Evaluations of Scale: Lessons Learned While Developing and Extending a Mineral and Bone Health Multiscale Systems Pharmacology Model

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ACoP9 Loews Coronado Bay Resort, CA
Tuesday October 09, 2018

Session 3b: Diagnostics and Methodologies for Evaluating QSP Models

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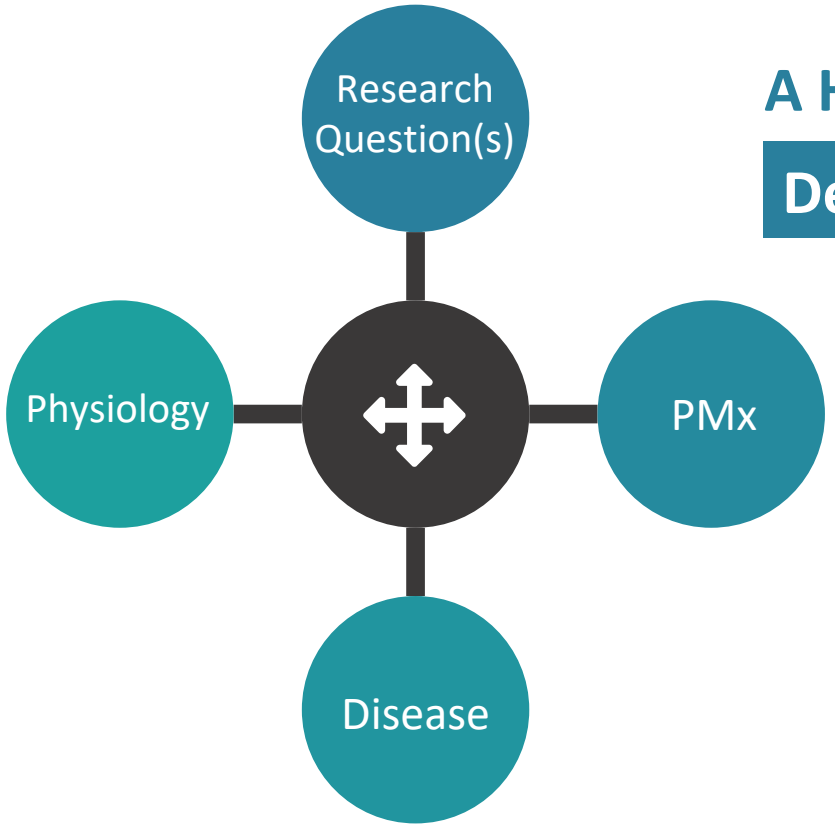
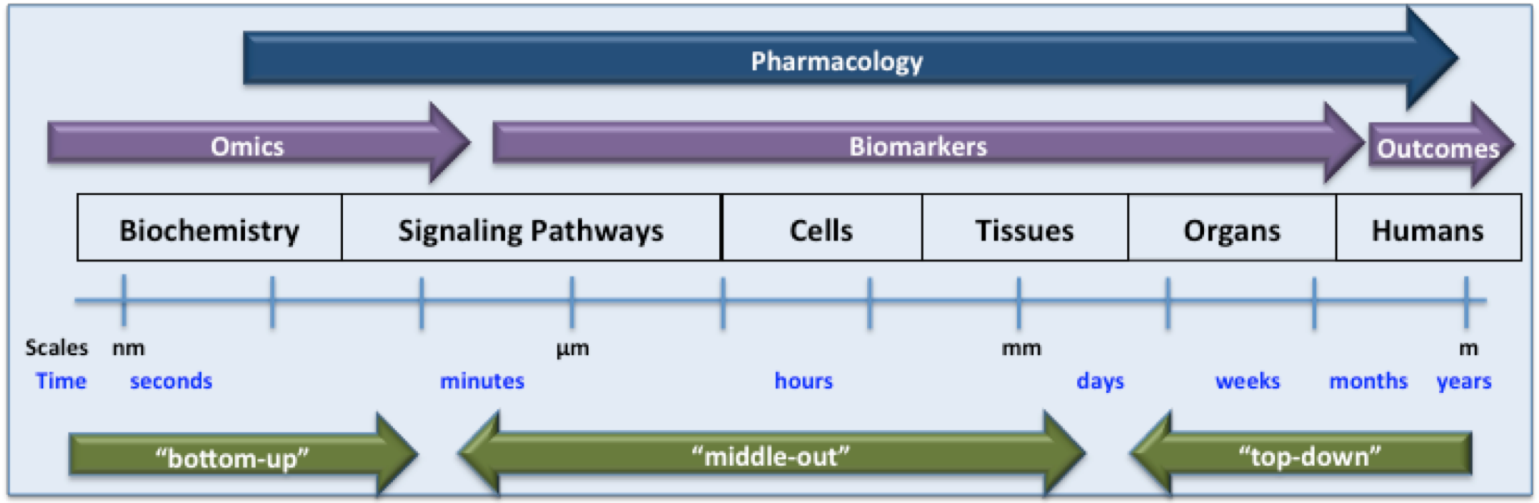
Systems Pharmacology: Mineral and Bone Health

Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63



A History of Model Evaluations

Define Needs: Time, Space, Precision



From Figure 1 of Riggs M. Multiscale Systems Models as a Knowledge Bridge Between Biology, Physiology and Pharmacology. *AAPS Newsmagazine (December, 2011)*

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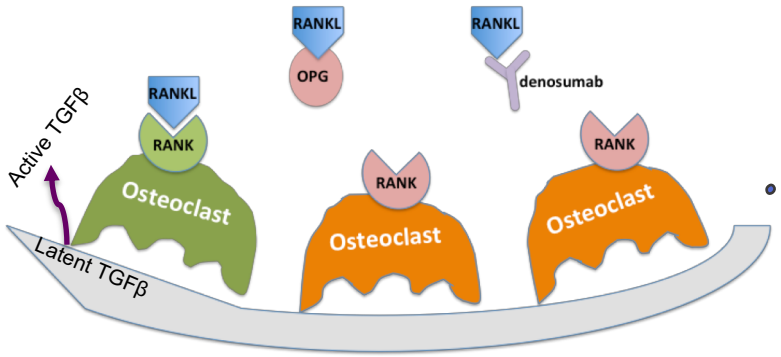
Model Evaluation Does model represent physiology

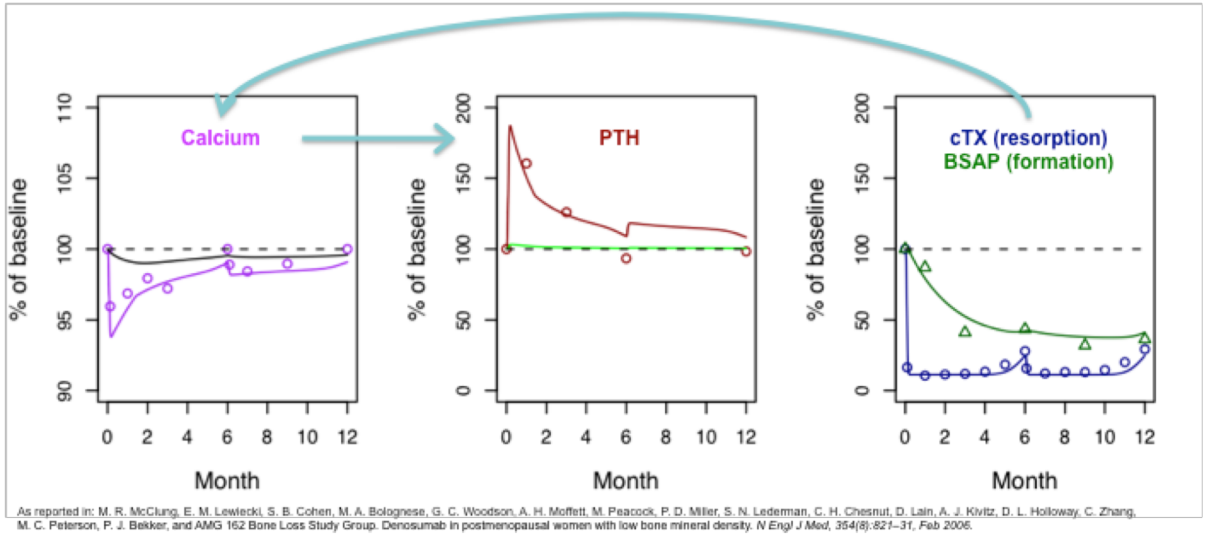
Much like with indirect response models: Maximal inhibition followed by “off” treatment allows for estimation of RANK-RANKL-OPG kinetics

