



TNX-2900

Prader-Willi Syndrome

NASDAQ: TNXP





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TNX-2900*: Prader-Willi Syndrome

Intranasal Potentiated Oxytocin (OT) with Magnesium

PROFILE

Prader-Willi Syndrome is the most common genetic cause of life-threatening childhood obesity

- Rare disease occurring in 1 in 10,000 to 1 in 30,000 births

Symptoms include lack of suckling as infants, poor muscle strength, and constant hunger (hyperphagia) in adolescents and young adults

- In animal models, OT has improved suckling and suppressed hunger
 - Tonix's patented potentiated OT formulation is believed to increase activity of OT at OT receptors (OXTR)

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Treatment of hyperphagia in adolescents and young adults with Prader-Willi Syndrome

Additional Indications: Rare Hyperphagia Conditions

Status: Granted Orphan Drug Designation and Rare Pediatric Disease Designation by FDA, received IND clearance for Phase 2 trial from FDA

Next Steps: Phase 2 ready

*TNX-2900 is has not been approved for any indication.





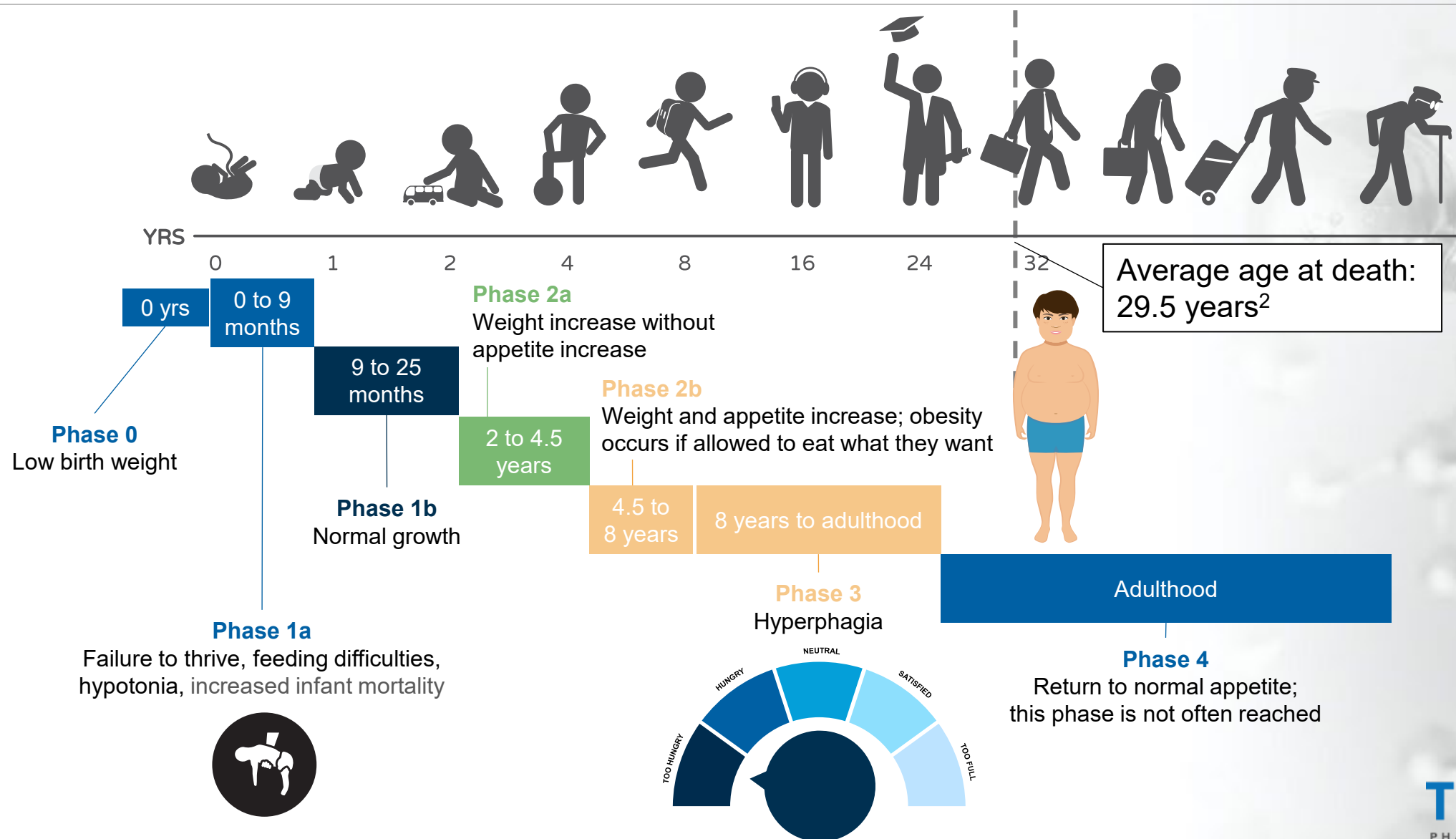
Prader-Willi Syndrome (PWS)

