

The Role of Vasopressin in the Social Deficits of Autism

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## 1. PURPOSE OF THE STUDY

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### a. Brief Summary

We will test the safety and effectiveness of intranasal vasopressin treatment for social deficits in children with autism spectrum disorders. This research also aims to identify those individuals that stand to benefit most from this drug intervention. Vasopressin treatment has enormous potential for enhancing quality of life in people with autism through improved social cognition and more meaningful social relationships, and if efficacious, will considerably reduce the emotional and financial burden of autism on patients, family members, and society.

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### b. Objectives

Vasopressin is one of the most promising candidate drugs to treat the presently intractable social deficits of autism. This project will be the first to test whether intranasal vasopressin administration enhances social functioning in individuals with autism. Inclusion of female participants is a major strength of this study as female exclusion, which frequently occurs in autism treatment studies, may jeopardize optimal testing of effective pharmacotherapies, and preclude identification of disease mechanisms. Our inclusion of females is particularly important because preclinical evidence suggests that males may respond more robustly to vasopressin treatment than females. Additionally, findings from both preclinical and clinical studies have shown that differences in pre-treatment social functioning and/or neuropeptide biology are associated with vasopressin and oxytocin treatment response outcomes. Ours will be the first study to test concomitantly whether pre-treatment social measurements and baseline neuropeptide levels contribute to individual differences in vasopressin treatment response efficacy.

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### c. Rationale for Research in Humans

The purpose of the study is to test the tolerability and effectiveness of intranasal Vasopressin administration in children with autism spectrum disorders.

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## 2. STUDY PROCEDURES

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### a. Procedures

We will test the effects of single-dose and 4-week intranasal vasopressin administration or placebo on social abilities in 50 high functioning male and female participants with autism aged 6 to 12 years. We will use a double-blind, randomized, placebo controlled, parallel design with dose-escalation to determine both the tolerability and effectiveness of vasopressin treatment for cognitive and behavioral problems associated with autism. We plan to enroll and screen up to 100 participants to meet our target of 50 randomized subjects.

Before the start of the 4-week dosing period, subjects will be given a 1-week open-label placebo lead-in to allow for enhanced compliance and efficacy for nasal drug

administration.

Subjects aged 6 to 9.5 years of age will receive the maximum dose of 24 IU (12 IU bid). Subjects aged 9.6 to 12 years of age will receive the maximum dose of 32 IU (16 IU bid).

The dose escalation regimen of vasopressin for subjects aged 6 to 9.5 years is as follows.

Single dose administration: 12 IU; Week 1: 4 IU twice daily;

Week 2: 8 IU twice daily; Week 3: 12 IU twice daily; and, Week 4: 12 IU twice daily.

The dose escalation of vasopressin for subjects aged 9.6 to 12 years is as follows. Single dose administration: 16 IU; Week 1: 4 IU twice daily; Week 2: 8 IU twice daily; Week 3: 16 IU twice daily; and Week 4: 16 IU twice daily.

Participants will meet DSM-IV criteria for autism spectrum disorder, confirmed with gold standard research diagnostic methods. A comprehensive behavioral characterization will be obtained prior to drug administration. The primary outcome measure for this study is change in social behavior as determined by parent ratings on the Social Responsiveness Scale (SRS) after completion of 4-week vasopressin administration.

Secondary outcome measures include changes on other behavioral functioning as measured by the clinician administered Clinical Global Impressions (CGI) scale and parent ratings on the Repetitive Behavior Scale-Revised (RBS-R), the Spence Children's Anxiety Scale (SCAS), and the Pediatric Quality of Life Inventory (PedsQL), Vineland Adaptive Behavior Scale, 2nd Edition (VABS-2) social subscale, Aberrant Behavior Checklist (ABC), Multidimensional Social Competence Scale (MSCS) following 4-week vasopressin administration and changes in functioning on laboratory-based assessments of social behavior and cognition (i.e., social mimicry, facial emotion recognition, eye gaze to social cues using eye-tracking technology, social memory, and social perceptual abilities including theory of mind) following single-dose and 4-week drug administration. Secondary outcome measures also include assessment of drug tolerability following single-dose, 1-week, 2-week, 3-week, and 4-week dosing. These measures include vital signs (HR/BP and temperature), body-mass index (BMI), clinical chemistry labs (NA<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, BUN, vasopressin), osmolality (urine, blood), electrocardiogram (ECG), and parental report of side effects measured using the Dosage Record and Treatment Emergent Symptom Scale (DOTES) and the Overt Aggression Scale (OAS). Parent ratings on the SRS and the Wing Subgroups Questionnaire (WSQ), as well as participant blood samples for neuropeptide quantification, will be collected pre-treatment. Pre-treatment scores on the SRS and plasma neuropeptide (vasopressin and oxytocin) levels will be used on an exploratory basis to predict treatment response outcomes.

After completion of the double-blind 4-week treatment period participants will be informed of their treatment group and subjects randomized to placebo will have the option of participating in a 4-week open-label vasopressin treatment extension period. Participants initially randomized to placebo treatment during the randomized controlled

trial will undergo vasopressin dose- escalation and safety testing in the open-label extension period in a comparative fashion to participants initially randomized to vasopressin treatment. Participants who were initially assigned to vasopressin treatment during the randomized controlled trial will end the study.

During this time participants will again undergo all previously performed safety assessments. This will provide further information regarding the tolerability of longer term vasopressin treatment (i.e., up to 8 weeks). During the open-label extension period we will conduct pharmacokinetic (PK) analysis to determine the Tmax of vasopressin in our study population. The timing of the blood draws during the open-label extension arm will take place at 15 minutes post-vasopressin dosing for 1/3 of the participants, at 30 minutes post vasopressin dosing for 1/3 of the participants, and at 60 minutes post-vasopressin dosing for 1/3 of the participants. These analyses will take place at week-5, week-6, and week-8 for all participants.

Specific aims and hypotheses: To test our overarching hypothesis, we will pursue the following aims:

Specific Aim 1. Test the effects of single-dose vasopressin administration on laboratory- based social behavior and cognitive measures in children with autism. Predictions: Following single-dose vasopressin administration, participants will exhibit increased accuracy in recognizing facial emotions, increased eye gaze to social cues, enhanced memory for faces and names, increased social mimicry, and enhanced social perceptual abilities on theory of mind tasks compared to their pre-treatment performance and to the performance of placebo-treated participants.

Specific Aim 2. Test the effects of 4-week vasopressin administration using parent ratings of psychosocial and behavioral functioning and laboratory-based social behavior and cognition measures in children with autism. Predictions: Following 4-week vasopressin administration, participants will exhibit improvements in social and behavioral functioning as assessed by and clinician ratings on the CGI and parent ratings on the SRS, RBS-R, SCAS, and PedsQL, VABS-2, and ABC compared to their performance pre-treatment and as well as compared to the performance of placebo-treated participants. Following 4-week vasopressin administration, participants will also show improvements on all aforementioned laboratory-based measures of social functioning compared to their performance after single-dose vasopressin administration and compared to the performance of placebo-treated participants.

Specific Aim 3. Test the tolerability of single-dose and 4-week intranasal vasopressin in children with autism.

Predictions: No significant differences in rates of side effects will be observed between vasopressin and placebo treated groups following single-dose and 4-week treatment.

Exploratory Aim 4. Test whether single-dose and/or 4-week vasopressin administration preferentially enhances social functioning in male compared to female children with

autism. Predictions: Vasopressin treatment will be more effective in male compared to female participants consistent with evidence from preclinical studies.

Exploratory Aim 5. Test whether pre-treatment social functioning (i.e., severity of social impairments as measured by pre-treatment parent SRS ratings and WSQ social subtype) and/or plasma neuropeptide (i.e., vasopressin and oxytocin) levels predict vasopressin treatment response efficacy in children with autism.

Methods and procedures:

Experimental design. Using a double-blind, randomized, placebo controlled, parallel design we will test the effects of single-dose and 4-week intranasal vasopressin administration on social functioning in children with autism.

Consent/assent will be obtained before initiating any study procedures. The primary outcome measure is change in social behavior as determined by parent ratings on the SRS after completion of the 4-week treatment trial. The SRS measures the severity of social/communication deficits as they occur in natural environments. The SRS can be used as a measure of response to intervention as well as a screening instrument.

Secondary outcome measures include changes in other behavioral functioning (e.g., communication, repetitive/disruptive behaviors, anxiety, quality of life) as measured by clinician ratings on the CGI and parent ratings on the RBS-R, SCAS, PedsQL, VABS-2, ABC, MSCS after completion of the 4-week treatment trial.

Secondary outcome measures also consist of laboratory-based assessments of social behavior and cognition (described below) after both single- dose and 4-week vasopressin treatment. Drug tolerability assessments, including vital signs (HR/BP and temperature), ECG, and parent report of side effects will be conducted following single- dose, 1-week, 2-weeks, 3- weeks, and 4-weeks of drug administration. BMI will be assessed after 1-week, 2-weeks, 3- weeks and 4-weeks of dosing. Clinical chemistry labs and osmolality (urine, blood) will be obtained after 1-week, 2-weeks, and 4-weeks of dosing. In cases when a blood draw cannot be obtained the urine osmolality (which is highly correlated with blood osmolality) will be able to be used as a safety measure. A similar schedule will be followed in the optional 4-week open-label extension study.