Denosumab: RANKL inhibition



- ↓ available RANKL
- ↓ RANK--RANKL interaction
- ↓ Osteoclast activity (sCTx)
- ↓ Activation of TGF-β
- ↓ Osteoblast activity (BSAP)
- ↑ bone mineral density (BMD)

- ↓ Calcium release from bone
- ↓ Serum calcium
- ↓ Ca sensing in PT gland
- ↑ PTH release (calcium-sparing)



As reported in: M. R. McClung, E. M. Lewiecki, S. B. Cohen, M. A. Bolognese, G. C. Woodson, A. H. Moffett, M. Peacock, P. D. Miller, S. N. Lederman, C. H. Chesnut, D. Lain, A. J. Kivitz, D. L. Holloway, C. Zhang, M. C. Peterson, P. J. Bekker, and AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med, 354(8):821–31, Feb 2006.*

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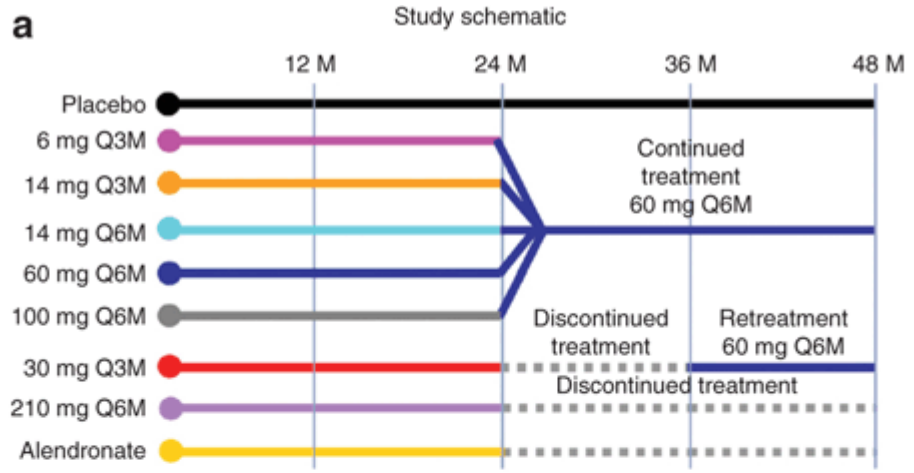
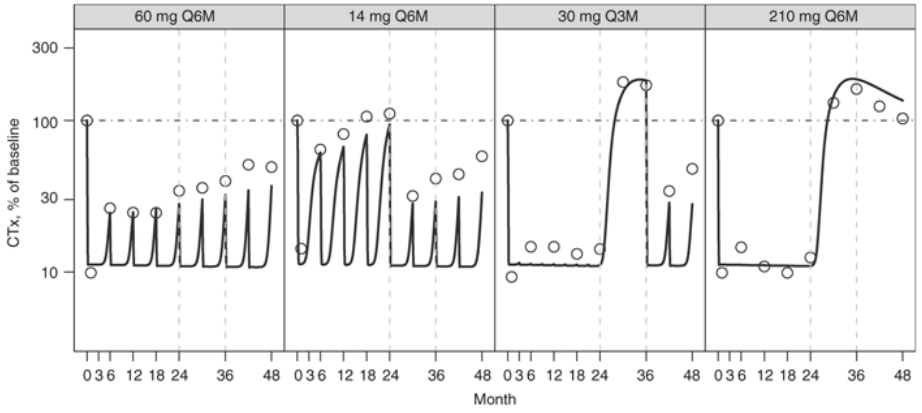
Model Evaluation Does model represent physiology

Much like with indirect response models: Maximal inhibition followed by “off” treatment allows for estimation of RANK-RANKL-OPG kinetics

Denosumab: RANKL inhibition → Bone Marker Changes

Dose-Ranging: 6 → 210 mg, Q3M and Q6M, d/c, re-Tx





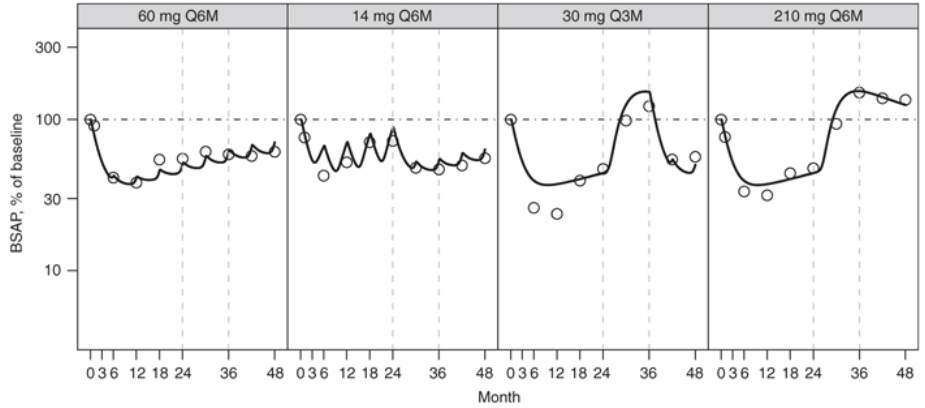


Fig.3 and 4; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

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Model Evaluation Does model represent physiology

SP “middle-out”/ up – Use the model to extend to measured response (BMD)

