QSP modeling shows efficacy of an NK3R antagonist to reduce treatment-induced vasomotor symptoms

Chris Schelling[1], Rick Ridgewell[1], Christina Friedrich[2], Katherine Kudrycki[2], R. Baillie[2], Douglas Chung[2], Mike Reed[2]

[1]Acer Therapeutics Newton, MA USA; [2]Rosa & Co., San Carlos, CA 94070, USA, *mreed@rosaandco.com

Introduction

Background:

- Vasomotor symptoms (VMS, hot flashes) are common in cancer patients treated with hormone-deprivation therapy
  - 84% of women treated with tamoxifen[1]
  - 80% of men treated with leuprolide[2]
- NK3 receptor (NK3R) antagonists reduce VMS in postmenopausal women without added estrogen
- ACER-801, an NK3R antagonist, is being evaluated to reduce frequency and severity of therapy-induced VMS

Objectives:

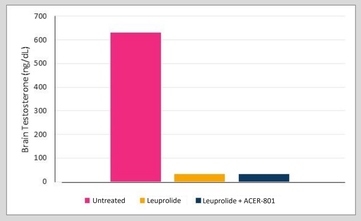
- Use a quantitative systems pharmacology (QSP) model of the hypothalamus-pituitary-gonadal (HPG) axis to evaluate ACER-801 for treatment of induced VMS
- Verify ACER-801 efficacy when co-administered with tamoxifen or leuprolide
- Identify optimal dosing strategies

Results:

- Co-administered ACER-801 reduces tamoxifen-induced VMS frequency and severity
- Co-administered ACER-801 reduces leuprolide-induced VMS frequency and severity
- Twice daily dosing decreased VMS more than once daily

Results

ACER-801 treatment should not interfere with hormone deprivation therapy in cancer patients



Leuprolide treatment in a male VP decreases testosterone to castration levels of <50 ng/dL. Acer-801 co-administration does not increase the testosterone concentrations.

References

1. Moon, Z. J Psychosom Obstet Gynaecol. 2017 Sep;38(3):226-235.
2. Schow, DA. 1998 South Med J. 1998 Sep;91(9):855-7.
3. Jin, Y. 2008 J Clin Oncol. Dec 20;26(36):5849-54.
4. Challapalli, A. 2018 Clin Transl Radiat Oncol. Mar 21;10:29-35.

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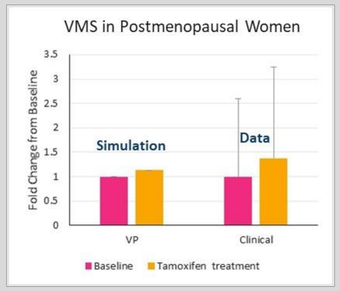
Conclusions

Research using the HPG QSP model demonstrates:

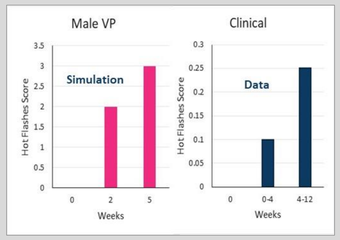
- ACER-801 is predicted to be efficacious in reducing NKB binding and vasomotor symptoms due to menopause or tamoxifen- or leuprolide-induced hormone deprivation
- Twice daily dosing was superior in lowering VMS compared to once daily dosing

Model simulations match published data



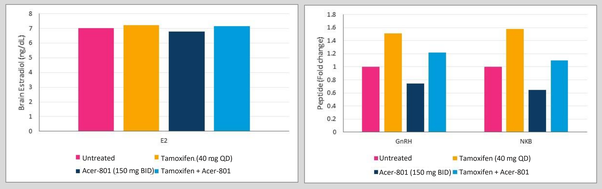
Comparison of model simulation to clinical data. Induced VMS are often measured as a combined score.

In women, tamoxifen therapy increases VMS[3].



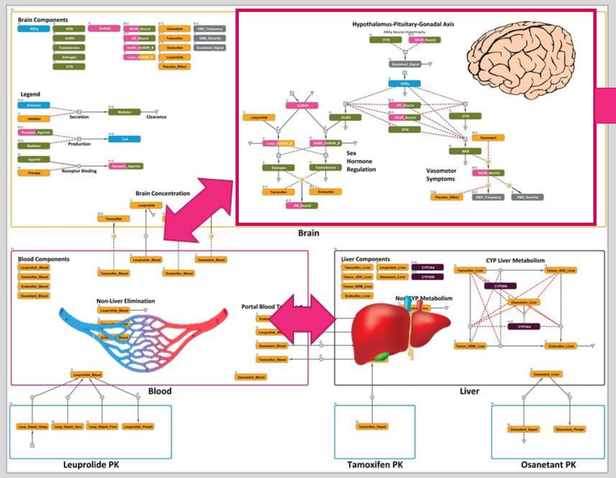
In men, VMS increases over time. KNDY neuron hypertrophy is the possible cause of hot flashes in men[4].