There will be a total of up to 10 assessment time-points during this study. During the first assessment session (screening visit) participants will undergo autism diagnostic screening, intelligence testing, medical (history and physical) and psychiatric (history) examination (incl. CGI ratings), females of childbearing age or who have started having menstrual cycles will undergo urine pregnancy testing; vital signs screening, height and weight measurement, ECG assessment, and clinical chemistry labs will be assessed. Participants' will undergo pre-treatment assessment of behavioral and cognitive functioning in order to determine baseline levels on the various outcome measures. Parent ratings on the SRS, RBS-R, SCAS, PedsQL, VABS-2, ABC, MSCS, WSQ, as well as participants' blood samples for quantification of basal plasma vasopressin and oxytocin concentrations will be obtained.

Laboratory measures of social behavior and cognition will be administered to facilitate in the analysis of post-treatment changes in functioning by accounting for any pre-existing

individual differences. Briefly, these laboratory tasks involve assessing the ability of the participants to recognize basic emotions from images of faces presented on a computer screen. We will also record participants' eye gaze using eye-tracking technology while the participants view the emotional faces. We will determine participants' ability to infer emotions after viewing the eye-region of facial stimuli. We will also assess participants' memory for faces and names, and social perception abilities will be assessed using tests of theory of mind.

On completion of the screening procedures, subjects and their parents will be instructed on administration of a placebo nasal spray and will be provided with a supply of the placebo to administer at home. This one week open-label placebo lead-in component will enhance compliance and efficacy of nasal drug delivery during the study.

One to four weeks later, participants will return to the clinic and will be randomized in a double-blind fashion to a treatment condition (vasopressin or placebo). Stratification will be based on gender and age. Prior to drug administration, pre-treatment side effects information will be collected with the DOTES and OAS, participants will provide a blood sample for neuropeptide quantification and parent SRS ratings will be collected for a second time. Neuropeptide levels from the two blood samples and repeated parent assessment of the severity of participants' social impairments will allow us to test for stable individual differences in these measures. Parent SRS and WSQ ratings, as well as participants' neuropeptide levels, will allow us to test on an exploratory basis whether these baseline measures predict treatment response outcomes. Participants will then receive a single-dose of either intranasal vasopressin (12 IU or 16 IU; depending on age) or placebo and 20 minutes later will have vital signs (HR/BP and temperature) assessed prior to initiating the laboratory behavioral measures.

Before participants leave the clinic they will again have their vital signs assessed (~2 hours post-dosing) and an ECG will be performed to determine cardiac functioning. Parents will be provided with instructions on the dose-escalation schedule that will occur at home and will be provided with a dosing schedule that they will be required to follow and sign off on each day. Participants will continue vasopressin or placebo administration for 4-weeks at home and their parents will be responsible for reporting any adverse events to research staff. Parents will also be informed that their children's free water intake should be adjusted downward to decrease the potential occurrence of hyponatremia and water intoxication during the treatment period. Following 1-week, 2-weeks, and 3-weeks of dosing, participants are asked to return to the clinic for visits when drug tolerability will be assessed (vital signs, BMI, clinical chemistry labs (not at week-3), ECG, and parental side effects reports will be collected. On completion of the 4-week double-blind treatment period, participants will return to the clinic for assessments. Parent SRS, RBS-R, SCAS, VABS-2, ABC, MSCS, and PedsQL ratings and participants blood samples will be collected for neuropeptide analysis. Participants will be tested on laboratory based social behavior and cognition tests, and clinician's impressions of treatment response will be made using the CGI. Vital signs, BMI, clinical chemistry labs, osmolality (urine, blood), ECG, and parental drug side effects report will also be monitored to determine drug tolerability.

After completion of the double-blind 4-week treatment period participants will be informed of their treatment group and will have the option of participating in a 4-week open-label vasopressin treatment extension period. Participants initially randomized to placebo treatment during the randomized controlled trial will undergo vasopressin dose-escalation and safety testing in the open-label extension period in a comparative fashion to participants initially randomized to vasopressin treatment. Participants who were initially assigned to vasopressin treatment during the randomized controlled trial will have the option of continuing on their maximum tolerated dose for an additional 4-week open-label extension period. During this time participants will again undergo all previously performed safety assessments. This will provide further information regarding the tolerability of longer term vasopressin treatment (i.e., up to 8 weeks). During the open-label extension period we will conduct PK analysis to determine the Tmax of vasopressin in our study population. The timing of the blood draws during the open-label extension arm will take place at 15 minutes post-vasopressin dosing for 1/3 of the participants, at 30 minutes post-vasopressin dosing for 1/3 of the participants, and at 60 minutes post-vasopressin dosing for 1/3 of the participants. These analyses will take place at week-5, week-6, and week-8 for all participants.

Up to 30 mL of blood will be collected during the blood draws mentioned above. At all of the timepoints that blood draws are mentioned above there will also be urine samples collected for urine osmolality.

Urine and blood osmolality sample collection at Screening and Weeks 1, 2, 4, 5, 6, and 8 will be obtained. This will allow for a contingency plan in cases when blood samples are not able to be obtained at any given collection time-point since urine osmolality is highly correlated with plasma osmolality.

On completion of the 4-week open-label treatment period, participants will return to the clinic for assessments including the parent SRS, RBS-R, SCAS, VABS-2, ABC, MSCS and PedsQL ratings. Participants will be tested on laboratory based social behavior and cognition tests, and clinician's impressions of treatment response will be made using the CGI.

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**b. Procedure Risks**

Given that this research is the first of its kind to determine the effects of intranasal vasopressin for the treatment of social deficits in children with autism, we have chosen doses and a treatment duration that we believe will be both safe and effective. Subjects aged 6 to 9.5 years of age will receive the maximum dose of 24 IU (12 IU bid). Subjects aged 9.6 to 12 years of age will receive the maximum dose of 32 IU (16 IU bid). The dose escalation of vasopressin or placebo for subjects aged 6 to 9.5 years is as follows: Single dose administration: 12 IU; Week 1: 4 IU twice daily; Week 2: 8 IU twice daily; Week 3: 12 IU twice daily; and, Week 4: 12 IU twice daily.

The dose escalation of vasopressin or placebo for subjects aged 9.6 to 12 years is as follows: Single dose administration: 16 IU; Week 1: 4 IU twice daily; Week 2: 8 IU twice daily; Week 3: 16 IU twice daily; and, Week 4: 16 IU twice daily. During the initial single-dose assessment at the Stanford psychiatry clinic a dose of 12 IU or 16 IU of vasopressin or placebo will be administered to the children. This will provide us with

an opportunity to determine the tolerability of the highest dose to be used in the study while participants are at the psychiatry clinic with medically trained professionals on hand and in close proximity to Stanford hospital. This dose- escalation will provide an opportunity to determine if an participants have an adverse response to the drug. We also have a thorough safety plan in place to deal with any unexpected side effects during the initial single-dose and during the outpatient-dosing period (see below).

**Safety Monitoring:** A medical and psychiatric history will be obtained and a physical examination conducted during the screening phase, prior to randomization. All participants will be in good general medical health. Additional evaluations will be conducted following 1-week, 2-weeks, 3-weeks of dosing and at completion of the 4-week treatment period. Seizure history will be reviewed carefully during the screening visit, and as stated in the protocols exclusion criteria, children with seizure disorder, or a history of seizure-like activity, will be excluded. Drug side effects will be evaluated with the Dosage Record and Treatment Emergent Symptom Scale (DOTES) at screening and following 1-week, 2-weeks, 3-weeks, and 4-weeks of dosing. The DOTES is a general rating scale published by the Early Clinical Drug Evaluation Unit of the NIMH. The scale has been widely used clinically for children and adults to assess many central nervous system (CNS) side effects as well as some behavioral side effects. We have modified the original version of the DOTES to include specific questions related to potential side effects that might be related to vasopressin such as hyponatremia/water intoxication. Vital signs (HR/BP and temperature) will be assessed pre-treatment and 20-minutes and ~2 hrs after the first vasopressin dose, as well as following 1-week, 2-weeks, 3-weeks, and 4-weeks of dosing. BMI will be assessed at screening, 1- week, 2-weeks, 3-weeks, and 4-weeks of dosing. In order to increase safety monitoring, blood and urine safety measurement will be conducted during the screening phase and after 1-week, 2-weeks, and 4-weeks of dosing. Clinical blood work will assess NA<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, BUN, and vasopressin. Additionally, osmolality (urine, blood) will be assessed. In order to determine the impact of vasopressin on heart function, ECG recordings will be obtained at screening and following the single- dose, 1-week, 2-weeks, 3- weeks and 4-weeks of treatment. Finally, based on preclinical animal studies there is some evidence to suggest that vasopressin may be involved in the expression of aggressive behavior. Although the relationship between vasopressin and aggression in humans is currently unknown, we will take every precaution to assess such behavioral changes throughout the study.

The Overt Aggression Scale (OAS) will be administered at screening and following 1- week, 2-weeks, 3-weeks, and 4-weeks of dosing. The OAS is designed to assess observable aggressive or violent behavior and has been used in children with different neuropsychiatric disorders.

Identical safety measures as outlined above will be performed during the optional 4-week open-label extension study.

**Procedures for Handling Adverse Events:** Single-dose (initial administration): If, following the initial dosing, body temperature changes more than 2°F, heart rate changes more than 20 bpm, blood pressure changes more than 20%, or any signs of adverse reactions to the drug are noted (e.g., listlessness, vomiting, seizure activity) then close monitoring will occur and the participant will be assessed by the study physician. If

indicated, participants will be immediately escorted to the Lucile Packard Children's Hospital (LPCH) Emergency Room, for treatment and their participation in the study will be terminated. The LPCH Emergency Room is within a short distance from the Stanford University Psychiatry and Behavioral Sciences building (~2 blocks), where initial dosing will occur. LPCH is a state-of-the-art hospital outfitted with the most advanced medical equipment. The hospital employs qualified staff to handle any type of medical emergency in children and adolescents.