Denosumab: RANKL inhibition → Bone Markers → BMD Change

Dose-Ranging: 6 → 210 mg, Q3M and Q6M, d/c, re-Tx

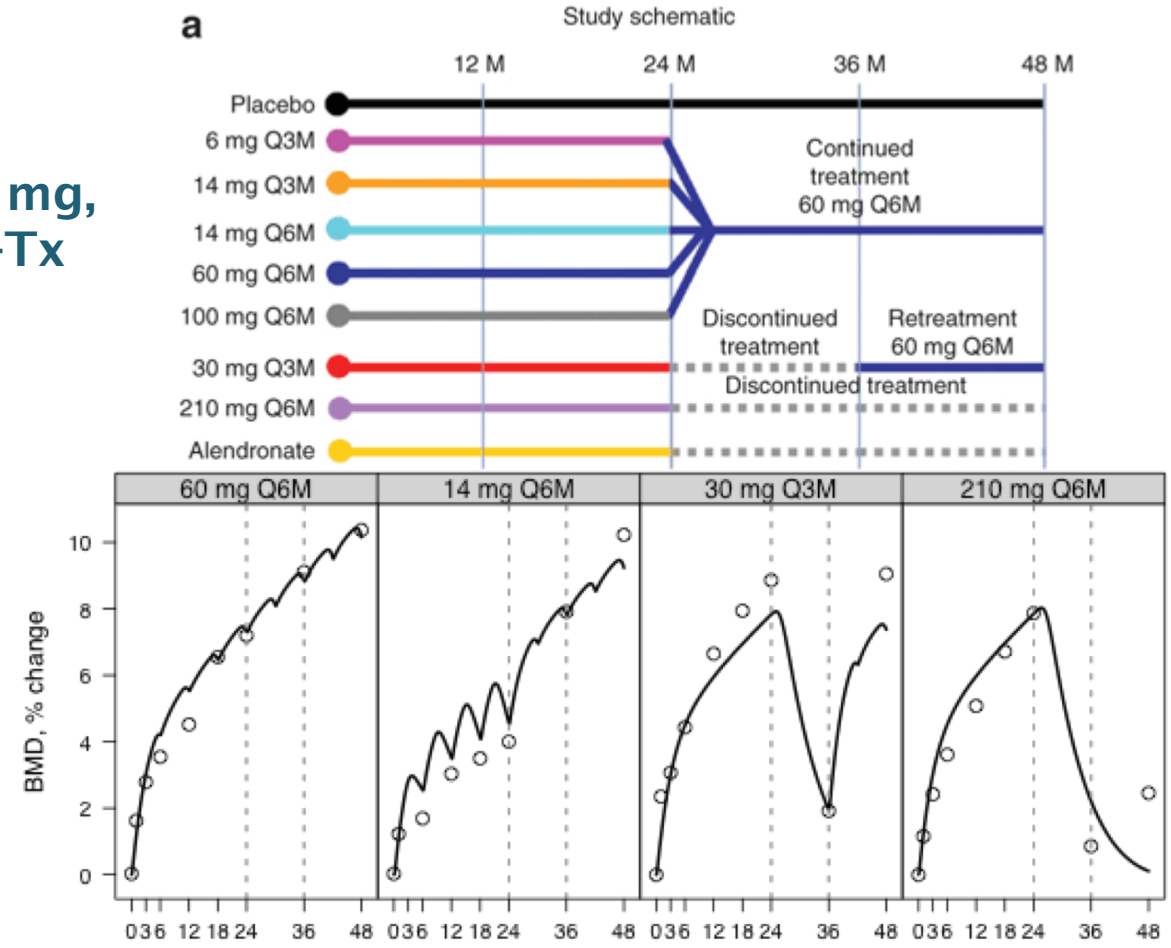

Fig.3 and 4; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

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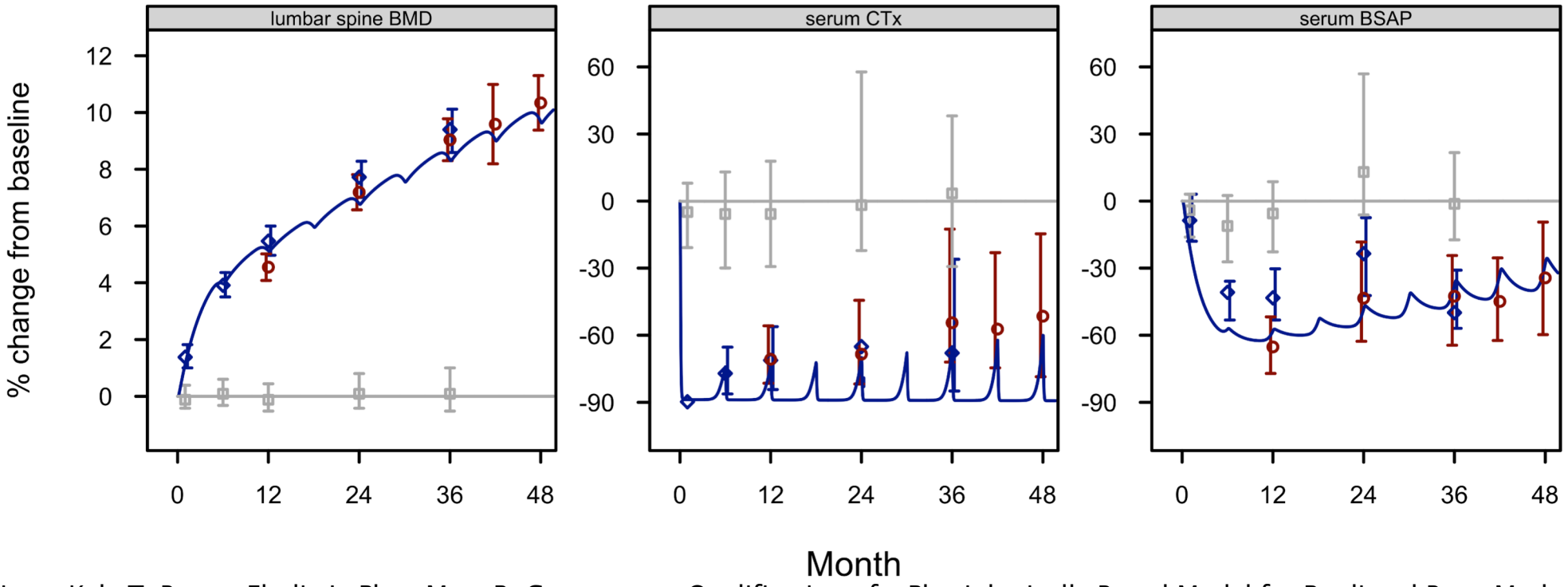
Model Evaluation Are the results reproducible?

SP "middle-out"/ up – Use the model to extend to measured response (BMD)

Denosumab: RANKL inhibition → Bone Markers → BMD Change

Observed (symbols) and simulated (lines) BMD, CTx, and BSAP during during treatment with 60mg Q6M denosumab for 4 years. Observed values from denosumab treatment groups: NCT00089791 (FREEDOM, blue symbols) and NCT00043186 (red symbols); and placebo treatment group: NCT00089791 (grey symbols).



Matthew M. Riggs, Kyle T. Baron, Elodie L. Plan, Marc R. Gastonguay. Qualification of a Physiologically-Based Model for Predicted Bone Marker and Bone Mineral Density Changes Associated with Denosumab Treatment. Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Minneapolis, MN; October 14, 2012 (Abstract# SU0363). Available at: http://metrumrg.com/index.php/publications

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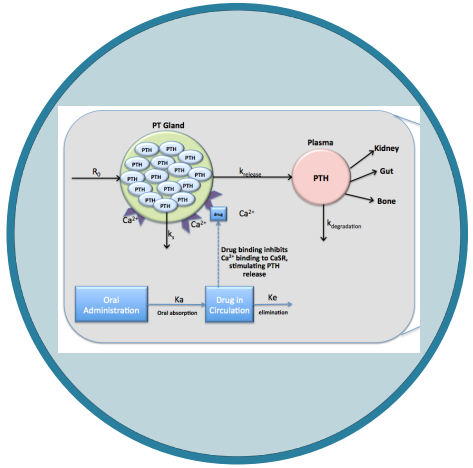
Model Evaluation PTH short-term time scale, long-term effect

Time, it's all about relativity



Calcilytic

Translational, clinical, literature data

Threshold / Maximum Release of PTH from PT gland: ceiling effect for BMD response well below teriparatide clinical data

Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Baltimore, MD; October 6, 2013 (Abstract# SU0407)