Cause	~65% of cases are due to a new deletion on paternal chromosome 15; first genetic imprinting disorder recognized in humans
Prevalence	1 in 10,000 to 1 in 30,000 ^{1,2} ; most common syndromic cause of obesity
Symptoms	In infants, severe hypotonia and difficulty sucking. In children and adolescents, delayed global development, decreased growth resulting in short stature, intellectual difficulties, hypogonadism, hyperphagia, life-threatening obesity, behavioral problems
Diagnosis	Genetic testing: DNA methylation
Treatment	No cure, but human growth hormone treatment is FDA approved for growth failure in PWS children

¹Angulo MA, et al. *J Endocrinol Invest*. 2015;38(12):1249-1263.
²McCandless, Shawn E et al. SUN-604 U.S. Prevalence & Mortality of Prader-Willi Syndrome: A Population-Based Study of Medical Claims, *Journal of the Endocrine Society*, Volume 4, Issue Supplement_1, April-May 2020, SUN-604, <https://doi.org/10.1210/endo/bvaa046.993>



Progression of Prader-Willi Syndrome¹

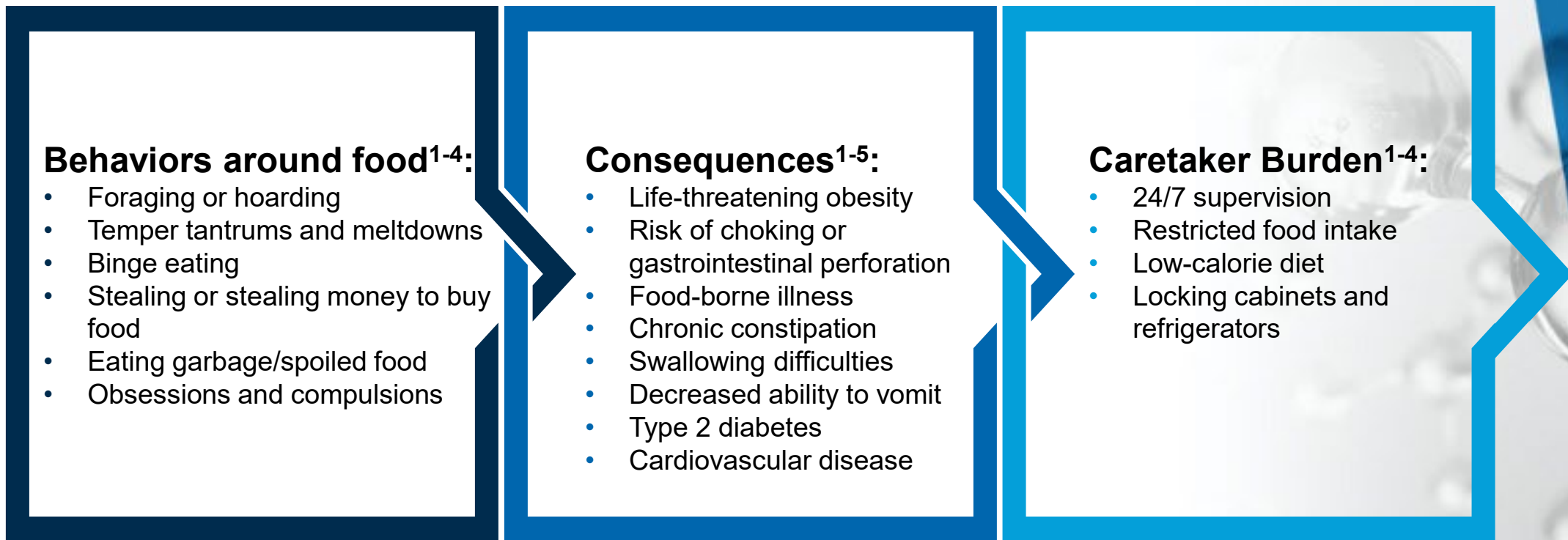


¹ Angulo MA, et al. *J Endocrinol Invest*. 2015;38(12):1249-1263.

² Butler MG, et al. *Genet Med*. 2017;19(6):635-642.



Dangers of PWS Hyperphagia



There is no treatment for PWS-related hyperphagia⁴

¹ Miller JL, et al. *Am J Med Genet A*. 2011;155A(5):1040-1049.
² Butler MG, et al. *Genet Med*. 2017;19(6):635-642.
³ Butler MG. NORD. Updated 2018. Accessed May 25, 2022. <https://rarediseases.org/rare-diseases/prader-willi-syndrome/>
⁴ Prader-Willi Syndrome Association USA. Accessed May 25, 2022. <https://www.pwsausa.org/what-is-prader-willi-syndrome/>
⁵ Muscogiuri G, et al. *J Endocrinol Invest*. 2021;44(10):2057-2070.



Abnormalities of the Oxytocin System in Patients with PWS

PWS patients have



Increased oxytocin in blood plasma^{1,2}



Decreased oxytocin mRNA¹



Low levels of oxytocin receptor expression²



Decreased or abnormal oxytocin neurons (especially in the PVN)¹

PVN=paraventricular nucleus.

¹ Correa-da-Silva F, et al. *J Neuroendocrinol.* 2021;33(7):e12994.

² Jurek B, et al. *Physiol Rev.* 2018;98(3):1805-1908.



History of Oxytocin Use

Synthetic oxytocin has been used to induce labor for over 65 years¹



Due to the role of endogenous oxytocin in pain regulation and social behavior, the administration of exogenous oxytocin has been studied in a wide variety of therapeutic areas²



Intravenous application of oxytocin has been met with many challenges:

- Short half-life:
 - Intravenous oxytocin has a half-life of roughly 3 minutes³
- Difficulty crossing the blood-brain barrier⁴



¹den Hertog CE, et al. *Eur J Obstet Gynecol Reprod Biol.* 2001;94(1):8-12.