Outpatient dosing phase: For any adverse events, families will be instructed to contact the research coordinator at 650-736-1235 during business hours, and through the Stanford page operator after hours and during weekends/holidays. (A project coordinator will be available 24/7 to respond to safety concerns.) If the adverse event is life threatening, participants will be asked to call 911 or to attend the nearest emergency room. If the adverse event is not life threatening, the study coordinator will contact the study physician who will contact the family directly and inquire about the adverse event. If the study physician judges the side effects as minor or benign, a decision will be made whether or not the participant will continue in the study. If side effects are judged as severe and might be related to vasopressin, the participants will be asked to stop the study drug immediately and will be invited to come in to the clinic within 24 hours for a direct evaluation and potential termination of their participation in the study. If the study physician feels that the adverse event requires immediate medical attention, parents will be instructed to contact 911 or go to the nearest emergency room. The study physician will also have the ability to break the blind if it is felt that doing so is in the best interest of the participants' health.

Any serious adverse events will be reported to the Data and Safety Monitoring Board (DSMB) and Stanford Institutional Review Board (IRB) within 24 hours and to the Food and Drug Administration (FDA) within seven calendar days.

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**c. Use of Deception in the Study**

No deception will be used.

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**d. Use of Audio and Video Recordings**

Audio and video recordings will be used during the ADOS and ADI-R assessments. A senior clinical psychologist will supervise diagnostic testing. Video recording will be used in order to quantify the subject's social mimicry while they view videos of people yawning and laughing. Two independent raters will study the videos to assess for mimicry behavior.

The results of these analyses can be shared for scientific purposes, shown in classrooms to students for educational purposes, can be shown in public presentations to non-scientific groups, and can be submitted for public distribution/made available by purchase on a DVD.

However, audio and video recordings will not be used for any other purpose or shown

outside of the research group unless explicit written permission is obtained from both the parents and/or children.

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**e. Alternative Procedures or Courses of Treatment**

**f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?**

Yes.

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**g. Study Endpoint(s)**

Primary outcome measure: Social Responsiveness Scale following 4- week vasopressin administration.

Secondary outcome measures: The Clinical Global Impressions scale, Repetitive Behavior Scale-Revised; Spence Children's Anxiety Scale, Pediatric Quality of Life Inventory, Vineland Adaptive Behavior Scale, 2nd Edition; and Aberrant Behavior Checklist following 4-week vasopressin administration and changes in functioning on laboratory-based assessments of social behavior and cognition (i.e., social mimicry, facial emotion recognition, eye gaze to social cues using eye-tracking technology, social memory, and social perceptual abilities including theory of mind) following single-dose and 4-week drug administration.

Secondary outcome measures also include assessment of drug tolerability following single- dose, 1-week, 2-week, 3-week, and 4-week dosing. These measures include vital signs (HR/BP and temperature), weight, clinical chemistry labs (NA+, K+, Cl-, BUN, and vasopressin), electrocardiogram, and parental report of side effects measured using the Dosage Record and Treatment Emergent Symptom Scale and the Overt Aggression Scale.

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**3. BACKGROUND**

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**a. Past Experimental and/or Clinical Findings**

Autism is a pervasive developmental disorder characterized by core deficits in social behavior and communication, and the presence of repetitive or stereotyped behaviors. Autism spectrum disorders affect an estimated 1 in 88 children in the US. Individuals with autism demonstrate diminished eye gaze, abnormal facial and emotion processing, and impaired social judgment. These deficits jeopardize the development of appropriate social skills and maintenance of social relationships.

Although several medications are approved for the treatment of autism (i.e., the atypical antipsychotics risperidone and aripiprazole), none are effective in ameliorating the characteristic social deficits. Moreover, these medications have unfavorable side effects (e.g., lethargy, weight gain). Identifying the underlying pathophysiology of the core social deficits associated with autism and developing new medications that target these impairments is clearly an important challenge. The proposed project leverages promising preclinical findings to test for the first time whether intranasal administration of the neuropeptide vasopressin enhances social functioning in children, particularly in males, with autism.

Vasopressin has enormous potential for enhancing an individual's quality of life through improved social cognition and more meaningful social relationships. The discovery of effective novel therapeutics provides an outstanding opportunity to reduce the emotional and financial burden of autism on patients, family members, and society.

**Preclinical findings:** Vasopressin and oxytocin regulate social behavior and show translational promise as pharmacotherapies to treat social impairments. The neurobiological systems critical for normative social functioning are arguably the most promising candidates by which to identify “drugable” targets to treat autism. Two such candidates are vasopressin and oxytocin. Vasopressin and oxytocin are primarily synthesized in the hypothalamus and released into the brain via distributed neural pathways and systemic circulation via the posterior pituitary.

Vasopressin and oxytocin are nearly structurally identical nonapeptides and likely evolved due to duplication of a common ancestral gene. Extensive animal research over four decades has demonstrated the importance of both vasopressin and oxytocin in social functioning. Specifically, brain vasopressin and oxytocin systems promote social behavior (e.g., partner preference formation, parenting behavior) and social cognition (e.g., learning and memory for social information) in a variety of mammalian species. In contrast, vasopressin and oxytocin peptide and receptor impairments induced by pharmacological or transgenic manipulations produce numerous social deficits in animals.

**Clinical findings:** The behavioral effects of intranasal vasopressin and oxytocin administration in neurotypical and patient populations and gaps in our knowledge. On the basis of these promising preclinical findings, multiple investigators have begun to test the potential of these neuropeptides as therapeutic agents to enhance social functioning in people. These studies have mostly focused on the prosocial effects of intranasal oxytocin on social functioning in both neurotypical individuals and individuals with various psychiatric disorders (e.g., anxiety, schizophrenia, autism). Importantly, several independent groups have recently demonstrated that single-doses of oxytocin administered to teenage and adult males with autism improve the processing and retention of social information, improve emotion recognition when viewing the eye region of faces, and increase trust and preference for social partners during a computer simulated ball-toss game.

Several groups, including our own, are now testing the effects of longer-term oxytocin administration to younger patients, inclusive of boys and girls, with autism. In contrast to oxytocin, there have been only a handful of studies that have investigated the effects of intranasal vasopressin on social functioning in humans. Notably, these studies have shown that vasopressin enhances memory for happy and angry faces], increases recognition of positively and negatively valenced social words, and enhances neural activity in known vasopressin brain circuitry during a cooperation task.

Single intranasal doses of the vasopressin analog desmopressin have also been shown to enhance speech and word formation in patients with post-stroke aphasia and improve short and long-term memory in patients with central diabetes insipidus suggesting potential cognitive enhancing properties of this hormone. In humans, intranasally administered vasopressin results in elevated cerebrospinal fluid levels of measured vasopressin, strongly suggesting that it achieves access to the brain.

Importantly, intranasally administered vasopressin and its analogs (e.g., desmopressin) are well tolerated in humans with no significant side effects reported in any of the studies outlined above. In fact, vasopressin and its analogs have been used for over 30 years in both children and adults to treat central diabetes insipidus, nocturnal enuresis, and varying states of shock with very few side effects given precautions are adhered to (e.g., water restriction to prevent hyponatremia/water intoxication). Surprisingly, despite a growing body of evidence documenting the prosocial effects of vasopressin, and the relevance of this system to autism, no studies have tested whether vasopressin administration enhances social functioning in this disorder. Given the research efforts now directed toward testing oxytocin as a treatment for the social deficits in autism, there is an obvious need to investigate the treatment potential of this closely related neuropeptide to ameliorate the social deficits in autistic individuals.

Why is a vasopressin treatment trial critically needed in patients with autism? In addition to its structural and functional similarity to oxytocin, vasopressin merits investigation as a candidate drug for use in autism for several other reasons. First, preclinical findings from transgenic and wild type animals suggest that important aspects of social cognition are mediated through vasopressin V1a receptors.

In oxytocin receptor null (*Oxtr*<sup>-/-</sup>) mice, central administration of either oxytocin or vasopressin directly in to the brain improves sociability deficits, enhances exploration of social novelty, and reverses cognitive flexibility deficits. Interestingly, pre-treatment with a selective V1a receptor antagonist prior to central oxytocin administration almost completely attenuates the prosocial and cognitive enhancing effects of oxytocin, indicating that V1a receptors mediate this effect. Experiments using wild-type mice, rats, and voles likewise show that administration of selective V1a antagonists in the presence of normal brain oxytocin signaling impairs social functioning.

These findings are particularly evident in males, in which vasopressin has been shown to selectively regulate social functioning. In fact, an intriguing and important aspect of vasopressin and oxytocin physiology is that these neuropeptides exert largely sexually dimorphic behavioral effects as determined by a series of influential pharmacological and autoradiographical studies. These studies have shown that whereas oxytocin preferentially regulates pair bond formation, reproductive physiology (e.g., parturition and lactation), and parental care in females, vasopressin preferentially regulates mating behavior, pair bond formation, and parental care in male. Second, recent genetic association studies suggest that several single nucleotide polymorphisms and their haplotypes in the oxytocin receptor gene increase risk for autism. Genome-wide scans likewise indicate that the 3p25 region, which contains the oxytocin receptor gene, may be a linkage site for autism.

