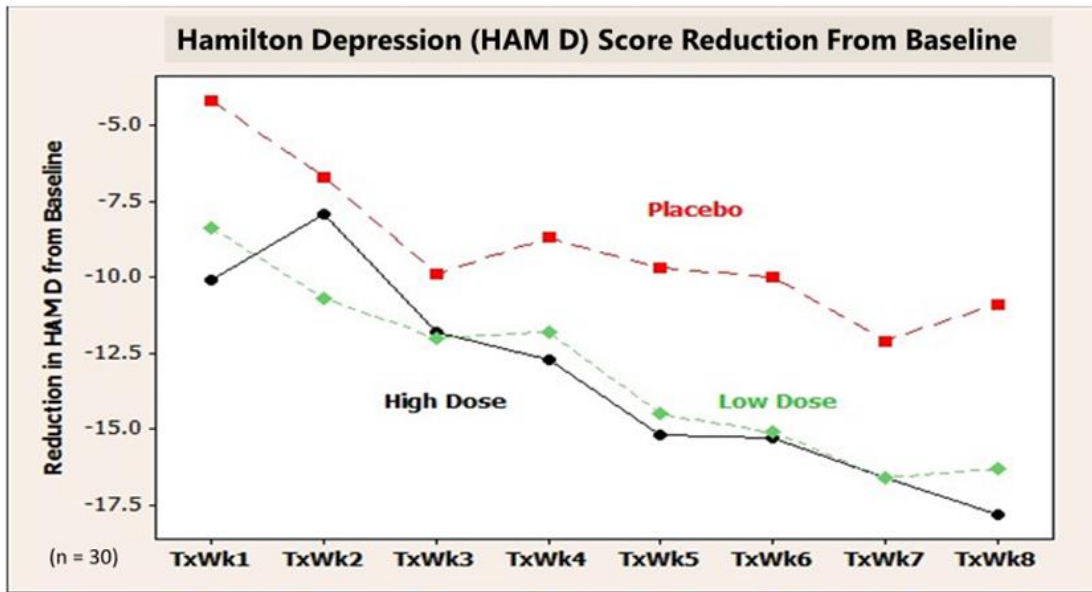


PH10 Demonstrates Antidepressant Effects in MDD Patients

- Randomized, double-blind, placebo-controlled, 8-week, parallel design POC study conducted in Mexico City
- 30 male and female patients ages 18-65 with major depressive disorder (MDD)
- Microgram dosing: MDD patients self-administered 3.2 µg or 6.4 µg of PH10 or placebo 2X per day, every day for 8 weeks
- 6.4 µg dose significantly reduced depressive symptoms as early as one week based on the Hamilton Depression Scale (HAM-D17) compared to placebo (p=0.022)
- Very well tolerated, no dissociative side effects or serious adverse events

Rapid onset antidepressant effects in MDD patients with minimal side effects

PH10 Phase 2a MDD Monotherapy Study (n = 22)



Microgram doses of PH10 neuroactive nasal spray improved MDD symptoms with rapid-onset efficacy

PH10 Dose	HAM D Score	P (PH10 vs Placebo)	Cohen's D (Effect Size)
3.2 µg (Low Dose)	16.3	.101	0.74
6.4 µg (High Dose)	17.8	.022	0.95
Placebo	10.9		

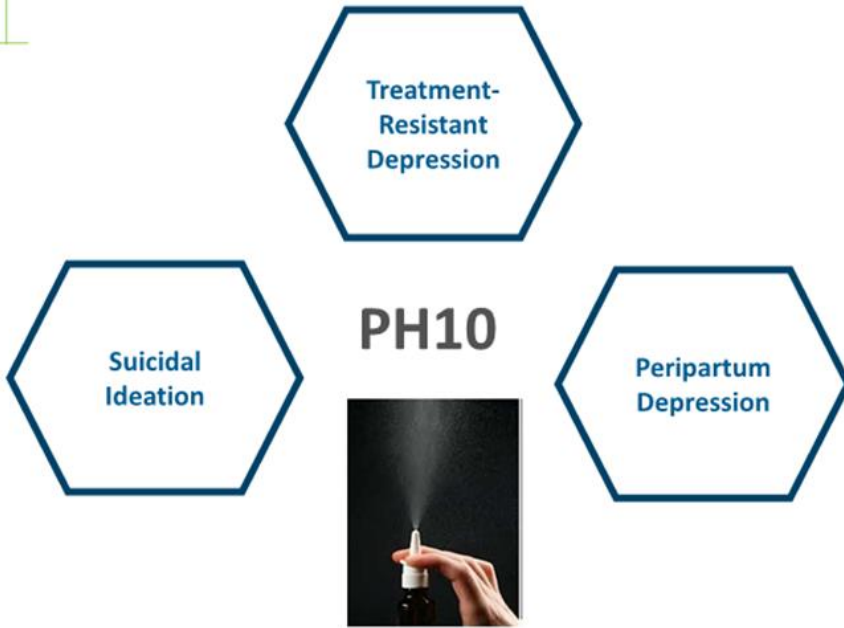
PH10 U.S. Phase 2b Development Plan for MDD