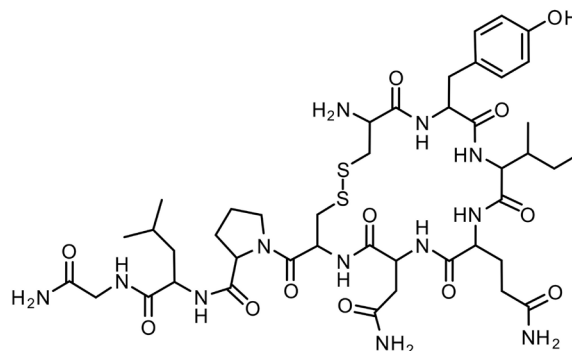
²Bakermans-Kranenburg MJ, et al. *Transl Psychiatry.* 2013;3(5):e258.

³Oxytocin, Package insert. Hikma Pharmaceuticals USA Inc.; 2011.

⁴Quintana DS, et al. *Mol Psychiatry.* 2021;26(1):80-91.



Functions of Natural and Therapeutic Oxytocin



Childbirth¹⁻³:

Natural

- Stimulates uterine contractions during childbirth

Therapeutic

- Widely used for the induction of labor in an estimated 25% of women in Western countries

Breastfeeding^{1,4,5}:

Natural

- Oxytocin is responsible for the let-down reflex
- Contracts the muscles around the glands that produce milk

Therapeutic

- Approved to stimulate milk production, but discontinued in the US

Behavioral regulation^{1,6}:

Natural

- Oxytocin plays a role in prosocial behaviors and bonding
- Signals satiety and suppresses appetite

Therapeutic

- No approved oxytocin therapy

¹ McCormack SE, et al. *Endocr Rev.* 2020;41(2):121-145.

² Kuwabara Y, et al. *Arch Gynecol Obstet.* 1987;241(1):13-23.

³ Boie S, et al. *Cochrane Database Syst Rev.* 2018;8(8):CD012274.

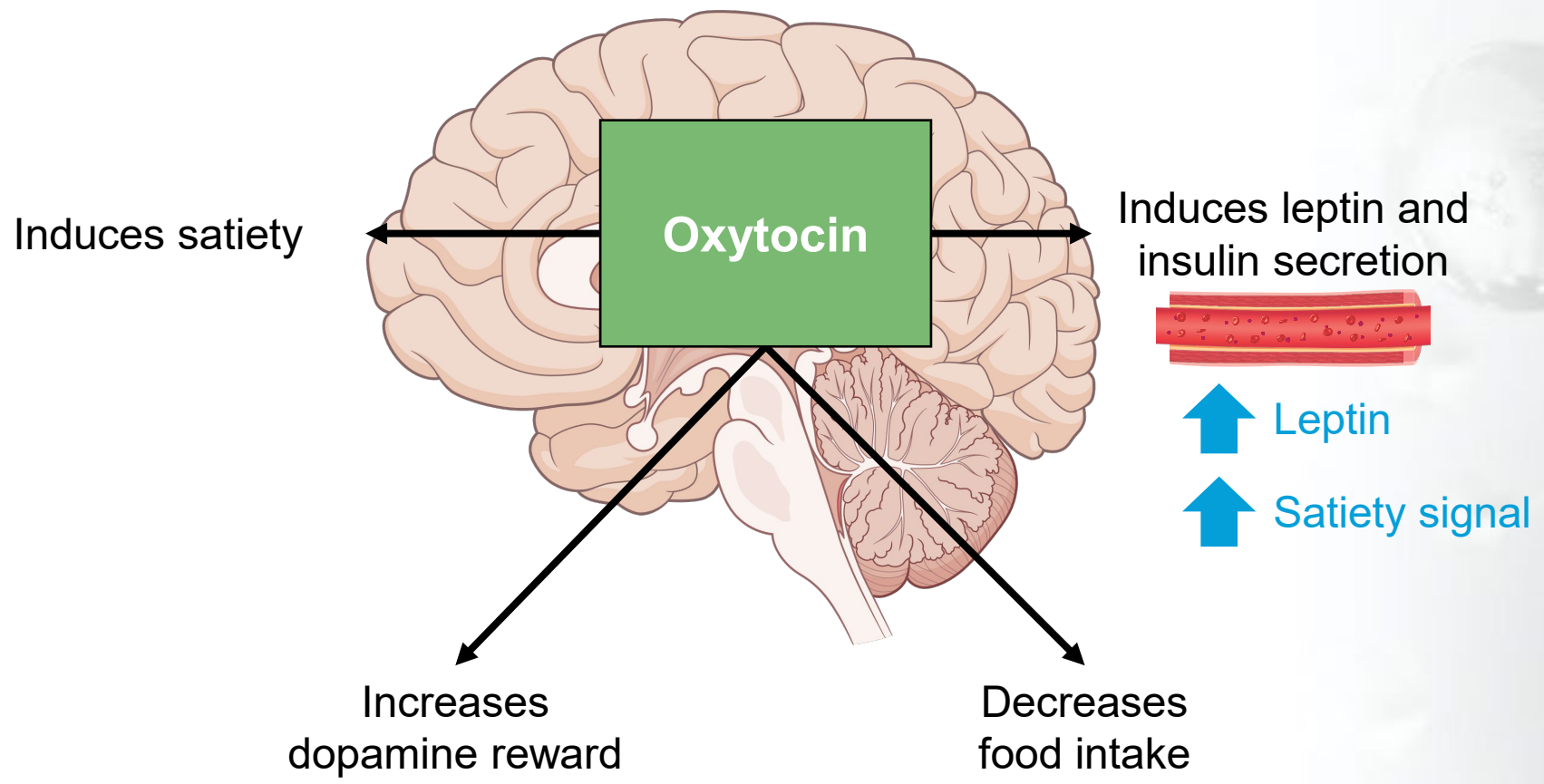
⁴ World Health Organization. World Health Organization; 2009. <https://www.ncbi.nlm.nih.gov/books/NBK148970/>