PTH-Ca Effects from Ca Sensing Receptor Inhibition

Model-Based Decision Support

- Use model-based approach to quantify the physiologic response to calcilytics to support development of DS-9194b, an orally administered investigational calcilytic
- Develop target criteria for PTH response (extent and duration) for first-in-human clinical study of an investigational drug (DS-9194b)
- Assess maximal PTH response and effects of urine Ca excretion using DS-9194b first-in-human clinical data; support development criteria with expectations for maximal BMD changes achievable through CaSR antagonism

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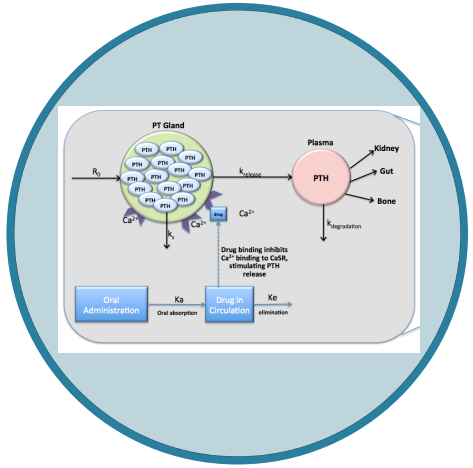

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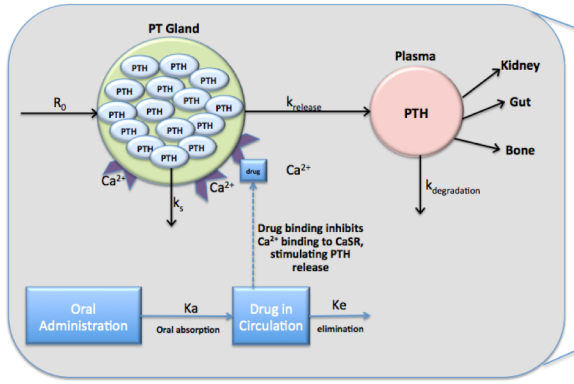

Figure 3: *Model of PTH pool within PT gland: PTH release stimulated by CaSR antagonist drug concentration.*

Equations related to PTH release

$$\frac{d}{dt}PREPTH = R_0 - k_s \cdot PREPTH - k_{release} \cdot PREPTH \cdot INH$$

$$\frac{d}{dt}PTH = k_{release} \cdot PREPTH \cdot INH - PTH \cdot k_{deg}$$

$$INH = 1 - (I_{CA} \cdot (1 - I_{DRUG}))$$

$$I_{CA} = \frac{CA^{\gamma_1}}{EC_{50,CA}^{\gamma_1} + CA^{\gamma_1}} \qquad I_{DRUG} = \frac{DRUG^{\gamma_2}}{EC_{50,DRUG}^{\gamma_2} + DRUG^{\gamma_2}}$$

$$R_0 = PREPTH_{ss} \cdot k_s + PTH_{ss} \cdot k_{deg}$$

Equations related to renal Ca2+ handling

$$REABS_{active} = \frac{Reabs_{max} \cdot CA}{Reabs_{50} + CA} \cdot PTH_{effect} \cdot RCA$$

$$\frac{d}{dt}RCA_1 = ktr \cdot \left[1 + \frac{SMAX \cdot DRUG}{EC_{50,rca} + DRUG}\right] - ktr \cdot RCA_1 \qquad ktr = \frac{n+1}{MTT} \qquad n = 8$$

$$\frac{d}{dt}RCA_m = ktr \cdot [RCA_{(m-1)} - RCA_m] \qquad m = 2,3,4,5,6,7,8$$

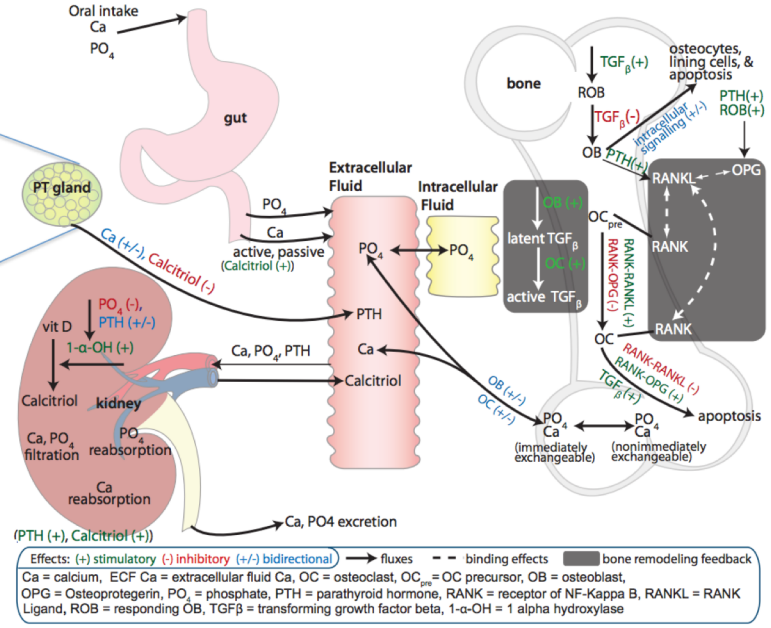

Figure 4: *Schematic of physiologically-based, multiscale systems pharmacology model; modified from figure 1 of Peterson and Riggs, 2010.* [1]

$$RCA1,ss = RCA2,ss = \ldots = RCAn,ss = 1$$

$$\text{with :} \quad kin = ktr \cdot \left[1 + \frac{SMAX \cdot DRUG}{EC_{50,rca} + DRUG}\right]$$

Figure 5: *System of transit compartments allowing for delay in development of DS-9194b effect on renal Ca^{2+} reabsorption. In the final model, n=8.*

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Model Evaluation PTH short-term time scale, long-term effect

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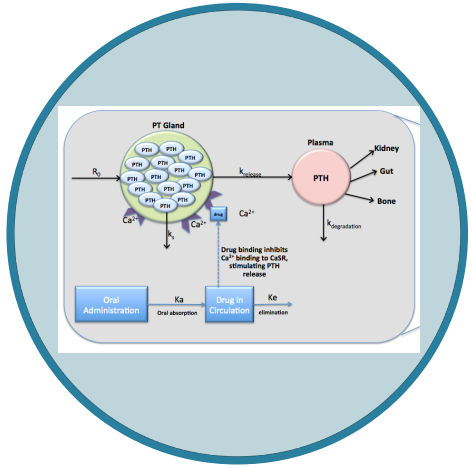

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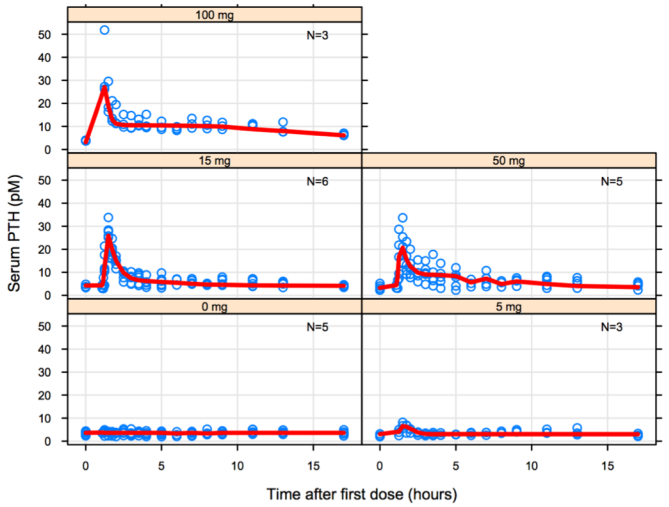
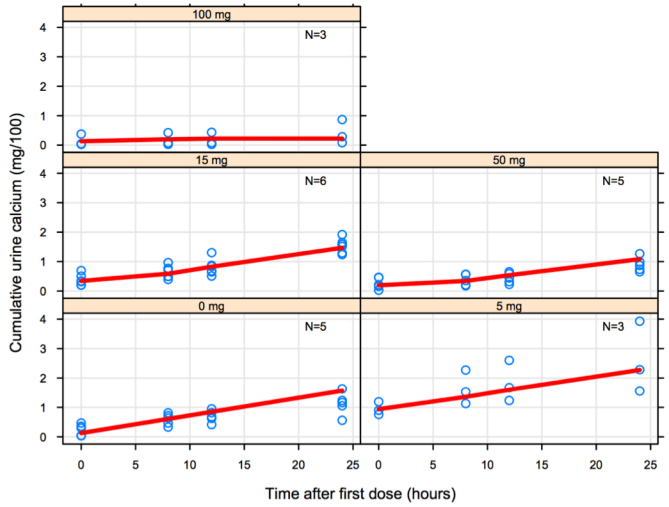
RESULTS – MSPM PREDICTION OF PTH RESPONSE