Tamoxifen treatment in a female virtual patient (VP) increases hormone concentrations

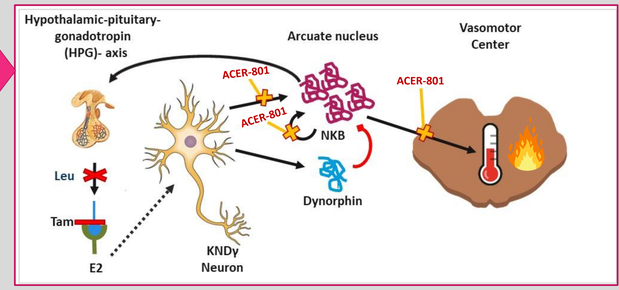


In post-menopausal women, treatment with tamoxifen should not cause large increases in estradiol, but could result in changes in GnRH and NKB.

The model incorporates the HPG axis and hormone feedback to evaluate the effect of drug treatment on induced VMS (iVMS)



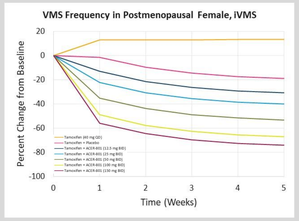
The model includes detailed NKB, dynorphin and estradiol effects on KNDy neurons, neuroendocrine feedback, and downstream effects on the HPG axis and sex hormones. The model includes tamoxifen (Tam), leuprolide (Leu), and ACER-801 PK/PD. Model development software: MATLAB® SimBiology®. Schmidt H, Jirstrand M. (2006) Bioinformatics 22, 514-5



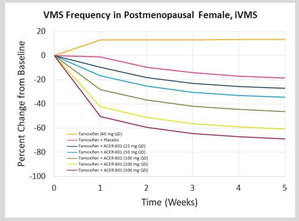
- Decreased estradiol causes decreased dynorphin and increased NKB, which trigger hot flashes in the vasomotor center
- Tamoxifen blocks the E2 receptor, mimicking loss of estradiol
- Leuprolide (GnRH agonist) decreases all sex hormone production
- ACER-801 blocks NKB receptor signals

BID dosing decreases VMS more than QD dosing

Twice Daily Dosing



Once Daily Dosing



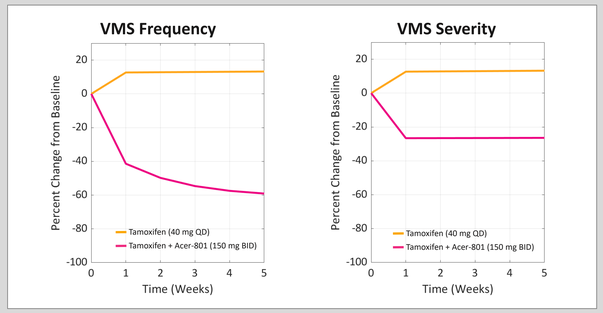
Drug dosing scenarios were tested in the model to optimize efficacy with ACER-801. Graphs show once daily dosing (QD, left) and twice daily dosing (BID, right) of the same total daily dose. BID dosing increases drug accumulation with a decrease in VMS frequency and severity (data not shown).

For more information, see:

SCAN ME

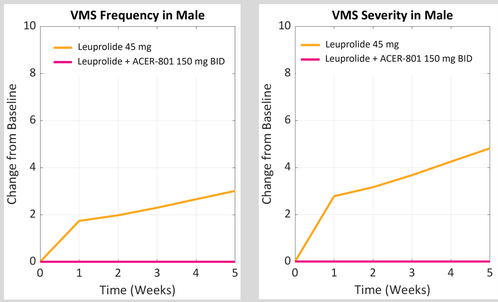
QSP modeling shows efficacy of an NK3R antagonist to reduce treatment-induced vasomotor symptoms: Handout with more information. Link to handout

Co-administered ACER-801 reduces tamoxifen-induced VMS frequency and severity



In a female VP, co-administration of ACER-801 and tamoxifen reduces both VMS frequency and severity.

Co-administered ACER-801 decreases VMS frequency in a leuprolide-treated male VP



Leuprolide treatment increases VMS in a male VP. Co-administration of ACER-801 with leuprolide reduces VMS to near 0 in this VP.

For more information about this work, please contact:
Mike Reed
Rosa & Co LLC
mreed@rosaandco.com