These findings suggest the intriguing supplementary hypothesis that in patients with oxytocin receptor impairments, vasopressin treatment may be even more efficacious than oxytocin administration, because although both vasopressin and oxytocin ligands show high affinity for all four receptors (i.e., vasopressin: V1a, V1b, V2; and oxytocin: OTR, respectively), they bind with greatest affinity to their own receptor(s). This hypothesis is further supported by evidence that *Oxtr*<sup>-/-</sup> mice have higher vasopressin V1a receptor expression in the brain than do wild-type mice suggesting that these animals may be more sensitive to vasopressin administration than oxytocin. These findings clearly highlight the need for careful studies that clarify the underlying neurobiological

actions of these neuropeptides as pharmacotherapeutic agents in patients with autism. To address this larger research question we must first test whether intranasal vasopressin administration improves social functioning in individuals with autism, and whether this medication is more efficacious in males compared to females. Factors that contribute to treatment response efficacy.

In addition to gender differences in treatment response, most vasopressin and oxytocin pharmacology studies have found treatment responders and non-responders. For example, previous preclinical research conducted by our group, and led by Dr. Karen Parker, has shown that baseline social phenotype profoundly influences the efficacy of vasopressin treatment to induce or enhance pro-social behaviors in male rodents. Similarly, a single- dose oxytocin treatment study in male adults with autism provides preliminary evidence for enhanced social functioning post- treatment in a subgroup of patients who show higher social motivation at baseline. Another recent study using transcutaneous electrical acupoint stimulation therapy showed enhanced social functioning post-treatment, which was associated with higher plasma vasopressin levels in children with autism. Interestingly, treatment benefits and higher vasopressin levels were most pronounced in children with “passive” and “aloof”, but not “active but odd” behavioral phenotypes as assessed by the WSQ at baseline. These findings suggest that individual differences in pre-treatment social impairments may contribute to treatment response efficacy and that these changes are associated with increased plasma neuropeptide levels. This intriguing hypothesis will be explored in the present study as outlined below.

Vasopressin is one of the most promising candidate drugs to treat the presently intractable social deficits of autism. This project will be the first to test whether intranasal vasopressin administration enhances social functioning in individuals with autism. Inclusion of female participants is a major strength of this study as female exclusion, which frequently occurs in autism treatment studies, may jeopardize optimal testing of effective pharmacotherapies, and preclude identification of disease mechanisms. Our inclusion of females is particularly important because preclinical evidence suggests that males may respond more robustly to vasopressin treatment than females. Additionally, findings from both preclinical and clinical studies have shown that differences in pre-treatment social functioning and/or neuropeptide biology are associated with vasopressin and oxytocin treatment response outcomes. Ours will be the first study to test concomitantly whether pre-treatment social measurements and baseline neuropeptide levels contribute to individual differences in vasopressin treatment response efficacy.

**b. Findings from Past Animal Experiments**

See Section 3.a.

**4. RADIOISOTOPES OR RADIATION MACHINES**

**a. Standard of Care (SOC) Procedures**

Identify Week/Month of Study	Name of Exam	Identify if SOC or Research
N/A	N/A	N/A

**b. Radioisotopes**

- i. Radionuclide(s) and chemical form(s)  
N/A
- ii. Total number of times the radioisotope and activity will be administered (mCi) and the route of administration for a typical study participant  
N/A
- iii. If not FDA approved: dosimetry information and source documents (package insert, Medical Internal Radiation Dose [MIRD] calculation, and peer reviewed literature)  
N/A

**c. Radiation Machines – Diagnostic Procedures**

- i. Examination description (well-established procedures)  
N/A
- ii. Total number of times each procedure will be performed (typical study participant)  
N/A
- iii. Setup and techniques to support dose modeling  
N/A
- iv. FDA status of the machine and information on dose modeling (if procedure is not well-established)  
N/A

**d. Radiation Machines – Therapeutic Procedures**

- i. Area treated, dose per fraction/number of fractions, performed as part of normal clinical management or due to research participation (well-established procedures)  
N/A
- ii. FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions (if procedure is not well-established)  
N/A

**5. DEVICES USED IN THE STUDY**

**a. Investigational Devices (Including Commercial Devices Used Off-Label)**

Investigational Device	
Name:	N/A
Description:	N/A
Significant Risk? (Y/N)	N/A
Rationale for Non-Significant Risk	N/A

**b. IDE-Exempt Devices**

<b>IND-Exempt Device</b>	
Name:	N/A
Description:	N/A

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## 6. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

### a. Investigational Drugs, Biologics, Reagents, or Chemicals

<b>Investigational Product</b>	
Name:	Vasopressin
Dosage:	Subjects aged 6 to 9.5 years of age will receive the maximum dose of 24 IU (12 IU bid). Subjects aged 9.6 to 12 years of age will receive the maximum dose of 32 IU (16 IU bid).
Administration Route:	Intranasal

### b. Commercial Drugs, Biologics, Reagents, or Chemicals

<b>Commercial Product</b>	
Name:	N/A
Dosage:	N/A
Administration Route	N/A
New and different use? (Y/N)	N/A

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## 7. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

N/A

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## 8. PARTICIPANT POPULATION

### a. Planned Enrollment

Fifty children with autism spectrum disorders between the ages of 6 and 12 years (maximum 12 years and 11 months) will be recruited to participate in this study at Stanford. All participants will be enrolled at Stanford. We plan to enroll and screen up to 100 participants to meet our target of 50 randomized subjects.

### b. Age, Gender, and Ethnic Background

Males and females from all racial and ethnic backgrounds will be eligible to participate in this study.

### c. Vulnerable Populations

We are recruiting up to 100 potentially decisionally impaired children (ages 6 to 12 years) with an autism spectrum disorder. This study is specifically directed at children with autism in order to test the tolerability and effectiveness of vasopressin in this population

### d. Rationale for Exclusion of Certain Populations

N/A

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**e. Stanford Populations**

N/A

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**f. Healthy Volunteers**

N/A

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**g. Recruitment Details**

Potential participants will be identified from the Autism and Developmental Disorders Clinic at Stanford and current research registry participants. Flyers will be posted. Additionally, subjects may be recruited via the Interactive Autism Network (IAN). The IAN Project will inform families about our study in two distinct ways: via e-mail (for IAN Research families meeting our study criteria) and via the IAN Community Research Opportunities Bulletin Board (for the public at large). If the subject is interested in participating they will call the research staff and the research staff will explain the study using the advertisement phone script. If the participant is still interested in participating then the research staff will obtain their informed consent as outlined above.

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**h. Eligibility Criteria**

i. Inclusion Criteria

All participants will meet the following: a) medically healthy outpatients between 6 and 12 years of age (cut off: 12 years and 11 months); b)  $IQ \geq 50$  (Stanford-Binet); c) SRS Total Score  $\geq 70$ ; d) ability to complete laboratory and cognitive testing; e) diagnosis of ASD based on expert clinical opinion and confirmed on the Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), and DSM-IV-TR criteria; f) Clinical Global Impression (CGI) severity rating of 4 or higher; g) care provider who can reliably bring participant to clinic visits, provide trustworthy ratings, and interact with the participant on a regular basis; h) stable medications for at least 4 weeks; i) no planned changes in psychosocial interventions during the trial; no concurrent participation in any other clinical research trials; and, j) willingness to provide blood samples and undergo electrocardiogram.

ii. Exclusion Criteria

Participants will be excluded if one or more of the following is met: a) DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or Psychotic disorder; b) regular nasal obstruction or nosebleeds; c) active and unstable medical problems (e.g., migraine; asthma; seizure disorder; anaphylaxis; epilepsy; diabetes serious liver, renal, or cardiac pathology); d) clinically significant abnormal vital signs or ECG reading; e) evidence of a genetic mutation know to cause Autism (e.g., Fragile X Syndrome) or metabolic disorder; f) significant hearing or vision impairments; g) drinks large volumes of water (e.g., habitual or psychogenic polydipsia); h) pregnant or sexually active females not using a reliable method of contraception (urine pregnancy test will be conducted); i)

history of hypersensitivity to vasopressin, its analogs (e.g., Desmopressin), or compounding preservatives (e.g., chlorobutanol); j) current use of any medications known to interact with vasopressin including: 1) carbamazepine (i.e., Tegretol); chlorpropamide; clofibrate; urea; fludrocortisone; tricyclic antidepressants (all of which may potentiate the antidiuretic effect of vasopressin when used concurrently); 2) demeclocycline; norepinephrine; lithium; heparin; alcohol (all of which may decrease the antidiuretic effect of vasopressin when used concurrently); 3) ganglionic blocking agents including benzohexonium, chlorisondamine, pentamine (all of which may produce a marked increase in sensitivity to the pressor effects of vasopressin); k) prior or current use of AVP; and l) abnormal chemistry result.

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**i. Screening Procedures**

Consents will be obtained before any screening procedures can begin. A review of the medical and psychiatric history of participants will take place during the screening procedures to determine eligibility to the study. Clinically significant abnormal vital signs, ECG readings, and clinical chemistry labs will be determined according to Lucile Packard Children's Hospital (LPCH) standards and expert opinion from trained physicians.

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**j. Participation in Multiple Protocols**

Participants will not be allowed to be enrolled in any other medication or behavioral trials during their participation in the current research study.

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**k. Payments to Participants**

The subjects will be paid \$20 for each fully completed study visit.

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**l. Costs to Participants**

There will be no costs charged to the participants.