Principal Investigator: Dr. Michael Liebowitz, Columbia University, New York

- Randomized, double-blind, placebo-controlled, multi-center monotherapy study
- MDD patients with zero or 1 prior failure on a standard antidepressant
- Twice a day administration of PH10 (3.2 µg or 6.4 µg) or placebo for 4 weeks
- Rapid onset potential within one week
- Target enrollment, n= ca. 150-200 patients
- Target start, 2H 2020 / 1H 2021

Primary Endpoint: Change in MADRS-10 from baseline compared to placebo

PH10 Beyond MDD



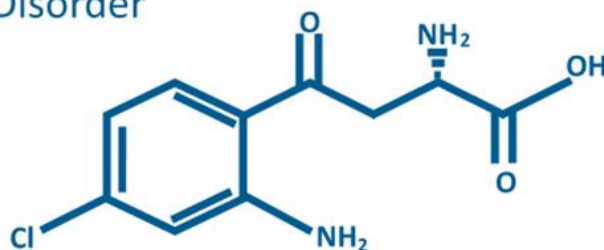
**Potential Next Steps:
Phase 2a studies**

AV-101

L-4-chlorokynurenine


Novel oral NMDA receptor GlyB antagonist for:

- Major Depressive Disorder
- Suicidal Ideation
- Neuropathic Pain
- Epilepsy
- Levodopa-Induced Dyskinesia associated with Parkinson's Therapy



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 Nasdaq: VTGN

AV-101 for MDD

- Oral prodrug of 7-Cl-KYNA, a selective NMDA receptor glycine site antagonist (full antagonist)
- Well-tolerated in all clinical studies to date
- No dissociative side effects or treatment-related SAEs
- Non-addictive, non-sedating
- FDA Fast Track designations in MDD and pain



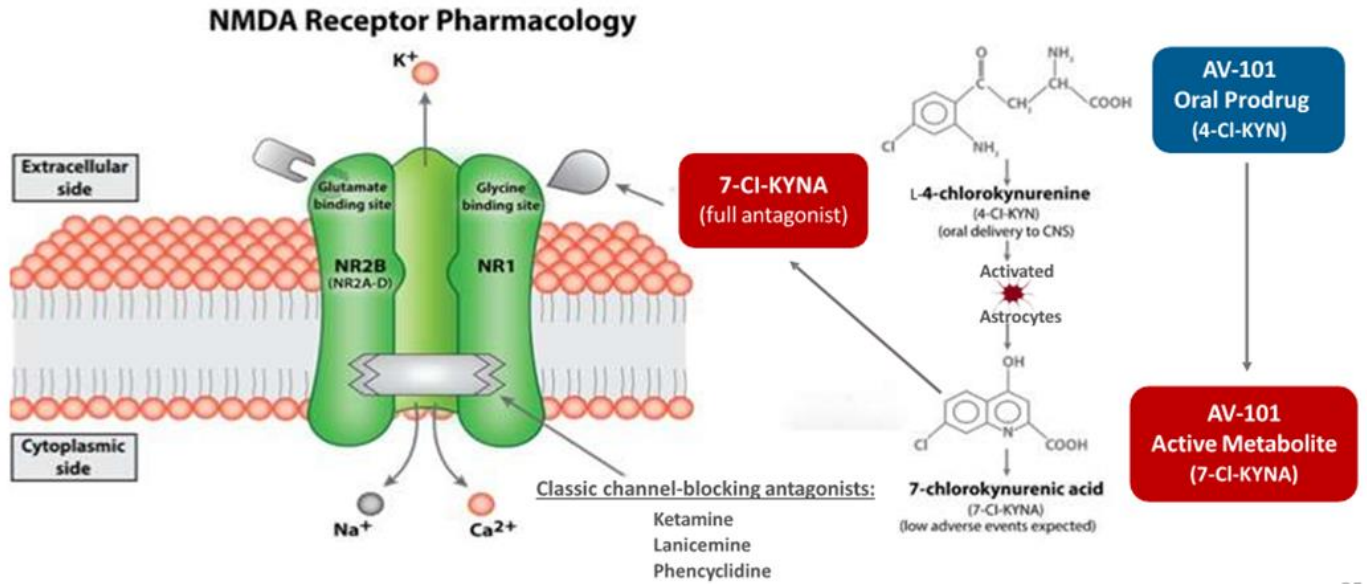
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AV-101's Mechanism of Action