Quantitative, physiologically-based explanation of observed PTH response to CaSR antagonism:

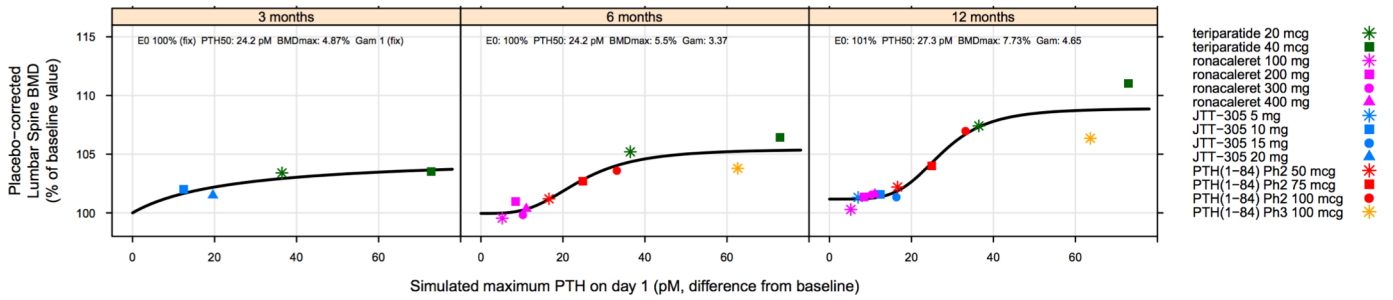


RESULTS – PTH EFFECT ON CALCIUM IN URINE (UCA)

MSPM also provides explanation of observed reduction in Ca^{2+} excretion due to hypothesized direct CaSR action in the kidney:



RESULTS – PTH vs. BMD: Maximal PTH predicted 3-, 6- and 12-month lumbar spine BMD



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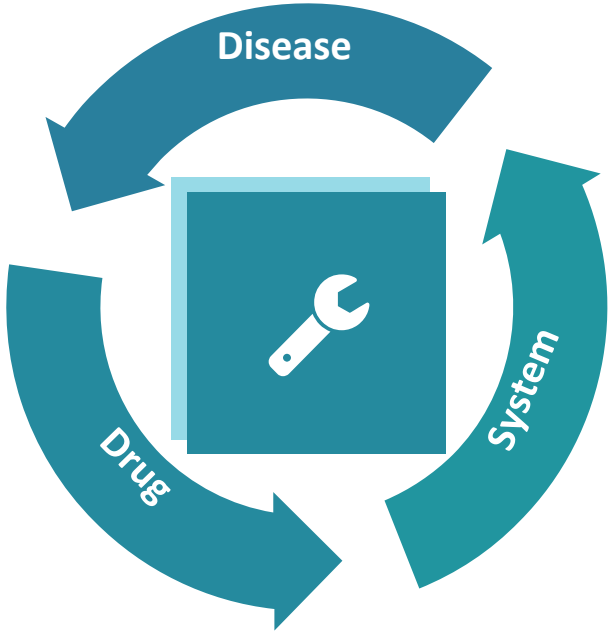
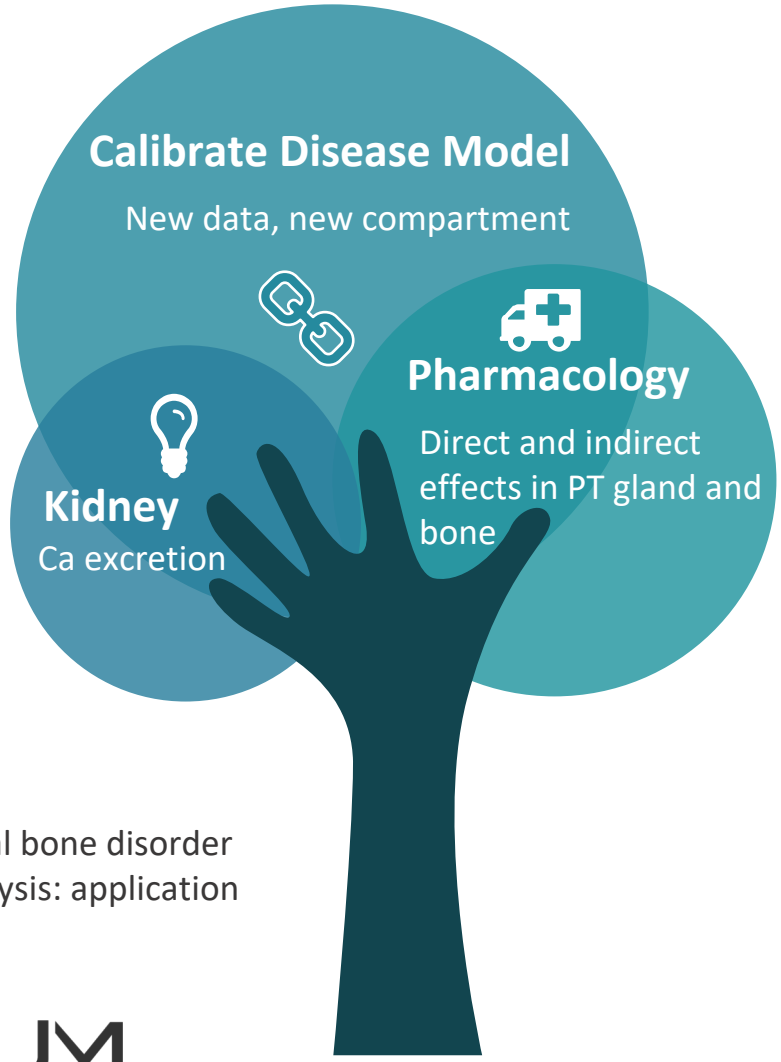
Model Evaluation Integrate System, Disease, Drug

Start with a concept, add clinical data, watch it grow.

Chronic Kidney Disease-Mineral Bone Disorder





Riggs MM, Baron KT, Melhelm M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. ACoP9 Abstract #T-078.