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**m. Planned Duration of the Study**

The entire study will take up to four years to complete and will be followed by a period of six months of data analysis. One patient could be in the study for a maximum of 12 weeks including the initial screening period, the 4-week double-blind treatment trial and the optional 4-week open-label extension study.

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**9. RISKS**

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**a. Potential Risks**

- i. Investigational devices  
N/A
- ii. Investigational drugs  
N/A

iii. Commercially available drugs, biologics, reagents or chemicals

Vasopressin side effects: There is presently no readily available list of side effects based on a common-rare continuum for vasopressin. There are several routes of administration for vasopressin: intramuscular (IM), subcutaneous (SC), intravenous (IV), and intranasal (IN). In the present study, the IN administration route will be used. There are limited side effects associated with the IN route of administration for vasopressin. However, as discussed below, there are a number of potential side effects observed when vasopressin is administered by injection (i.e., IM, SC, IV). It is crucial to differentiate between the side effects specifically associated with different routes of administration.

Intranasal administration: Information regarding the safety profile of IN vasopressin administration comes mostly from several clinical trials examining the effectiveness of vasopressin for enhancing neurocognitive functioning. Additionally, although the typical administration route for treatment of central diabetes insipidus (CDI) is some form of vasopressin injection, there are patients (including children) who have primarily used a nasal route of administration to treat their disease, or use a vasopressin nasal spray as an adjunct to vasopressin injections. Importantly, a large number of studies have provided convincing evidence for IN vasopressin being very well tolerated. As mentioned, the majority of these studies have aimed to investigate the impact of IN vasopressin on neurocognitive processes.

Given the relatively large size of vasopressin (>1 kD), injections of this polypeptide are not considered to reach the brain in significant quantities due to the restrictions of the blood-brain barrier (BBB). Nasal routes of administration are purported to overcome the restrictions of the BBB for large molecule peptides, including vasopressin, making it a preferred administration route for targeted CNS treatment. Born et al. provided convincing evidence of this by showing that IN vasopressin (40 and 80 IU) administered to healthy adult males and females significantly increased CSF concentrations of the peptide compared to placebo administration; vasopressin levels had not returned to baseline at the end of the 80-minute sampling period. Blood concentrations of vasopressin also increased but were only slightly (non-significantly) correlated with CSF levels. The nasal route of administration is generally considered much safer than injections of vasopressin for multiple reasons; not only is the risk of local infection or transfer of contagious blood borne disease substantially reduced, there appear to be far fewer peripheral effects noted with IN administration of vasopressin. For example, several recent studies have outlined the ability of IN vasopressin (20 and 40 IU) to enhance complex psychosocial functioning and associated brain activity when given in single-doses to healthy adults. Only minor and transient side effects (relaxation/tiredness, increased happiness, headache, dizziness, bitter taste, nasal irritation, increased diastolic blood pressure) were reported by a small number of participants and were experienced following both administration of vasopressin and placebo.

Chronic dosing with IN vasopressin, as proposed in the current study, has also been shown in several studies to be very well tolerated. In a study of 26 elderly individuals utilizing a double-blind, randomized, placebo-controlled, 10-week trial of IN vasopressin administration (20 IU, bid) for treatment of sleep disturbances, no major side effects were

reported across multiple safety measures. A self-rating scale of complaints did not reveal any side effects of the IN vasopressin treatment. Cardiovascular monitoring revealed a systolic blood pressure that was slightly elevated 60 minutes after vasopressin administration, but not 8-12 hours later. Measurements of diastolic blood pressure and heart rate did not indicate any treatment effects. Examination of blood pressure and heart rate on a weekly basis during the 10-week study period revealed values in the normal range and no treatment related differences. At the end of the trial, measurement of sodium, osmolality, and hematocrit did not reveal any treatment effects, and values were entirely within the normal range. Taken together, the studies outlined above suggest that IN vasopressin administration at the doses proposed here is very well tolerated. Below is a list of side effects reported from a small number of participants following IN vasopressin (and placebo) treatment.

Reported side effects following IN vasopressin (and placebo) administration (NB: These side effects were all minor and transient):

- Relaxation or tiredness
- Headache
- Dizziness
- Increased happiness
- Increased systolic blood pressure
- Increased diastolic blood pressure
- Bitter taste
- Nasal irritation

Vasopressin administered by injection: Ten IU of vasopressin (0.5 mL) given IM will usually elicit full physiologic response in adult patients. The manufacturer recommends that in the average postoperative adult an initial 5 IU dose, increased to 10 IU if necessary, should be given IM every three- or four-hours for treating abdominal distention. In preparation for roentgenography, the average patient will require two IM injections of 10 IU given two hours and one half-hour, respectively, before films are exposed. For treating CDI, vasopressin may be administered SC or IN. The dose of injection is 5 to 10 IU repeated two or three times daily as needed. When vasopressin is administered IN for treating CDI the dosage and interval should be adjusted for each patient.

Many of the side effects listed by the manufacturer are associated with injections of vasopressin and result from its vasoconstrictive properties mediated by vasopressin V1 receptors. These include cardiac arrest and/or shock, circumoral pallor, arrhythmias, decreased cardiac output, angina, myocardial ischemia, and peripheral vasoconstriction. Gastrointestinal side effects may include abdominal cramps, diarrhea, intestinal hyperactivity, nausea and vomiting. Bronchial constriction, tremor, vertigo and “pounding” in the head have also been reported. Skin changes may also occur following vasopressin injection and include sweating, urticarial (rash), and cutaneous gangrene. Additionally, some individuals may have a severe hypersensitivity to vasopressin or its excipients (e.g., chlorobutanol as preservative). In recent years, there has been an increase in the use of IV vasopressin treatment for hemodynamically unstable infants and children following cardiothoracic surgery. This treatment has been associated with reports of water intoxication/hyponatremia associated with prolonged IV vasopressin.

Careful monitoring of cardiovascular parameters and serum sodium values is important when vasopressin is given to intensive care patients or to those with underlying cardiovascular pathology or a known sensitivity to the drug or its excipients. For outpatients, drinking a glass of water when taking vasopressin is reported to reduce some of the skin and gastrointestinal effects. However, close monitoring of fluid intake and output should also be considered during vasopressin treatment, and less free water should be given, in cases where hyponatremia may be a concern. Importantly, several studies have shown that regulation of fluids and close monitoring of electrolyte balance substantially reduces the risk of hyponatremia in children being treated with IV vasopressin.

Reported side effects following injections (IM, SC, IV) of vasopressin:

- Abdominal cramps
- Diarrhea
- Intestinal hyperactivity
- Nausea
- Vomiting
- Passage of gas
- Blanching of skin
- Sweating
- Tremor
- Vertigo
- “Pounding” in head
- Bronchial constriction
- Urticarial
- Circumoral pallor
- Cutaneous gangrene
- Anaphylaxis (cardiac arrest and/or shock)
- Arrhythmias
- Decreased cardiac output
- Angina
- Myocardial ischemia
- Peripheral vasoconstriction
- Gangrene
- Hyponatremia/water intoxication (possibly resulting in seizure or coma)

FDA indications for vasopressin administration: The formulation of vasopressin to be used in the proposed research is Vasopressin Injection, USP (American Regent, Shirley NY). This drug does not currently have FDA marketing approval for any indication. This study is a Phase II clinical trial that aims to investigate both the effectiveness and tolerability of IN vasopressin treatment for social, cognitive, and behavioral problems in children with autism. Although the FDA has not provided marketing approval for this formulation, the manufacturer recommends its use for the prevention and treatment of postoperative abdominal distention, CDI, and for abdominal roentgenography to dispel interfering gas shadows. Several other US research groups have received FDA approval to investigate the effects of IN vasopressin administration for enhancing neurocognitive functioning in both healthy adults and patients with autism (e.g., see NCT01327027,

NCT01566539, NCT01680718, NCT01093768).

Contraindications and precautions for vasopressin administration: The safety concerns listed in the section above for vasopressin injections are considered rare if precautions are adhered to. The package insert for Vasopressin Injection, USP lists several precautions and contraindications associated with this drug. Contraindications for the use of vasopressin include anaphylaxis or hypersensitivity to the drug or its components (e.g., chlorobutanol as preservative). It is recommended that this drug not be used in patients with vascular disease, especially disease of the coronary arteries, except with extreme caution. In such patients, even small doses may precipitate angina pain, and with larger doses, the possibility of myocardial infarction should be considered. Vasopressin may also produce hyponatremia/water intoxication and is contraindicated in patients who habitually drink large volumes of water (e.g., habitual or psychogenic polydipsia). For this reason, the early signs of drowsiness, listlessness, and headaches should be recognized to prevent terminal coma and convulsions. Vasopressin should also be used with caution in the presence of epilepsy, migraine, asthma, heart failure, or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system. These contraindications are reflected in the extensive exclusion criteria and safety monitoring used in this study. Several studies utilizing vasopressin treatment in children provide convincing evidence for vasopressin being well tolerated if fluid intake is monitored closely during the treatment period.

An additional concern that has been raised with the use of vasopressin is the potential for increased aggression. These concerns are based on specific preclinical animal studies; however, to the investigators' knowledge there is no evidence that vasopressin increases aggressive behavior when administered to humans. Research on vasopressin and aggression in rodents has generally shown that vasopressin increases aggression in: 1) non-monogamous adult male residents when an adult male intruder is introduced into his "territory" (i.e., home cage), and 2) monogamous adult male residents when an adult male intruder is introduced into his territory, which sometimes includes the mate and pups. It is arguable that increased aggression in these behavioral assays is adaptive, and in the context of the latter example, increased aggression in the presence of mate/pups in the home territory is a protective response that is prosocial in nature, at least with regard to the resident male's family. Nevertheless, we acknowledge that monitoring aggression in children in our pilot treatment trial is an important precaution. Therefore, we will regularly inquire about aggressive behavior throughout the study.