4-Cl-KYN (prodrug) → 7-Cl-KYNA (active metabolite)



AV-101 in Published Phase 1 Clinical Trials

AV-101 is very well-tolerated and orally bioavailable

- Plasma half-life is about 2 hr
- Dosed up to 1440 mg daily for 2 weeks
- Adverse events were placebo-like, except for some feelings of euphoria (“well-being”)
- No ketamine-like psychosis
- No QT prolongation
- No abnormalities in clinical chemistry or hematology



Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

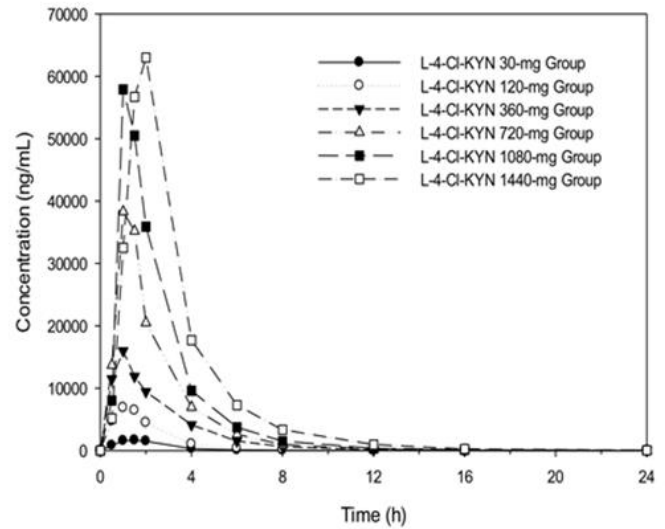


Clinical pain research

Randomized, double-blind, placebo-controlled, dose-escalation study: Investigation of the safety, pharmacokinetics, and antihyperalgesic activity of L-4-chlorokynurenine in healthy volunteers

Mark Wallace^{a,b}, Alexander White^b, Kathy A. Grako^c, Randal Lane^c, Allen (Jo) Cato^c, H. Ralph Snodgrass^d

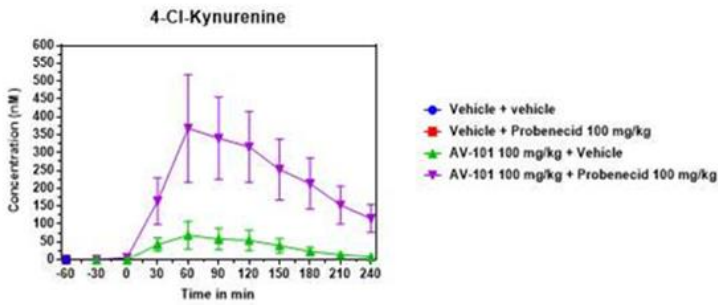
Plasma levels of AV-101 in normal volunteers following single oral dosing



AV-101 and Adjunctive Probenecid

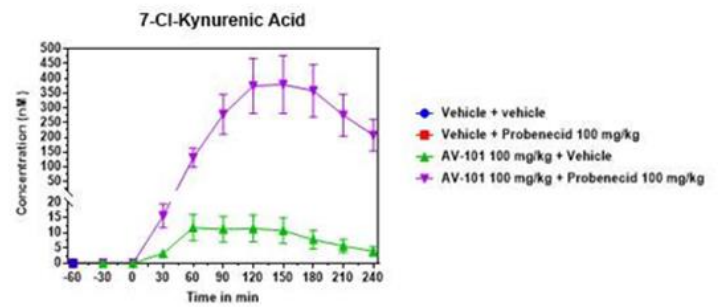
Substantial increases in rodent brain concentrations of AV-101 and 7-CI-KYNA