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Model Evaluation Integrate System, Disease, Drug

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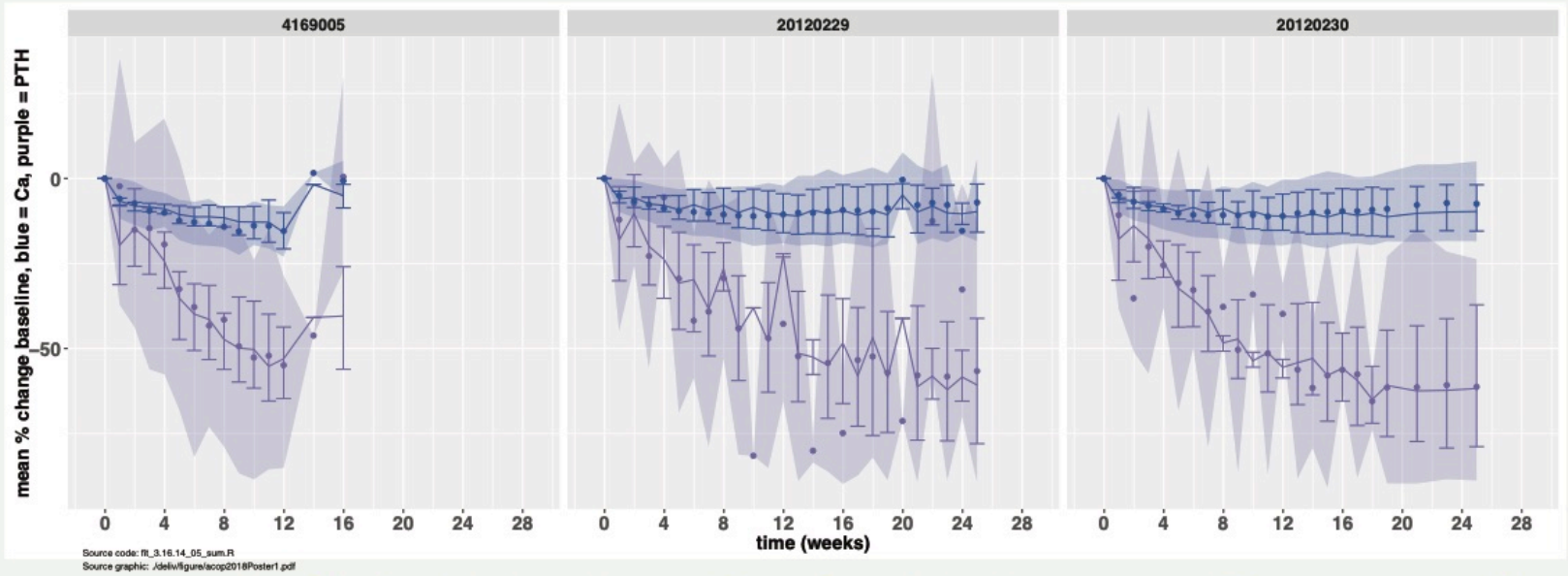
Chronic Kidney Disease-Mineral Bone Disorder

Long-Term Predictive Checks



Despite continued decline in PTH (e.g., beyond weeks 4-6), feedback controls lead to leveling and partial rebound in Ca.

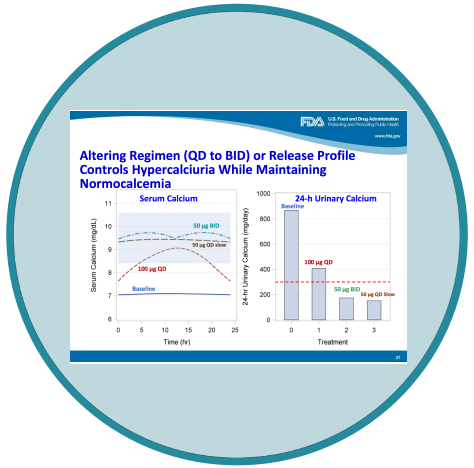
Figure 2: *Predictive check: change from baseline (percentage) for serum calcium (blue) and PTH (purple)*

Phase 3 Study 20120229 was included as external validation. Observed data: solid circle (mean) and 10th - 90th percentile range (shaded region); Simulated data: mean (solid line) and 10th - 90th percentile range (error bars).

Riggs MM, Baron KT, Melhelm M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. ACoP9 Abstract #T-078.

Model Evaluation First, Understand the Question

Open science opens doors



PTH for Hypoparathyroidism

Clinical data

FDA suggested BID or sustained release likely to retain efficacy while minimizing risk of hypercalciuria

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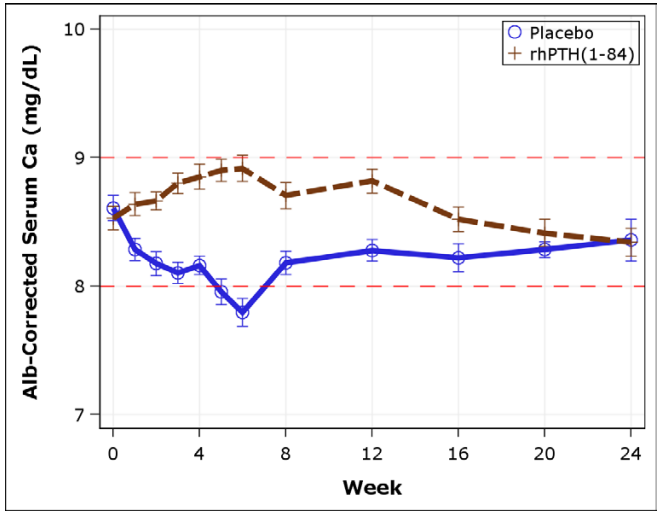
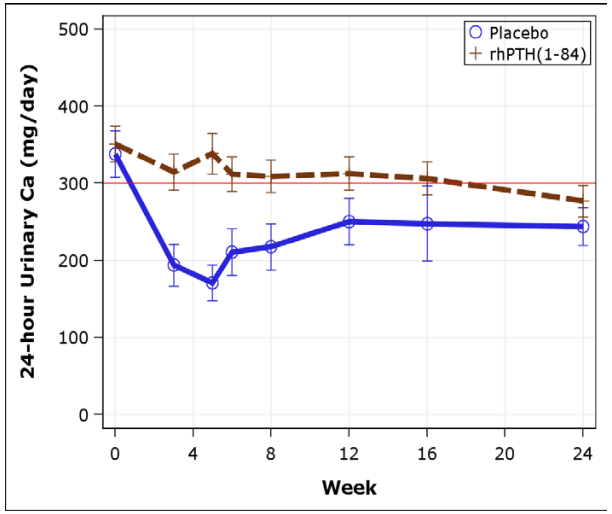
Control on 24-hour Urinary Calcium was Not Apparent with Natpara in the Registration Trial (CL1-11-040)

Mean (±SE) Serum Calcium



Mean (±SE) 24-hr Urinary Calcium



2

Presented at FDA September 12, 2014 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (UCM413617) by Manoj Khurana, PhD Immo Zadezensky, PhD Nitin Mehrotra, PhD

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Model Evaluation First, Understand the Question

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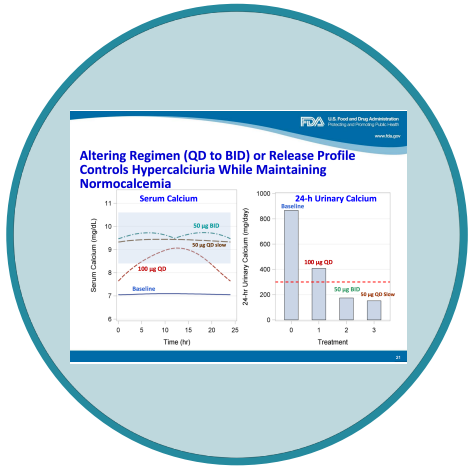