⁵ MPR. December 12, 2013. Accessed June 23, 2022. <https://www.empr.com/home/news/retrophin-to-reintroduce-syntocinon-nasal-spray/>

⁶ Bartz JA, et al. *Trends Cogn Sci.* 2011;15(7):301-309.



Oxytocin Plays Major Role in Satiety¹⁻³



¹ Correa-da-Silva F, et al. *J Neuroendocrinol.* 2021;33(7):e12994.
² McCormack SE, et al. *Endocr Rev.* 2020;41(2):121-145.
³ Kerem L, et al. *Int J Mol Sci.* 2021;22(14):7737.



Intranasal Use of Oxytocin



- Intranasal oxytocin was introduced as a lactation aid in the early 1960s¹
- Numerous studies have investigated chronic and acute intranasal oxytocin for the treatment of neuropsychiatric disorders and pain²
 - Intranasal oxytocin has been studied in anxiety disorders,³ autism,⁴ PTSD,⁵ schizophrenia,⁶ and pain⁷
- Chronically administered intranasal oxytocin is generally very well tolerated⁸⁻¹¹
- Intranasal oxytocin has been found to be generally safe and well tolerated in a variety of healthy populations ranging from infancy to old age^{12,13}

¹Skarsten KW. *Tidsskr Nor Lægeforen*. 1962;82:8-10.

²Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.

³Jones C, et al. *Dialogues Clin Neurosci*. 2017;19(2):193-201.

⁴Guastella AJ, et al. *Biol Psychiatry*. 2010;67(7):692-694.

⁵Pitman RK, et al. *Psychiatry Res*. 1993;48(2):107-117.

⁶Feifel D, et al. *Biol Psychiatry*. 2016;79(3):222-233.

⁷Boll S, et al. *Neuroscience*. 2018;387:149-161.

⁸Rung JM, et al. *Psychopharmacology (Berl)*. 2021;1-14.

⁹Horta M, et al. *Neurosci Biobehav Rev*. 2020;108:1-23.

¹⁰Finger E, et al. *Neurology*. 2015;84(2):174-181.

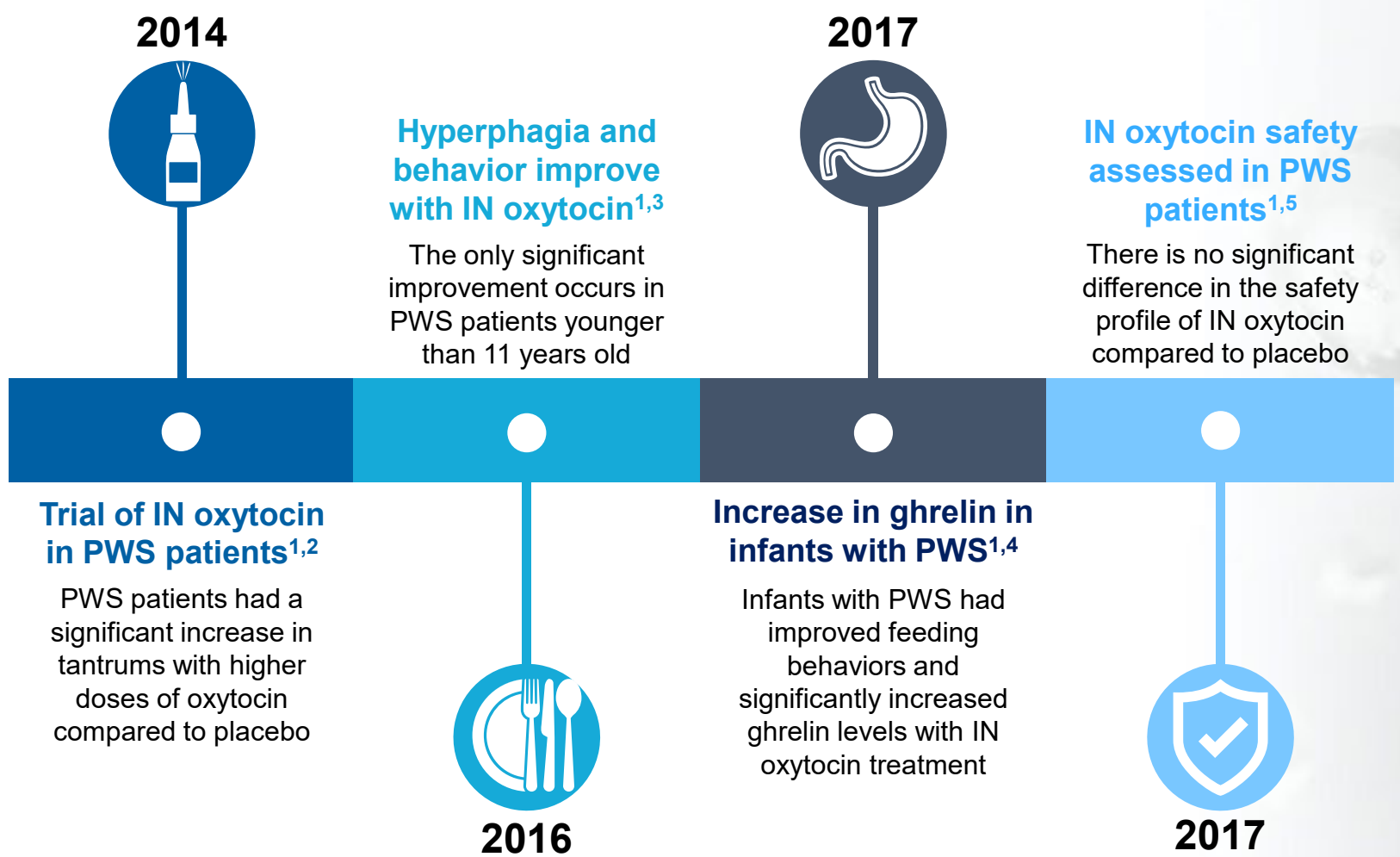
¹¹Barraza JA, et al. *Exp Clin Psychopharmacol*. 2013;21(2):85-92.