Probenecid increases AV-101 brain levels by ~ 7 fold



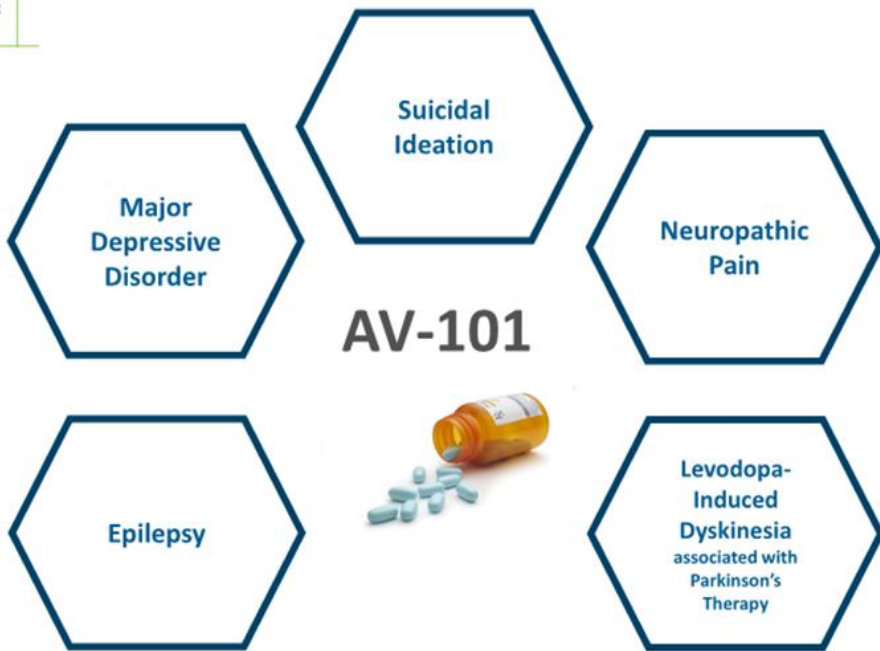
• **Figure-1** → Levels of 4-Cl-KYN in PFC of adult male Sprague-Dawley rats following IP administration (T=0) of AV-101 and probenecid alone or in combination (100 mg/kg, each). ← Data are represented as mean ± SEM. N = 4-6/group. ¶

Probenecid increases 7-CI-KYNA brain levels by > 35 fold



• **Figure-2** → Levels of 7-Cl-KYNA in PFC of adult male Sprague-Dawley rats following IP administration (T=0) of AV-101 and probenecid alone or in combination (100 mg/kg, each). ← Data are represented as mean ± SEM. N = 4-6/group. ¶

AV-101 with Adjunctive Probenecid for Multiple Indications



**Potential Next Steps:
Phase 2a POC studies with
adjunctive probenecid**

AV-101 for Major Depressive Disorder

- Ketamine-like antidepressant effects, no ketamine-like side effects in published preclinical studies¹
- No differentiation in initial Phase 2 MDD study (1440 mg with adjunctive ADT)
- Well-tolerated, no psychotomimetic side effects or serious adverse events
- Preclinical studies with adjunctive probenecid suggest path forward
- AV-101/probenecid preclinical studies 1H 2020
- Potential Phase 1b study launch in 2H 2020/1H 2021 to enable Phase 2a
- FDA Fast Track designation granted



Potential Next Step: Phase 2a study with adjunctive probenecid

1. Zanos, P., et al. (2015) "The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition." *J Pharmacol Exp Ther* 355:76-85

AV-101 for Suicidal Ideation



U.S. Department
of Veterans Affairs

Baylor
College of
Medicine



Baylor / VA Phase 1b NMDAR Target Engagement Study (n=10)