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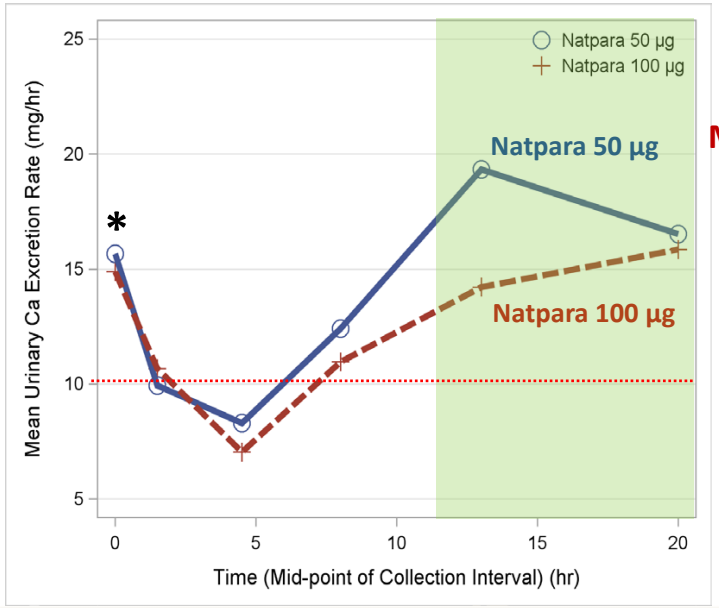
Reduction in Urinary Calcium Excretion is Short-lived

C09-002 Study – Natpara Pharmacodynamics: Urinary Calcium



Modest ↓24-h Ca excretion:

50 µg – 13%

100 µg – 23%

*** Day -1, 16-24h data**

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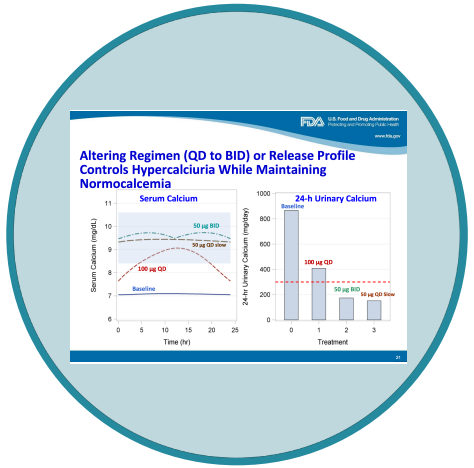
Model Evaluation @ Level Needed to Support Question

Open science opens doors



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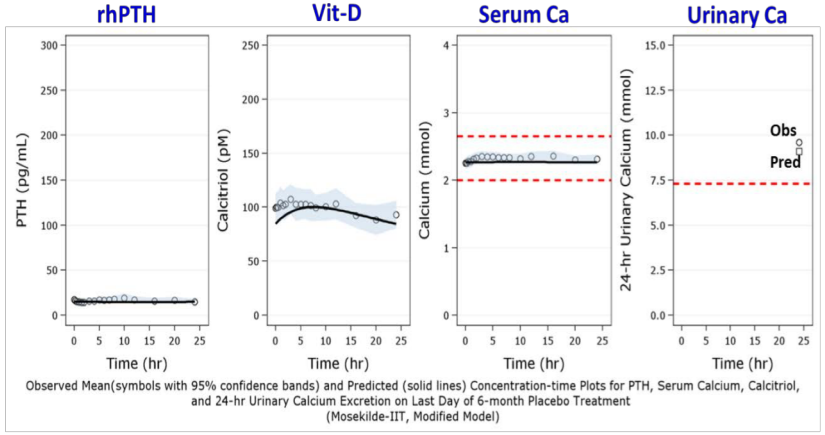
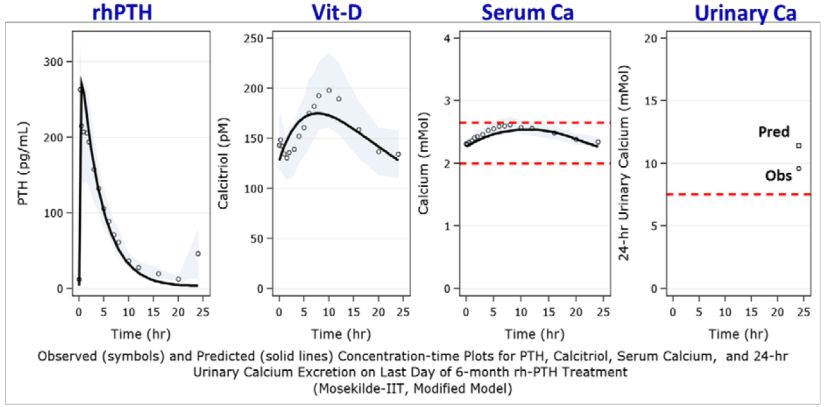


Observed Mean(symbols with 95% confidence bands) and Predicted (solid lines) Concentration-time Plots for PTH, Serum Calcium, Calcitriol, and 24-hr Urinary Calcium Excretion on Last Day of 6-month Placebo Treatment (Mosekilde-IIT, Modified Model)

Figure 16 **Evaluation of model – model reasonably predicts the observed PK and PD data for placebo treatment in Mosekilde-IIT PKPD study. "Obs" implies Observed and "Pred" implies Predicted.**



Observed (symbols) and Predicted (solid lines) Concentration-time Plots for PTH, Calcitriol, Serum Calcium, and 24-hr Urinary Calcium Excretion on Last Day of 6-month rh-PTH Treatment (Mosekilde-IIT, Modified Model)

Figure 17 **Evaluation of model – model reasonably predicts the observed PK and PD data for rhPTH[1-84] treatment in Mosekilde-IIT PKPD study. "Obs" implies Observed and "Pred" implies Predicted.**

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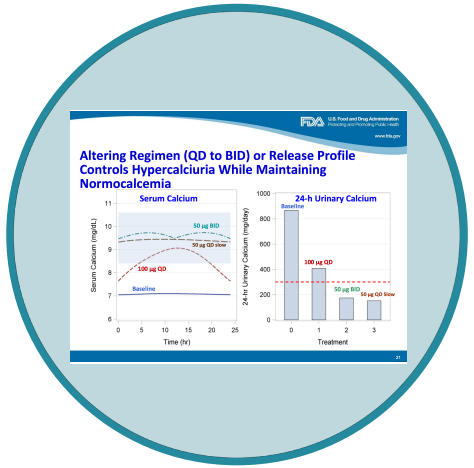
Model Evaluation With added confidence, investigate the question