¹²DeMayo MM, et al. *Drugs*. 2017;19(5):391-410.

¹³Verhees MWFT, et al. *Psychopharmacology (Berl)*. 2018;235(8):2471-2477.



Intranasal (IN) Oxytocin As PWS Treatment



Despite strong evidence for the role of OT in satiety, there are challenges in using OT for the treatment of PWS

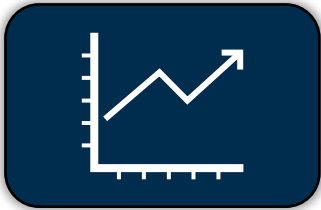
¹ McCormack SE, et al. *Endocr Rev.* 2020;41(2):121-145.
² Einfeld SL, et al. *Am J Med Genet A.* 2014;164A(9):2232-2239.
³ Kuppens RJ, et al. *Clin Endocrinol (Oxf).* 2016;85(6):979-987.
⁴ Tauber M, et al. *Pediatrics.* 2017;139(2):e20162976.
⁵ Miller JL, et al. *Am J Med Genet A.* 2017;173(5):1243-1250.



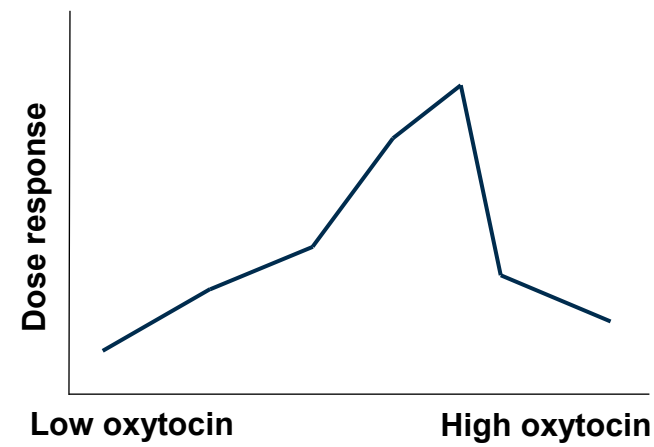
Challenges in Intranasal Oxytocin Studies in PWS



- No significant difference with IN oxytocin treatment but significantly increased tantrums at higher doses⁴
- Significant improvement in hyperphagia but only in patients younger than 11 years old⁵



- Central oxytocin levels are difficult to measure¹
- Dose response is not linear but an inverted-U shape^{1,2}