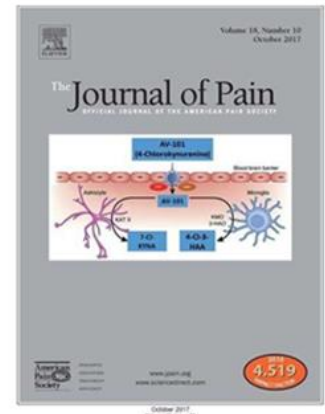
- Double-blind, placebo-controlled, cross-over study sponsored by U.S. Department of Veterans Affairs (VA) and conducted at Baylor College of Medicine
- Two single doses of AV-101 (720 mg and 1440 mg) and placebo
- Focused on dose-response relationship between AV-101 and EEG biomarkers related to NMDAR function and blood biomarkers associated with suicidality
- High dose (1440 mg) of AV-101 associated with dose-related increase in 40 Hz ASSR
- Well-tolerated, no dissociative AE's or SAE's

Successful target engagement relevant to NMDAR antagonism and suicidal ideation

AV-101 for Neuropathic Pain in Preclinical Studies

- Significant dose-response with similar efficacy in a rat model of a mononeuropathy as compared to gabapentin (Neurontin) and pregabalin (Lyrica)¹
- Robust analgesic effects, similar to gabapentin and pregabalin, but fewer side effects as measured in the rotarod assay
- Potential oral non-opioid treatment option
- Non-addictive and non-sedating
- FDA Fast Track designation granted

Potential Next Step: Phase 2a study with adjunctive probenecid



1 - Yaksh, T.L., et al. (2017). "Characterization of the Effects of L-4-Chlorokynurenine on Nociception in Rodents." The Journal of Pain 18: 1184-1196

AV-101 for Seizures in Preclinical Studies

- By stimulating the NMDAR, glutamate is believed to be critical in the neuropathology and clinical symptoms of seizures
- Multiple published reports demonstrate that, if delivered by injection into brain, 7-Cl-KYNA substantially reduces the frequency of seizures in multiple animal models
- AV-101 dramatically reduced seizures in two rodent models of seizures¹
 - Seizure data obtained from spontaneously seizing CLE rats (n = 6)
 - ◆ Test Period per trial: 6 hours
 - ◆ Baseline: 8.3 ± 1 seizures
 - ◆ AV-101: 4.8 ± 1 seizures
 - 43% reduction in seizures, p<0.02 (two-tailed t-test)

Potential Next Step: Phase 2a study with adjunctive probenecid

1. Collaboration with E. Bertram, University of Virginia

AV-101 for Levodopa-induced Dyskinesia associated with Parkinson's Therapy in Preclinical Studies

- Antidyskinetic effects in the MPTP primate model similar to those generally observed with amantadine therapy, but without adverse effects experienced with amantadine
- Significantly ($p = 0.01$) reduced LID without affecting timing, extent, or duration of anti-Parkinsonian therapeutic benefits of levodopa¹
- Potential to replace oral amantadine for LID associated with Parkinson's therapy



Potential Next Step: Phase 2a study with adjunctive probenecid

1. Collaboration with [Dr. Thérèse Di Paolo](#), CHU de Québec – Université Laval Research Center

Distinguished Clinical and Regulatory Advisors



Maurizio Fava, M.D.

Professor of Psychiatry, Harvard Medical School; Director, Division of Clinical Research, Massachusetts General Hospital (MGH) Research Institute; Executive Director, MGH Clinical Trials Network and Institute



Sanjay Mathew, M.D.

Associate Professor of Psychiatry and Behavioral Sciences, Marjorie Bintliff Johnson and Raleigh White Johnson, Jr. Chair for Research in Psychiatry and Menninger Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine



Michael Liebowitz, M.D.

Professor of Clinical Psychiatry, Columbia University; Managing Director and Founder, The Medical Research Network, LLC; Director (retired), Anxiety Disorders Clinic at the New York State Psychiatric Institute



Gerard Sanacora, Ph.D., M.D.

Professor of Psychiatry, Yale School of Medicine; Director, Yale Depression Research Program; Scientific Director, Yale-New Haven Hospital Interventional Psychiatry Service



Thomas Laughren, M.D.

Director (retired), U.S. Food and Drug Administration (FDA) Division of Psychiatry Products, Office of New Drugs, Center for Drug Evaluation and Research (CDER)



Mark Wallace, M.D.