It is important to point out that there is presently no reliable data that outlines developmental risks of vasopressin administration in children. The main purpose of our study is to determine the safety and efficacy of intranasal vasopressin administration in children with autism. Thus, we will report any serious adverse events to the IRB and FDA according to law and will detail this information in published articles and presentations.

#### iv. Procedures

Brief description of overall plan for the study: We will test the effects of single-dose and 4-week intranasal vasopressin administration or placebo on social abilities in 50 high

functioning male and female participants with autism aged 6 to 12 years. We will use a double-blind, randomized, placebo controlled, parallel design with dose-escalation to determine both the tolerability and effectiveness of vasopressin treatment for cognitive and behavioral problems associated with autism. We plan to enroll and screen up to 100 participants to meet our target of 50 randomized subjects.

Before the start of the 4-week dosing period, subjects will be given a 1-week open-label placebo lead-in to allow for enhanced compliance and efficacy for nasal drug administration.

Subjects aged 6 to 9.5 years of age will receive the maximum dose of 24 IU (12 IU bid). Subjects aged 9.6 to 12 years of age will receive the maximum dose of 32 IU (16 IU bid). The dose escalation regimen of vasopressin for subjects aged 6 to 9.5 years is as follows: Single dose administration: 12 IU; Week 1: 4 IU twice daily; Week 2: 8 IU twice daily; Week 3: 12 IU twice daily; and, Week 4: 12 IU twice daily. The dose escalation of vasopressin for subjects aged 9.6 to 12 years is as follows: Single dose administration: 16 IU; Week 1: 4 IU twice daily; Week 2: 8 IU twice daily; Week 3: 16 IU twice daily; and, Week 4: 16 IU twice daily.

Participants will meet DSM-IV criteria for autism spectrum disorder, confirmed with gold standard research diagnostic methods. A comprehensive behavioral characterization will be obtained prior to drug administration. The primary outcome measure for this study is change in social behavior as determined by parent ratings on the Social Responsiveness Scale (SRS) after completion of 4-week vasopressin administration.

Secondary outcome measures include changes on other behavioral functioning as measured by the clinician rated Clinical Global Impressions (CGI) and the parent ratings on the Repetitive Behavior Scale-Revised (RBS-R), the Spence Children's Anxiety Scale (SCAS), and the Pediatric Quality of Life Inventory (PedsQL), Vineland Adaptive Behavior Scale, 2nd Edition (VABS-2) social subscale, and the Aberrant Behavior Checklist (ABC), Multidimensional Social Competence Scale (MSCS) following 4-week vasopressin administration and changes in functioning on laboratory-based assessments of social behavior and cognition (i.e., social mimicry, facial emotion recognition, eye gaze to social cues using eye-tracking technology, social memory, and social perceptual abilities including theory of mind) following single-dose and 4-week drug administration. Secondary outcome measures also include assessment of drug tolerability following single-dose, 1-week, 2-week, 3-week, and 4-week dosing. These measures include vital signs (HR/BP and temperature), body-mass index (BMI), clinical chemistry labs (NA<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, BUN, vasopressin), osmolality (urine, blood), electrocardiogram (ECG), and parental report of side effects measured using the Dosage Record and Treatment Emergent Symptom Scale (DOTES) and the Overt Aggression Scale (OAS).

Parent ratings on the SRS and the Wing Subgroups Questionnaire (WSQ), as well as participant blood samples for neuropeptide quantification, will be collected pre-treatment. Pre-treatment scores on the SRS and plasma neuropeptide (vasopressin and oxytocin) levels

will be used on an exploratory basis to predict treatment response outcomes.

After completion of the double-blind 4-week treatment period participants will be informed of their treatment group and subjects randomized to placebo will have the option of participating in a 4-week open-label vasopressin treatment extension period.

Participants initially randomized to placebo treatment during the randomized controlled trial will undergo vasopressin dose- escalation and safety testing in the open-label extension period in a comparative fashion to participants initially randomized to vasopressin treatment. Participants who were initially assigned to vasopressin treatment during the randomized controlled trial will end the study. During this time participants will again undergo all previously performed safety assessments. This will provide further information regarding the tolerability of longer term vasopressin treatment (i.e., up to 8 weeks). During the open-label extension period we will conduct pharmacokinetic (PK) analysis to determine the Tmax of vasopressin in our study population. The timing of the blood draws during the open-label extension arm will take place at 15 minutes post-vasopressin dosing for 1/3 of the participants, at 30 minutes post-vasopressin dosing for 1/3 of the participants, and at 60 minutes post-vasopressin dosing for 1/3 of the participants. These analyses will take place at week-5, week-6, and week-8 for all participants.

Specific aims and hypotheses:

To test our overarching hypothesis, we will pursue the following aims:

Specific Aim 1. Test the effects of single-dose vasopressin administration on laboratory-based social behavior and cognitive measures in children with autism.

Predictions: Following single-dose vasopressin administration, participants will exhibit increased accuracy in recognizing facial emotions, increased eye gaze to social cues, enhanced memory for faces and names, increased social mimicry, and enhanced social perceptual abilities on theory of mind tasks compared to their pre-treatment performance and to the performance of placebo-treated participants.

Specific Aim 2. Test the effects of 4-week vasopressin administration using parent ratings of psychosocial and behavioral functioning and laboratory-based social behavior and cognition measures in children with autism. Predictions: Following 4-week vasopressin administration, participants will exhibit improvements in social and behavioral functioning as assessed by parent ratings on the SRS, VABS-2, ABC, RBS-R, SCAS, and PedsQL and clinician ratings on the CGI compared to their performance pre-treatment and as well as compared to the performance of placebo-treated participants. Following 4-week vasopressin administration, participants will also show improvements on all aforementioned laboratory-based measures of social functioning compared to their performance after single-dose vasopressin administration and compared to the performance of placebo-treated participants.

Specific Aim 3. Test the tolerability of single-dose and 4-week intranasal vasopressin in children with autism. Predictions: No significant differences in rates of side effects will be observed between vasopressin and placebo treated groups following single-dose and 4-week treatment.

Exploratory Aim 4. Test whether single-dose and/or 4-week vasopressin

administration preferentially enhances social functioning in male compared to female children with autism. Predictions: Vasopressin treatment will be more effective in male compared to female participants consistent with evidence from preclinical studies.

Exploratory Aim 5. Test whether pre-treatment social functioning (i.e., severity of social impairments as measured by pre-treatment parent SRS ratings and WSQ social subtype) and/or plasma neuropeptide levels predict vasopressin treatment response efficacy in children with autism.

Methods and procedures: Experimental design. Using a double-blind, randomized, placebo controlled, parallel design we will test the effects of single-dose and 4-week intranasal vasopressin administration on social functioning in children with autism.

Consent/assent will be obtained before initiating any study procedures. The primary outcome measure is change in social behavior as determined by parent ratings on the SRS after completion of the 4-week treatment trial. The SRS measures the severity of social/communication deficits as they occur in natural environments. The SRS can be used as a measure of response to intervention as well as a screening instrument. Secondary outcome measures include changes in other behavioral functioning (e.g., communication, repetitive/disruptive behaviors, anxiety, quality of life) as measured by clinician ratings on the CGI and as measured by parent ratings on the RBS-R, SCAS, PedsQL, VABS-2, ABC, and MSCS after completion of the 4-week treatment trial. Secondary outcome measures also consist of laboratory-based assessments of social behavior and cognition (described below) after both single-dose and 4-week vasopressin treatment. Drug tolerability assessments, including vital signs (HR/BP and temperature), ECG, and parent report of side effects will be conducted following single-dose, 1-week, 2-weeks, 3-weeks, and 4-weeks of drug administration. BMI will be assessed after 1-week, 2-weeks, 3-weeks and 4-weeks of dosing. Clinical chemistry labs and osmolality (urine, blood) will be obtained after 1-week, 2-weeks, and 4-weeks of dosing. In cases when a blood draw cannot be obtained the urine osmolality (which is highly correlated with blood osmolality) will be able to be used as a safety measure. A similar schedule will be followed in the optional 4-week open-label extension study.

There will be a total of up to 10 assessment time-points during this study. During the first assessment session (screening visit) participants will undergo autism diagnostic screening, intelligence testing, medical (history and physical) and psychiatric (history) examination (incl. CGI ratings), females of childbearing age or who have started having menstrual cycles will undergo urine pregnancy testing; vital signs screening, height and weight measurement, ECG assessment, and clinical chemistry labs will be assessed.

Participants will undergo pre-treatment assessment of behavioral and cognitive functioning in order to determine baseline levels on the various outcome measures. Parent ratings on the SRS, RBS-R, SCAS, PedsQL, VABS-2, ABC, MSCS, WSQ as well as participants' blood samples for quantification of basal plasma vasopressin and oxytocin concentrations will be obtained.

Laboratory measures of social behavior and cognition will be administered to facilitate in

the analysis of post-treatment changes in functioning by accounting for any pre-existing individual differences. Briefly, these laboratory tasks involve assessing the ability of the participants to recognize basic emotions from images of faces presented on a computer screen. We will also record participants' eye gaze using eye-tracking technology while the participants view the emotional faces. We will determine participants' ability to infer emotions after viewing the eye-region of facial stimuli. We will also assess participants' memory for faces and names, and social perception abilities will be assessed using tests of theory of mind.