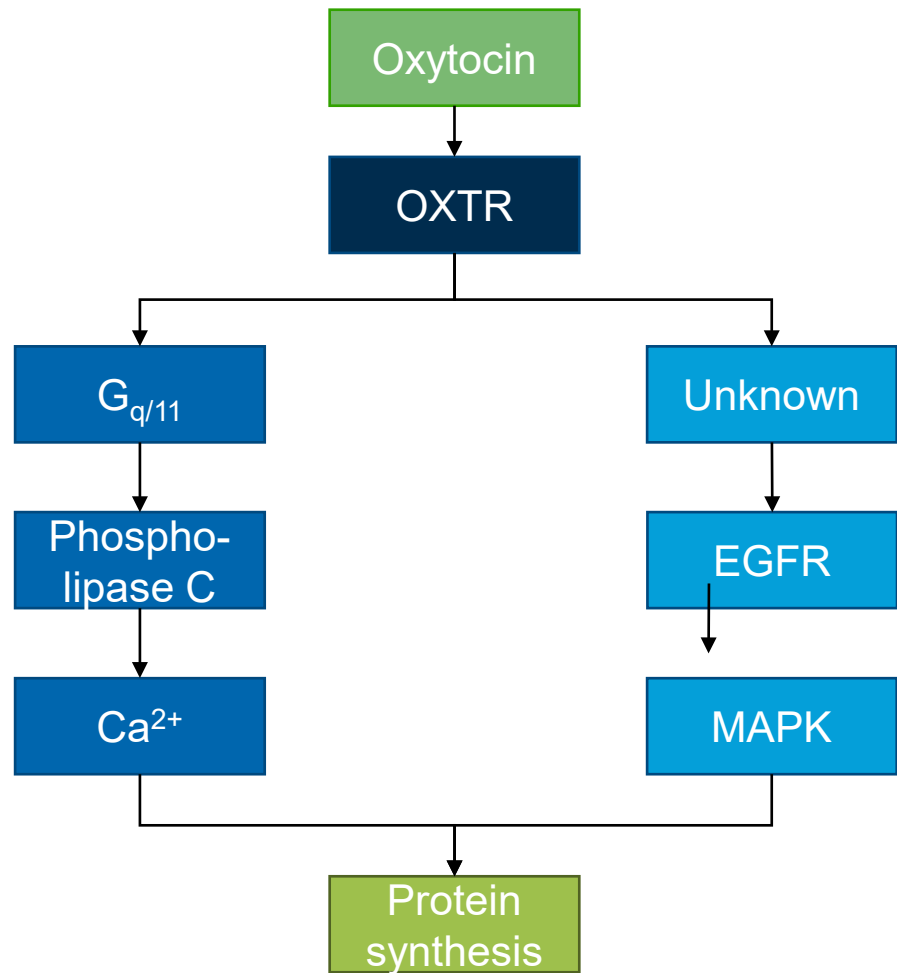
- Recent nonclinical reports show that magnesium is needed for full oxytocin receptor binding^{2,3}
- Magnesium enables a full dose response^{2,3}

¹ Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.
² Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.
³ Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.
⁴ Einfeld SL, et al. *Am J Med Genet A*. 2014;164A(9):2232-2239.
⁵ Kuppens RJ, et al. *Clin Endocrinol (Oxf)*. 2016;85(6):979-987.

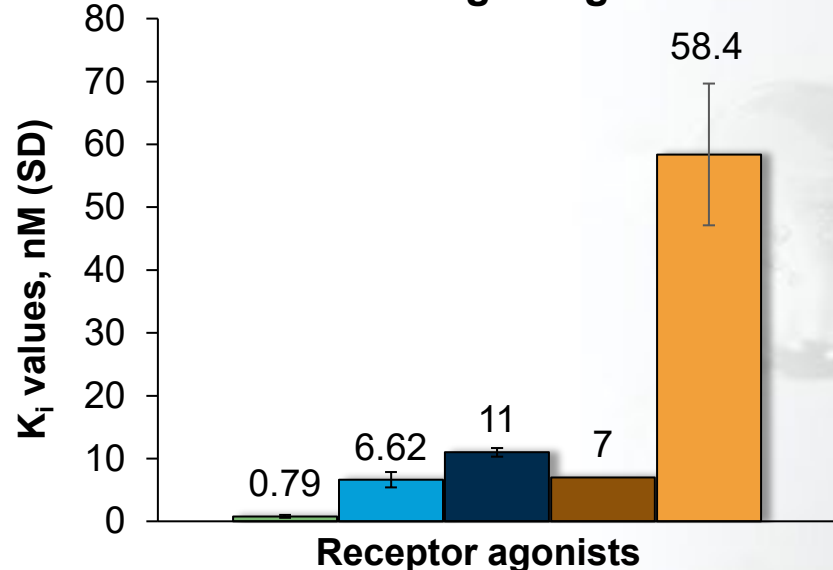


Oxytocin Receptor (OXTR)

OXTR Signaling Cascade



OXTR Binding to Agonists¹



- Oxytocin**
- TGOT** = highly selective agonist
- Atosiban** = functionally selective agonist (can act as an antagonist depending on the G-protein coupled to OXTR)
- Carbetocin** = oxytocin analog – weak agonist with mixed antagonist activity²
- WAY 267,464** = nonpeptide agonist more specific for the vasopressin receptor