Professor of Clinical Anesthesiology, Chair of the Division of Pain Medicine, Medical Director and Director at the University of California, San Diego

Experienced Team Leading Execution



Ralph Snodgrass, Ph.D.
President, Chief Scientific
Officer

- 23 years of experience in senior biotechnology management
- Progenitor; Lineberger Comprehensive Cancer Center



Shawn K. Singh
Chief Executive Officer

- 25 years of experience with biopharmaceutical companies, a healthcare venture capital firm and a profitable CRO
- Artemis Neuroscience; SciClone Pharmaceuticals; Cato BioVentures; Cato Research; Morrison & Foerster



Jerrold D. Dotson, CPA
Chief Financial Officer, Secretary

- 20 years of experience in senior management finance and administration
- Calypte Biomedical; Discovery Foods; California & Hawaiian Sugar; Clorox

**Mark A. Smith, M.D.,
Ph.D.**

Chief Medical Officer

- 20 years of large Pharma CNS drug development experience
- Teva Pharmaceuticals; Shire Pharmaceuticals; AstraZeneca Pharmaceuticals; DuPont Pharmaceutical Company; U.S. National Institute of Mental Health



Mark A. McPartland
Vice President, Corporate Development

- 20 years of experience in corporate development, capital markets and management consulting
- Stellar Biotechnologies; MZ Group; Hayden Communications; Alliance Advisors

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CNS DISEASES AND DISORDERS
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VistaGen and Baylor College of Medicine Announce Successful Results of First-Step Target Engagement Study with VistaGen's AV-101 Focused on Treating Suicidal Ideation in Veterans

Multiple electrophysiological biomarkers indicate AV-101's NMDA receptor target engagement

Both AV-101 doses were well-tolerated and not associated with dissociative or serious adverse events

Poster presented at 2019 Annual Meeting of American College of Neuropsychopharmacology

SOUTH SAN FRANCISCO, Calif. and HOUSTON, Texas, December 19, 2019 – [VistaGen Therapeutics](#) (NASDAQ: VTGN), a clinical-stage biopharmaceutical company developing new generation medicines for central nervous system (CNS) diseases and disorders with high unmet need, and Baylor College of Medicine (Baylor), today announced successful results from a first-step, Phase 1b clinical study with healthy U.S. military Veterans, which measured NMDAR (N-methyl-D-aspartate receptor) target engagement of VistaGen's investigational product candidate, AV-101, an oral NMDAR glycine site antagonist, for potential treatment of suicidal ideation in Veterans. The findings from the study were presented in a poster, titled "[Evoked and Resting State Gamma Mechanics to Test NMDA Receptor Engagement of Kynurenine Pathway Modulator AV-101 in Healthy Veterans](#)," at the 2019 Annual Meeting of the American College of Neuropsychopharmacology (ACNP) on December 11, 2019.

In the Phase 1b target engagement study, 10 healthy volunteer Veterans from Operation Enduring Freedom, Operation Iraqi Freedom or Operation New Dawn received single doses of AV-101 (720 mg and 1440 mg) and placebo, in a double-blind, randomized, cross-over controlled trial. The primary goal of the study was to identify and define a dose-response relationship between AV-101 and multiple electrophysiological (EEG) biomarkers related to NMDAR function, as well as blood biomarkers associated with suicidality. The findings suggest that, in healthy Veterans, the higher dose of AV-101 (1440 mg) was associated with dose-related increase in the 40 Hz Auditory Steady State Response (ASSR), a robust measure of the integrity of inhibitory interneuron synchronization.

Both doses of AV-101 were well-tolerated, and there were no dissociative adverse events or serious adverse events.

Dr. Marijn Lijffijt, assistant professor of [psychiatry research at Baylor](#) and the Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston served as Principal Investigator of the study. VistaGen and the U.S. Department of Veterans Affairs (VA) entered into a Material Transfer Cooperative Research and Development Agreement (MT CRADA) regarding clinical trial material for this study, and VA funding was provided for all other study costs.

"According to the VA, [over 20 veterans take their lives each day](#) – a number that is alarming and unfortunate," said Mark A. Smith, M.D., Ph.D., VistaGen's Chief Medical Officer. "Nearly every day we hear stories in the news about how the suicide rate is increasing, and how it's [even higher among U.S. Veterans than non-Veterans](#). Better therapies are needed for Veterans who are suffering from suicidal ideation. We interpret the findings of this biomarker study to mean that the high dose of AV-101 was sufficient to reduce NMDA function. Based on our recent preclinical studies demonstrating the ability of the transport inhibitor probenecid to markedly increase concentrations of AV-101 (approximately 7-fold) and its active metabolite 7-chloro-kynurenic acid (approximately 35-fold) in the rodent brain, it may be possible to increase and prolong NMDA antagonism even further when AV-101 and probenecid are combined. These human target engagement findings represent our first-step collaboration with Baylor and the VA, and they increase our confidence in AV-101's safety and its potential, especially with adjunctive probenecid, to treat this major health concern. We look forward to future discussions with Baylor and the VA regarding a second-step program involving Veterans who are battling suicidal ideation."