On completion of the screening procedures, subjects and their parents will be instructed on administration of a placebo nasal spray and will be provided with a supply of the placebo to administer at home. This one week open-label placebo lead-in component will enhance compliance and efficacy of nasal drug delivery during the study.

One to four weeks later, participants will return to the clinic and will be randomized in a double-blind fashion to a treatment condition (vasopressin or placebo). Stratification will be based on gender and age. Prior to drug administration, pre-treatment side effects information will be collected with the DOTES and OAS, participants will provide a blood sample for neuropeptide quantification and parent SRS ratings will be collected for a second time. Neuropeptide levels from the two blood samples and repeated parent assessment of the severity of participants' social impairments will allow us to test for stable individual differences in these measures. Parent SRS and WSQ ratings, as well as participants' neuropeptide levels, will allow us to test on an exploratory basis whether these baseline measures predict treatment response outcomes. Participants will then receive a single-dose of either intranasal vasopressin (12 IU or 16 IU; depending on age) or placebo and 20 minutes later will have vital signs (HR/BP and temperature) assessed prior to initiating the laboratory behavioral measures. Before participants leave the clinic they will again have their vital signs assessed (~2 hours post-dosing) and an ECG will be performed to determine cardiac functioning. Parents will be provided with instructions on the dose-escalation schedule that will occur at home and will be provided with a dosing schedule that they will be required to follow and sign off on each day. Participants will continue vasopressin or placebo administration for 4-weeks at home and their parents will be responsible for reporting any adverse events to research staff. Parents will also be informed that their children's free water intake should be adjusted downward to decrease the potential occurrence of hyponatremia and water intoxication during the treatment period.

Following 1-week, 2-weeks, and 3-weeks of dosing, participants are asked to return to the clinic for visits when drug tolerability will be assessed (vital signs, BMI, clinical chemistry labs (not at week-3), ECG, and parental side effects reports will be collected. On completion of the 4-week double-blind treatment period, participants will return to the clinic for assessments.

Parent SRS, RBS-R, SCAS, PedsQL, VABS-2, ABC, and MSCS ratings and participants blood samples will be collected for neuropeptide analysis.

Participants will be tested on laboratory based social behavior and cognition tests, and clinician's impressions of treatment response will be made using the CGI. Vital signs, BMI, clinical chemistry labs, osmolality (urine, blood), ECG, and parental drug side effects

report will also be monitored to determine drug tolerability.

After completion of the double-blind 4-week treatment period participants will be informed of their treatment group and will have the option of participating in a 4-week open-label vasopressin treatment extension period. Participants initially randomized to placebo treatment during the randomized controlled trial will undergo vasopressin dose-escalation and safety testing in the open-label extension period in a comparative fashion to participants initially randomized to vasopressin treatment. Participants who were initially assigned to vasopressin treatment during the randomized controlled trial will have the option of continuing on their maximum tolerated dose for an additional 4-week open-label extension period. During this time participants will again undergo all previously performed safety assessments. This will provide further information regarding the tolerability of longer term vasopressin treatment (i.e., up to 8 weeks). During the open-label extension period we will conduct PK analysis to determine the Tmax of vasopressin in our study population. The timing of the blood draws during the open-label extension arm will take place at 15 minutes post-vasopressin dosing for 1/3 of the participants, at 30 minutes post-vasopressin dosing for 1/3 of the participants, and at 60 minutes post-vasopressin dosing for 1/3 of the participants.

These analyses will take place at week-5, week-6, and week-8 for all participants. Up to 30 mL of blood will be collected during the blood draws mentioned above. At all of the timepoints that blood draws are mentioned above there will also be urine samples collected for urine osmolality.

Urine and blood osmolality sample collection at Screening and Weeks 1, 2, 4, 5, 6, and 8 will be obtained. This will allow for a contingency plan in cases when blood samples are not able to be obtained at any given collection time-point since urine osmolality is highly correlated with plasma osmolality.

On completion of the 4-week open-label treatment period, participants will return to the clinic for assessments including the parent SRS, VABS-2, ABC, RBS-R, SCAS, MSCS and PedsQL ratings. Participants will be tested on laboratory based social behavior and cognition tests, and clinician's impressions of treatment response will be made using the CGI.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

Vasopressin and its analogs have been used for over 30 years in both pediatric and adult patient groups to treat central diabetes insipidus, nocturnal enuresis, and varying states of shock with very few serious adverse effects given simple precautions are adhered to (e.g., water restriction to prevent hyponatremia and water intoxication). See above for a comprehensive discussion of potential risks associated with vasopressin administration. Obtaining blood can cause bruising and can hurt briefly which applying a topical anesthetic can minimize.

vii. Psychological well-being

There are minimal risks to individuals from interviewing, testing measures, and blood draws other than loss of time at school and parental work. The risks associated with the testing measures are minimal and are limited to performance anxiety or fatigue. There will be an attempt to schedule appointments for assessments at times that minimize loss of time from the child's school schedule and caregiver's work. Parents may experience some discomfort in responding to questions asked during the initial interview or to items on the various measures. Blood collection can also cause stress and anxiety for some individuals. Blood collection will occur at the Lucile Packard Children's Hospital (LPCH) Phlebotomy Clinic by trained pediatric phlebotomists, who have extensive experience working with children on the autism spectrum.

Research on vasopressin and aggression in rodents has generally shown that vasopressin increases aggression in: 1) non-monogamous adult male residents when an adult male intruder is introduced into his "territory" (i.e., home cage), and 2) monogamous adult male residents when an adult male intruder is introduced into his territory, which sometimes includes the mate and pups.<sup>1,2</sup> It is arguable that increased aggression in these behavioral assays is adaptive, and in the context of the latter example, increased aggression in the presence of mate/pups in the home territory is a protective response that is prosocial in nature, at least with regard to the resident male's family. Nevertheless, we acknowledge that monitoring aggression in children in our pilot treatment trial is an important precaution. Therefore, we will regularly inquire about aggressive behavior throughout the study.

viii. Economic well-being

Low to almost no risk.

ix. Social well-being

Low to almost no risk.

x. Overall evaluation of risk

Low risk.

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**b. International Research Risk Procedures**

N/A

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**c. Procedures to Minimize Risk**

Every precaution will be taken to use the safest and most gentle procedures possible.

Cognitive and behavioral assessments and paper-and-pencil tests: The risk of the cognitive and behavioral tests are minimal and are limited to performance anxiety or fatigue. To minimize these problems, testing will not begin until the participant is comfortable with the testing environment and the tester. Staff with experience working with children with disabilities will administer the tests, provide breaks as needed, and adjust the length of the test sessions to each individual. Participants will be provided with frequent positive feedback and will receive certificates in recognition of their participation. Each examiner will be attentive to participant fatigue and provide breaks

accordingly. Parents/legal guardians may experience discomfort in revealing personal information regarding psychiatric and medical status; hence, we will provide support and assure that personal information is kept in a locked cabinet with no personal identifiers on the forms except for a participant ID number.

Scheduling during school/caregiver work: There will be an attempt to schedule appointments for research assessments at times that minimize absence of the child from school and the caregiver from work.

Blood draws: Obtaining blood can hurt briefly and can cause bruising; this will be minimized by applying a topical anesthetic and by having experienced staff draw children's blood samples. All Lucile Packard Children's Hospital laboratory staff have considerable experience working with children. The phlebotomists are trained to work with youth of a wide age range and different neuropsychiatric disorders, including autism.

AVP-side effects: As discussed above, the use of IN AVP in several research studies has been associated with limited side effects. However, in light of the young age of participants, the lack of experience with IN AVP in individuals with autism, and the theoretical pharmacological effects, a series of protective measures will be applied to minimize risk, and increase monitoring. Briefly (see above for full list):

1. Vital signs (HR/BP, temperature) monitoring will be conducted before and after (20 minutes, 2 hours) initial single dose AVP administration, and following 1, 2, 3 and 4 weeks of dosing.
2. BMI will be measured at screening, and following 1-week, 2-weeks, 3-weeks and 4 weeks of dosing.
3. DOTES side effects report and OAS will be collected prior to initiation of dosing and on completion of 1, 2, 3 and 4 weeks of dosing.
4. ECG monitoring will be conducted at screening and after completion of single-dose, 1, 2, 3 and 4 weeks of dosing.
5. Clinical chemistry labs will be conducted at screening and following 1-week, 2-weeks, and 4-weeks of dosing.
6. A study investigator will be available 24 hours a day to respond to adverse events.
7. Participants and their families will be briefed on procedures for responding to potential adverse events (see Procedures for Handling Adverse Events section below).

All safety procedures will be repeated during the optional open-label extension period.

Procedures for Handling Adverse Events:

Single-dose (initial administration): If, following the initial dosing, body temperature changes more than 2°F, heart rate changes more than 20 bpm, blood pressure changes more than 20%, or any signs of adverse reactions to the drug are noted (e.g., listlessness, vomiting, seizure activity) then close monitoring will occur and the participant will be assessed by the study physician. If indicated, participants will be immediately escorted to the Lucile Packard Children's Hospital (LPCH) Emergency Room, for treatment and their participation in the study will be terminated. The LPCH Emergency Room is within a short distance from the Stanford University Psychiatry and Behavioral Sciences

building (~2 blocks), where initial dosing will occur. LPCH is a state-of-the-art hospital outfitted with the most advanced medical equipment. The hospital employs qualified staff to handle any type of medical emergency in children and adolescents.