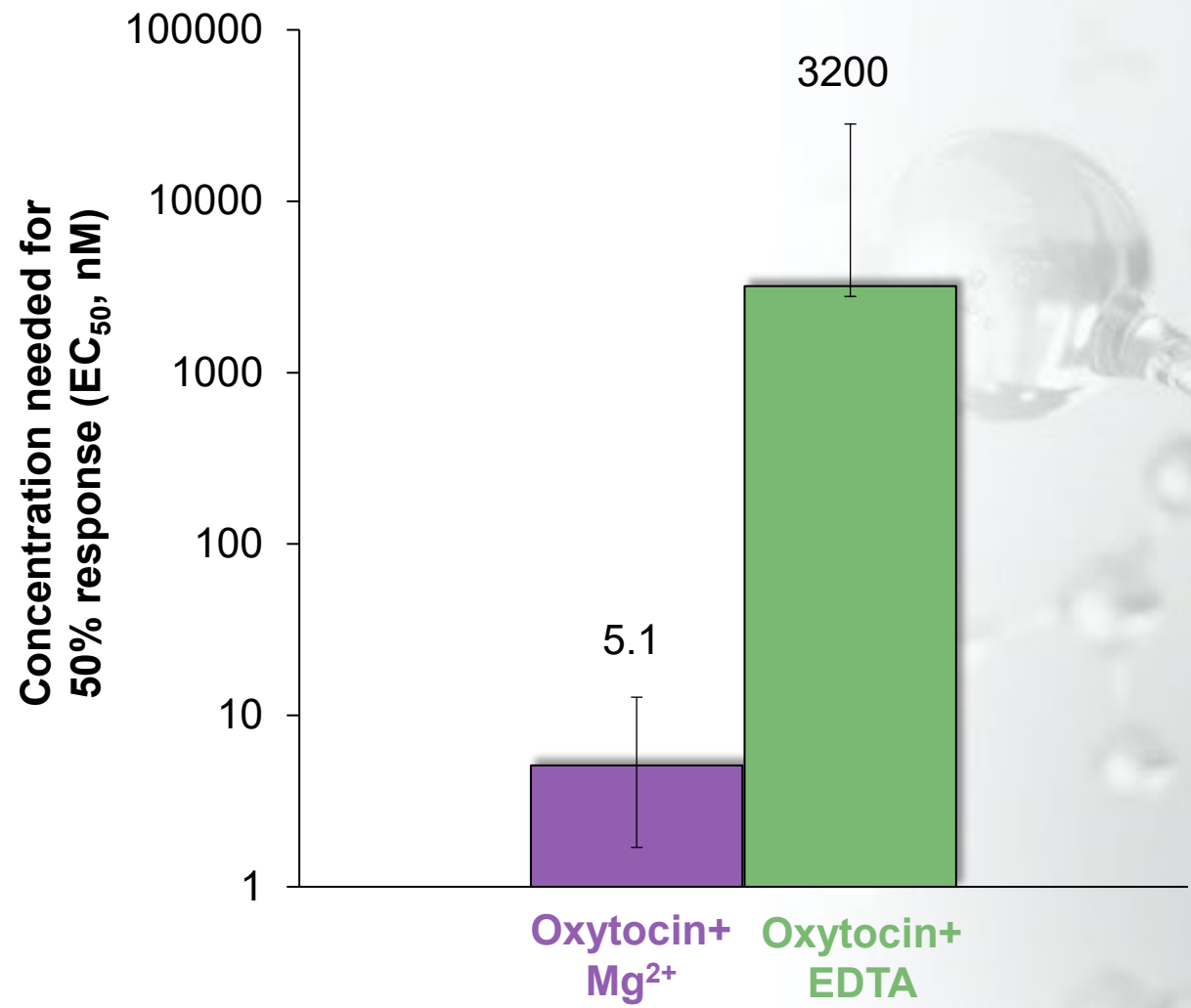
EGFR=epidermal growth factor receptor; MAPK=mitogen activated protein kinase; OXTR=oxytocin receptor

¹ Jurek B, et al. *Physiol Rev.* 2018;98(3):1805-1908.
² Meyerowitz JG, et al. *Nat Struct Mol Biol.* 2022;29(3):274-281.



Oxytocin+Mg²⁺ Activates OXTR Secondary Messengers

Magnesium is needed not only for oxytocin binding to OXTR but also for OXTR activation



BRET assay in HEK-293 cells

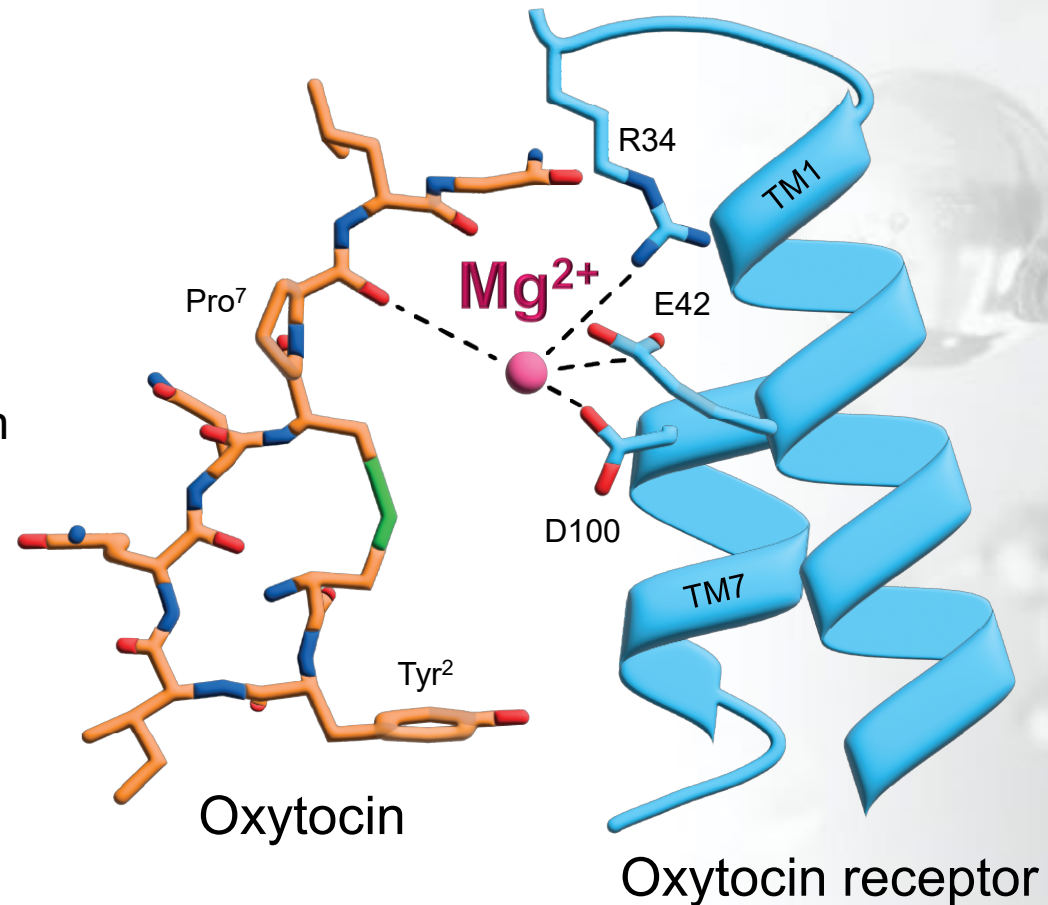
BRET=bioluminescence resonance energy transfer; EDTA=ethylenediaminetetraacetic acid; HEK=human embryonic kidney; OXTR=oxytocin receptor.