"Overall, this study is a promising start on the path to explore AV-101's potential to address the morbidity and mortality associated with suicidal depression," said Sanjay J. Mathew, M.D., vice chair for research and professor of psychiatry and behavioral sciences at Baylor, and a Staff Psychiatrist at MEDVAMC. "Substantially increased concentrations of 7-Cl-KYNA in VistaGen's recent preclinical studies of AV-101 with adjunctive probenecid are notable. Future clinical studies in military veterans could examine the effect of AV-101, at the 1440 mg dose combined with probenecid, in suicide risk. We look forward to further collaborations with VistaGen and the VA."

About VistaGen

VistaGen Therapeutics is a clinical-stage biopharmaceutical company developing new generation medicines for CNS diseases and disorders where current treatments are inadequate, resulting in high unmet need. VistaGen's [pipeline](#) is focused on clinical-stage CNS drug candidates with a differentiated mechanism of action, an exceptional safety profile in all clinical studies to date, and therapeutic potential in multiple large and growing CNS markets. For more information, please visit www.vistagen.com and connect with VistaGen on [Twitter](#), [LinkedIn](#) and [Facebook](#).

About Baylor College of Medicine

[Baylor College of Medicine](#) in Houston is recognized as health sciences university and is known for excellence in education, research and patient care. It is the only private medical school in the greater southwest and is ranked 22nd among medical schools for research and 4th for primary care by U.S. News & World Report. Baylor is listed 20th among all U.S. medical schools for National Institutes of Health funding and No. 1 in Texas. The Baylor pediatrics program ranked 8th among all pediatric programs, reflecting the strong affiliation with Texas Children's Hospital where our faculty care for pediatric patients and our students and residents train. Nationally our physician assistant program was ranked 3rd in the health disciplines category and our nurse anesthesia program ranked 2nd. Located in the Texas Medical Center, Baylor has affiliations with seven teaching hospitals and jointly owns and operates Baylor St. Luke's Medical Center, part of CHI St. Luke's Health. Currently, Baylor has more than 3,000 trainees in medical, graduate, nurse anesthesia, physician assistant, orthotics and genetic counseling as well as residents and postdoctoral fellows. Follow Baylor College of Medicine on [Facebook](#) and [Twitter](#).

About AV-101

AV-101 (4-Cl-KYN) belongs to a new generation of investigational medicines in neuropsychiatry and neurology known as NMDA (N-methyl-D-aspartate) receptor modulators. The NMDA receptor is a pivotal receptor in the brain and abnormal NMDA function is associated with numerous CNS diseases and disorders. AV-101 is an oral prodrug of 7-Cl-KYNA, a potent and selective full antagonist of the glycine co-agonist site of the NMDA receptor. With its exceptional safety profile in all studies to date, AV-101 has potential to be a new at-home, non-sedating treatment for multiple large market CNS indications where current treatments are inadequate to meet high unmet patient needs. VistaGen is currently focused on potential development of AV-101 for MDD, neuropathic pain, suicidal ideation and dyskinesia associated with levodopa treatment for PD. The FDA has granted Fast Track designation for development of AV-101 as both a potential [adjunctive treatment for MDD](#) and as a [non-opioid treatment for neuropathic pain](#).