Outpatient dosing phase: For any adverse events, families will be instructed to contact the research coordinator at 650-736-1235 during business hours, and through the Stanford page operator after hours and during weekends/holidays. (A project coordinator will be available 24/7 to respond to safety concerns.) If the adverse event is life threatening, participants will be asked to call 911 or referred to the nearest emergency room. If the adverse event is not life threatening, the study coordinator will contact the study physician who will contact the family directly and inquire about the adverse event. If the study physician judges the side effects as minor or benign, a decision will be made whether or not the participant will continue in the study. If side effects are judged as severe and might be related to AVP, the participants will be asked to stop the study drug immediately and will be invited to come in to the clinic within 24 hours for a direct evaluation and termination of their participation in the study. If the study physician feels that the adverse event requires immediate medical attention, parents will be instructed to contact 911 or go to the nearest emergency room. The study physician will also have the ability to break the blind if it is felt that doing so is in the best interest of the participants' health.

Any serious adverse events will be reported to the Data and Safety Monitoring Board (DSMB) and Stanford Institutional Review Board (IRB) within 24 hours and to the Food and Drug Administration (FDA) within seven calendar days.

Data safety and monitoring board: A DSMB will be established to monitor the proposed clinical trial that will be registered with, and will receive approval from, the FDA as an Investigation New Drug. (This study will also be listed on [clinicaltrials.gov](http://clinicaltrials.gov) and on Stanford University's Clinical Trials Directory.) The DSMB will include several physicians who are not involved in the research investigations. The DSMB will meet on a quarterly basis to assess data quality and timeliness, participant recruitment, accrual and retention, participant risk-versus-benefit (including review of all adverse reactions and SAEs), and any breaches of confidentiality. Reports will be submitted to the Stanford University IRB on a quarterly basis, as part of the annual IRB review process, as well as for the annual report. We will also submit annual reports to the FDA.

Confidentiality: All information from the evaluation and assessment of all participants are subject to standard confidentiality procedures followed at Stanford as mandated by the IRB. Information will not be released to any party, except with the written consent of the participant and his/her parents/legal guardians. Participants' identity will be concealed in data records and files by use of assigned ID codes. Research data will be maintained in locked storage cabinets in a locked file room. Only project staff will be allowed in this room. The screening, diagnostic, and neuropsychological tests are maintained in folders for each participant, stored in locked cabinets, in locked rooms, within a locked suite. When the data are transferred to data summary sheets, only the participant number appears on the sheet and it alone is entered into the database. We will continuously monitor both our procedures and our data to be sure we are in

compliance with confidentiality guidelines. Research staff members are carefully trained about the critical nature of participants' confidentiality and about the procedures for respecting and maintaining it. They are instructed to file data immediately after they have been collected, never to leave unlocked or opened data files unattended, never to discuss participants' behavior outside of the research study, and never to mention the name(s) of participants except to other research staff on this project. They are also instructed on the procedures for assigning ID numbers and for filing data separately from participant-identification information. All staff members complete training modules on human subjects' protection and take an examination to obtain certification.

Data and safety monitoring by PIs: Drs. Parker and Hardan will oversee all data and safety monitoring. They will hold weekly meetings with staff to discuss progress of the research study (data quality, timeliness, and participant recruitment), outcome and adverse event data and changes to the benefit-to-risk ratio that would change the design of the experiment, and issues related to confidentiality ensuring that procedures for obtaining information in a private manner were performed and that documentation was stored in the appropriate locked file cabinets. The PIs will also hold separate monthly educational meetings to discuss any new information relevant to this study. They will be responsible for reporting any serious and unexpected adverse reactions to the IRB and DSMB within 24 hours and to the FDA within seven calendar days. Any identifying information collected from participants in this study will be kept strictly confidential. As mentioned above, the participants will be assigned an exclusive ID code for all data, and all information in research files will be coded using that number rather than the participant's name. A name log will be kept in a locked desk in a locked office at all times. All data will be entered onto a secured database. Scientifically trained and properly authorized employees of the FDA and/or Stanford University may inspect the relevant records. We are committed to complying with FDA and IRB policies for reporting serious and unexpected adverse events.

For maximal benefit to the field, de-identified data will be made available to other investigators through the National Database for Autism Research (NDAR) and related information will be included in our consent form.

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**d. Study Conclusion**

Single-dose (initial administration): If, following the initial dosing, body temperature changes more than 2°F, heart rate changes more than 20 bpm, blood pressure changes more than 20%, or any signs of adverse reactions to the drug are noted (e.g., listlessness, vomiting, seizure activity) then close monitoring will occur and the participant will be assessed by the study physician. If indicated, participants will be immediately escorted to the Lucile Packard Children's Hospital (LPCH) Emergency Room, for treatment and their participation in the study will be terminated. The LPCH Emergency Room is within a short distance from the Stanford University Psychiatry and Behavioral Sciences building (~2 blocks), where initial dosing will occur. LPCH is a state-of-the-art hospital outfitted with the most advanced medical equipment. The hospital employs qualified staff to handle any type of medical emergency in children and adolescents.

Outpatient dosing phase: For any adverse events, families will be instructed to contact the

research coordinator at 650-736-1235 during business hours, and through the Stanford page operator after hours and during weekends/holidays. (A project coordinator will be available 24/7 to respond to safety concerns.) If the adverse event is life threatening, participants will be asked to call 911 or referred to the nearest emergency room. If the adverse event is not life threatening, the study coordinator will contact the study physician who will contact the family directly and inquire about the adverse event. If the study physician judges the side effects as minor or benign, a decision will be made whether or not the participant will continue in the study. If side effects are judged as severe and might be related to AVP, the participants will be asked to stop the study drug immediately and will be invited to come in to the clinic within 24 hours for a direct evaluation and termination of their participation in the study. If the study physician feels that the adverse event requires immediate medical attention, parents will be instructed to contact 911 or go to the nearest emergency room. The study physician will also have the ability to break the blind if it is felt that doing so is in the best interest of the participants' health.

Any serious adverse events will be reported to the Data and Safety Monitoring Board (DSMB) and Stanford Institutional Review Board (IRB) within 24 hours and to the Food and Drug Administration (FDA) within seven calendar days.

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**e. Data Safety Monitoring Plan (DSMC)**

**i. Data and/or events subject to review**

1. Vital signs (HR/BP, temperature) monitoring will be conducted before and after (20 minutes, ~2 hours) initial single dose administration, and following 1, 2, 3, and 4 weeks of dosing as well as weekly during the optional open-label extension.
2. BMI will be measured at screening, and following 1, 2, 3, and 4 weeks of dosing.
3. DOTES side effects report and OAS will be conducted prior to initiation of dosing and on completion of 1, 2, 3 and 4 weeks of dosing.
4. ECG monitoring will be conducted at screening and following single-dose, 1, 2, 3 and 4-weeks of dosing.
5. Clinical chemistry labs will be conducted at screening and following 1, 2, and 4-weeks of dosing.

All safety assessments outlined above will be repeated during the optional open-label extension period.

**ii. Person(s) responsible for Data and Safety Monitoring**

A DSMB will be established to monitor the proposed clinical trial that will be registered with, and will receive approval from, the FDA as an Investigation New Drug. (This study will also be listed on [clinicaltrials.gov](http://clinicaltrials.gov) and on Stanford University's Clinical Trials Directory.) The DSMB will include several physicians who are not involved in the research investigations. The DSMB will meet on a quarterly basis to assess data quality and timeliness, participant recruitment, accrual and retention, participant risk-versus-benefit (including review of all adverse reactions and Serious Adverse Events [SAEs]), and any breaches of confidentiality. Reports will be submitted to the Stanford University IRB on a quarterly basis, as part

of the annual IRB review process, as well as for the annual report. We will also submit annual reports to the FDA.

iii. Frequency of DSMB meetings

The data and safety monitoring committee will meet on a quarterly basis to assess data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit (including review of all adverse reactions and SAEs), and any breaches of confidentiality. Reports will be submitted to the Stanford University IRB on a quarterly basis, as part of the annual IRB review process, as well as for the annual report. We will also submit an annual report to the FDA.

iv. Specific triggers or stopping rules

A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization, results in persistent or significant disability/incapacity, an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes. Cancer/Overdose: All cases of cancer and overdose will be reported immediately.

v. DSMB Reporting

Any serious adverse events will be reported to the DSMB and Stanford IRB within 24 hours and to the FDA within seven calendar days.

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

No

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

Yes

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**f. Risks to Special Populations**

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. The research presents more than minimal risk to children, but holds out the prospect of direct benefit for the individual subject or is likely to contribute to the subject's well-being. Please provide rationale that: (a) the risk is justified by the anticipated benefit to the subjects; (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

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**10. BENEFITS**

As of now, there is no effective intervention strategy aimed at targeting the core symptoms of autism and curbing the long course and guarded prognosis of autism. Outcome studies indicate that about 2/3 of autistic adults remain severely handicapped and live in complete dependence or

semi-dependence. Available agents aim at controlling associated behavioral features such as aggression, agitation and compulsive behaviors. Agents that treat underlying chronic neurobiological abnormalities are lacking. The suggested innovative agent (vasopressin), if shown to be effective, will lead to the development of new strategies to treat individuals with autism spectrum disorders.

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## **11. PRIVACY AND CONFIDENTIALITY**

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.