Meyerowitz JG, et al. *Nat Struct Mol Biol.* 2022;29(3):274-281.



Oxytocin Requires Magnesium for Receptor Binding

- OXTR exists in 2 conformational states¹:
 - Low affinity
 - High affinity
- Magnesium ions are necessary for the high-affinity state^{1,2}
- Without magnesium ions present, oxytocin cannot achieve full binding to OXTR²



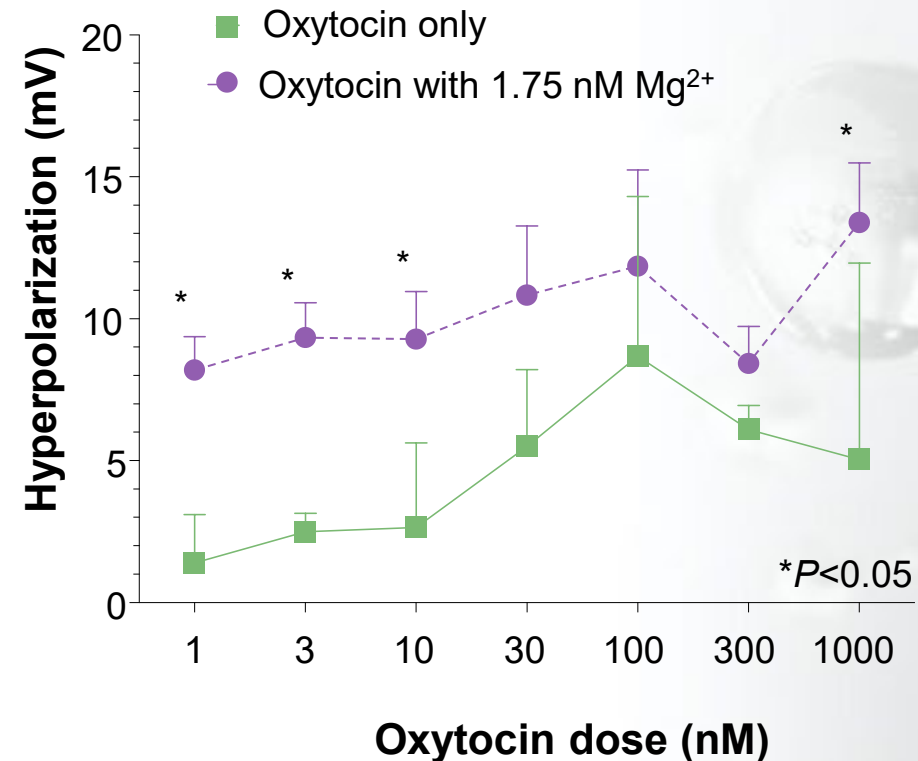
OXTR=oxytocin receptor.

¹ Jurek B, et al. *Physiol Rev.* 2018;98(3):1805-1908.

² Meyerowitz JG, et al. *Nat Struct Mol Biol.* 2022;29(3):274-281.

Addition of Mg^{2+} Expands the *in vivo* Useful Dose Range of Intranasal Oxytocin in Animals

- A nonlinear dose response has been demonstrated in the use of intranasal oxytocin
- This decreases efficacy at higher doses
- Addition of Mg^{2+} rescues the efficacy of oxytocin at high doses



In vitro whole-cell voltage-clamp recordings of rat trigeminal nerves exposed to oxytocin solution with and without additional magnesium ions



Highlights

- Hyperphagia in Prader-Willi syndrome (PWS) is severe and life-threatening
 - There is currently no treatment for hyperphagia in adolescents and young adults with PWS
- Oxytocin is one of the hormones responsible for signaling satiety
- The oxytocin receptor requires magnesium ions for the high-affinity conformation for signaling satiety
- TNX-2900* combines oxytocin with magnesium for improved receptor binding and potentially improved therapeutic action
- TNX-2900 is in development to treat hyperphagia in PWS

*TNX-2900 is an investigational drug and has not been approved for any indication

THANK YOU