About Suicide

According to the World Health Organization (WHO), every year approximately 800,000 people worldwide take their own life and many more attempt suicide.¹ Suicide is a major public health concern in the United States as rates of suicide have been increasing for both men and women and across all age groups. Suicide is the 10th leading cause of death in the U.S. and is one of just three leading causes that are on the rise.² The Center for Disease Control and Prevention (CDC) reported that in the U.S. the age-adjusted rate of suicide increased by 24 percent between 1999 and 2014.³ The number of U.S. citizens who die by suicide is, since 2010, higher than those who die in motor vehicle accidents. People of all genders, ages, and ethnicities can be at risk for suicide and suicidal behavior is complex and there is no single cause. In fact, many different factors contribute to someone making a suicide attempt, including, but not limited to, depression, other mental health disorders or substance abuse disorder; certain other medical conditions; chronic pain; prior suicide attempt; and family history of mental disorder or substance abuse.⁴ Additionally, it has been found that the Veteran population is at significantly higher risk for suicide. After adjusting for differences in age, risk for suicide was 19 percent higher among male Veterans compared with U.S. civilian adult men and 2.5 times higher among female Veterans compared with U.S. civilian adult women.⁵ Despite these many risk factors, suicide is not inevitable for those that have one or more risk factor(s). Starting a conversation, reducing stigma, providing support and resources and working to develop safe and novel treatments for those in need can help prevent suicide and save the lives of many.

1 <http://www.who.int/news-room/fact-sheets/detail/suicide>

2 <https://www.cdc.gov/media/releases/2018/p0607-suicide-prevention.html>

3 [Curtin SC, Warner M, Hedegaard H. Increase in suicide in the United States, 1999–2014. NCHS data brief, no. 241. Hyattsville, MD: National Center for Health Statistics. 2016.](#)

4 <https://www.nimh.nih.gov/health/topics/suicide-prevention/index.shtml>

5 <https://www.mentalhealth.va.gov/docs/2016suicidedatareport.pdf>

Veterans who are in crisis or having thoughts of suicide, and those who know a Veteran in crisis, should call the [Veterans Crisis Line](#) for confidential support 24 hours a day, seven days a week, 365 days a year at 800-273-8255 and press 1, chat online at [VeteransCrisisLine.net/Chat](#) or send a text message to 838255.

To reach the [National Suicide Prevention Lifeline](#) network, please call 1-800-273-8255 (available 24 hours every day). Learn more about VA's suicide-prevention resources and programs at [www.mentalhealth.va.gov/suicide_prevention/](#).

Additional materials can be found on VistaGen's Resources page [here](#).

Forward-Looking Statements

This release contains various statements concerning VistaGen's future expectations, plans and prospects, including without limitation, our expectations regarding development and commercialization of our three drug candidates: (i) PH94B for social anxiety disorder and multiple other anxiety disorders; (ii) PH10 for MDD and multiple additional depression disorders and suicidal ideation, and (iii) AV-101 for MDD, neuropathic pain, epilepsy, dyskinesia associated with levodopa therapy for Parkinson's disease and suicidal ideation. In addition, statements concerning the Company's future expectations may include statements regarding intellectual property and commercial protection of our drug candidates. Each of these statements constitute forward-looking statements for the purposes of the safe harbor provisions under the Private Securities Litigation Reform Act of 1995. These forward-looking statements are neither promises nor guarantees of future performance and are subject to a variety of risks and uncertainties, many of which are beyond our control, and may cause actual results to differ materially from those contemplated in these forward-looking statements. Those risks include the following: (i) we may encounter unexpected adverse events in patients during our clinical development of any product candidate that cause us to discontinue further development; (ii) we may not be able to successfully demonstrate the safety and efficacy of our product candidates at each stage of clinical development; (iii) success in preclinical studies or in early-stage clinical trials may not be repeated or observed in future studies, and ongoing or future preclinical and clinical results may not support further development of, or be sufficient to gain regulatory approval to market PH94B, PH10 and/or AV-101; (iv) decisions or actions of regulatory agencies may negatively affect the progress of, and our ability to proceed with, further clinical studies or to obtain marketing approval for our drug candidates; (v) we may not be able to obtain or maintain adequate intellectual property protection and other forms of marketing and data exclusivity for our product candidates; (vi) we may not have access to or be able to secure substantial additional capital to support our operations, including our ongoing preclinical and clinical development activities; and (vii) we may encounter technical and other unexpected hurdles in the manufacturing and development of any of our product candidates. Certain other risks are more fully discussed in the section entitled "Risk Factors" in our most recent annual report on Form 10-K, and subsequent quarterly reports on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our other filings with the Securities and Exchange Commission (SEC). Our SEC filings are available on the SEC's website at [www.sec.gov](#). In addition, any forward-looking statements represent our views only as of the issuance of this release and should not be relied upon as representing our views as of any subsequent date. We explicitly disclaim any obligation to update any forward-looking statements.

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