Open science opens doors



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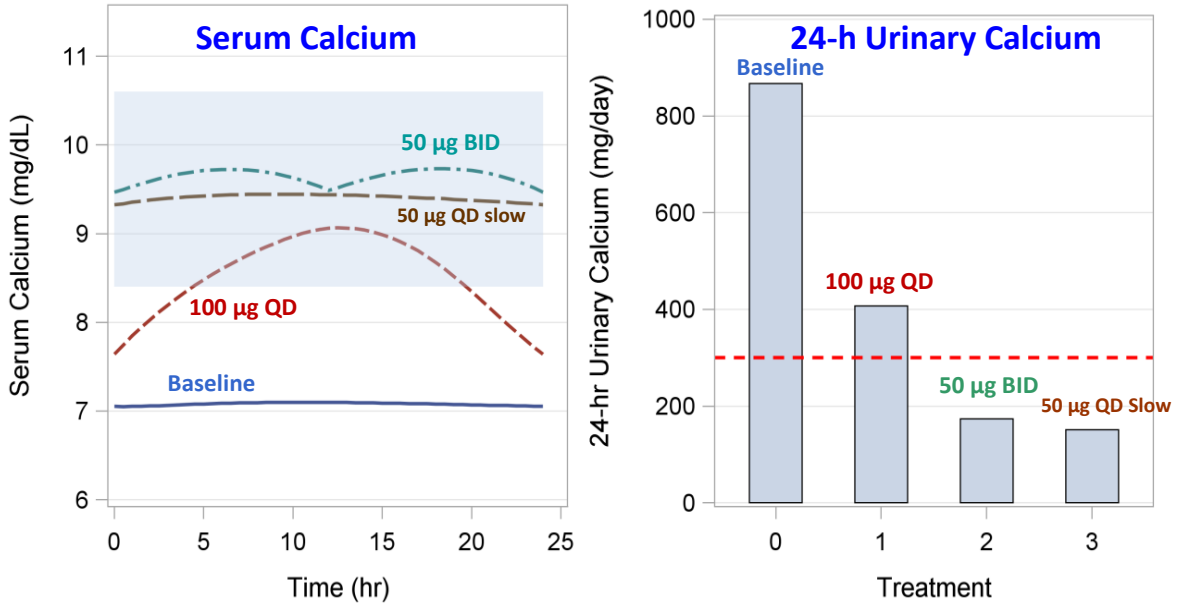
Altering Regimen (QD to BID) or Release Profile Controls Hypercalciuria While Maintaining Normocalcemia



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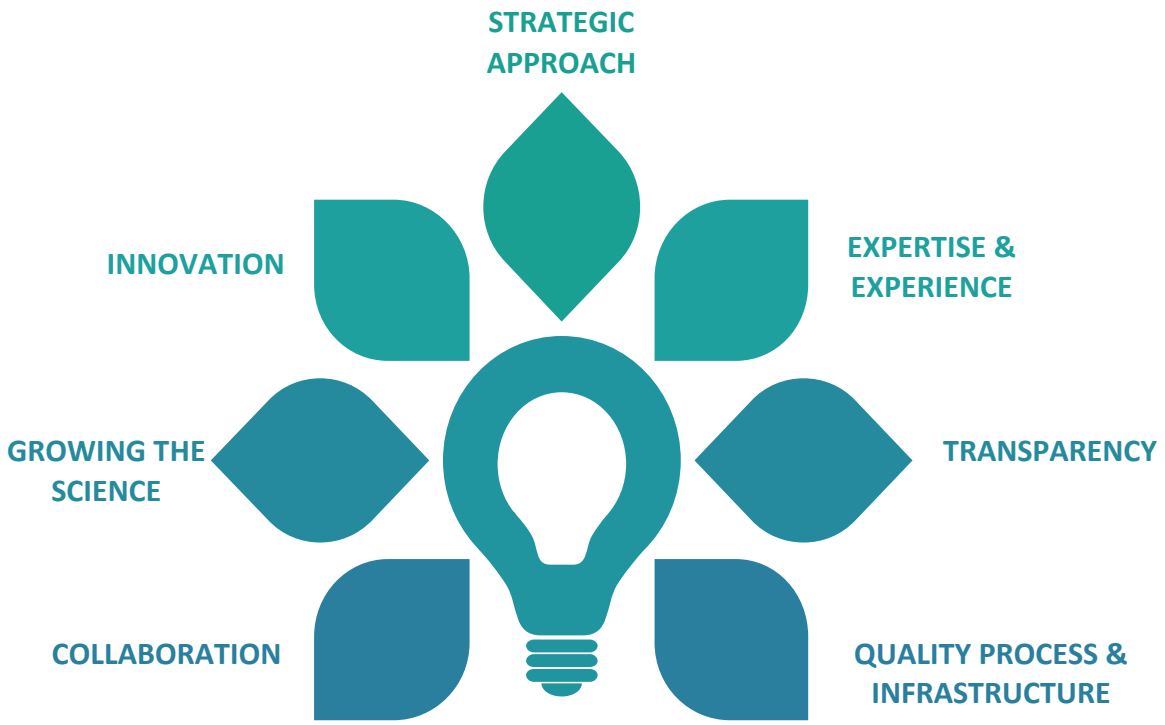
Model Evaluation An ODE to Open Science

Without open science , none of this would have been possible… be open, make it possible!!

https://github.com/metrumresearchgroup/OpenBoneMin



https://github.com/metrumresearchgroup/OpenBoneMin

README.md

About

A multiscale systems model of bone health and mineral homeostasis. Please see the wiki page for more information on this project.

Community contributions to this project are included here.

Documentation

- Documentation here

Installation

Installation of `OpenBoneMin` requires the `devtools` package

```
if(!require("devtools")) install.packages("devtools")
```

Use the `install_github` function inside `devtools` to install the `OpenBoneMin` package from GitHub to your local machine

```
devtools::install_github("metrumresearchgroup/OpenBoneMin")
```

You can test the installation by trying an example

```
example("sim_teri", package = "OpenBoneMin")
```

Usage

- Simulate teriparatide data

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iPSP An ODE to Open Science

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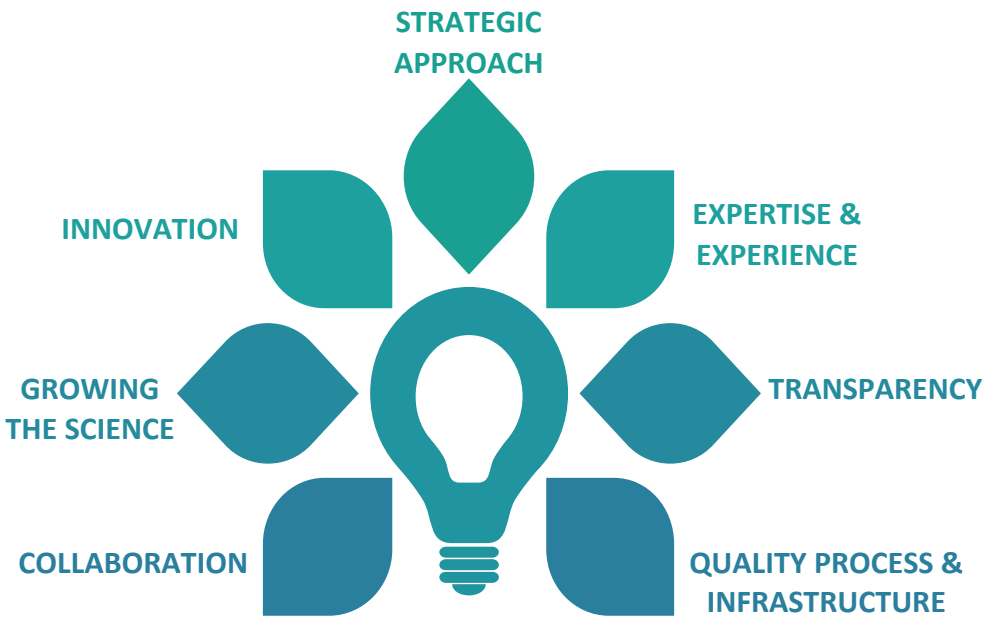

19 lines (9 sloc) | 434 Bytes — Raw | Blame | History

Community Contributions

This folder contains community contributions to the OpenBoneMin repo.

Contents

lump

Supplemenary code from:

Hasegawa C, Duffull SB. Automated Scale Reduction of Nonlinear QSP Models With an Illustrative Application to a Bone Biology System. CPT Pharmacometrics Syst Pharmacol. 2018 Jul 24. doi: 10.1002/psp4.12324. PMID 30043496

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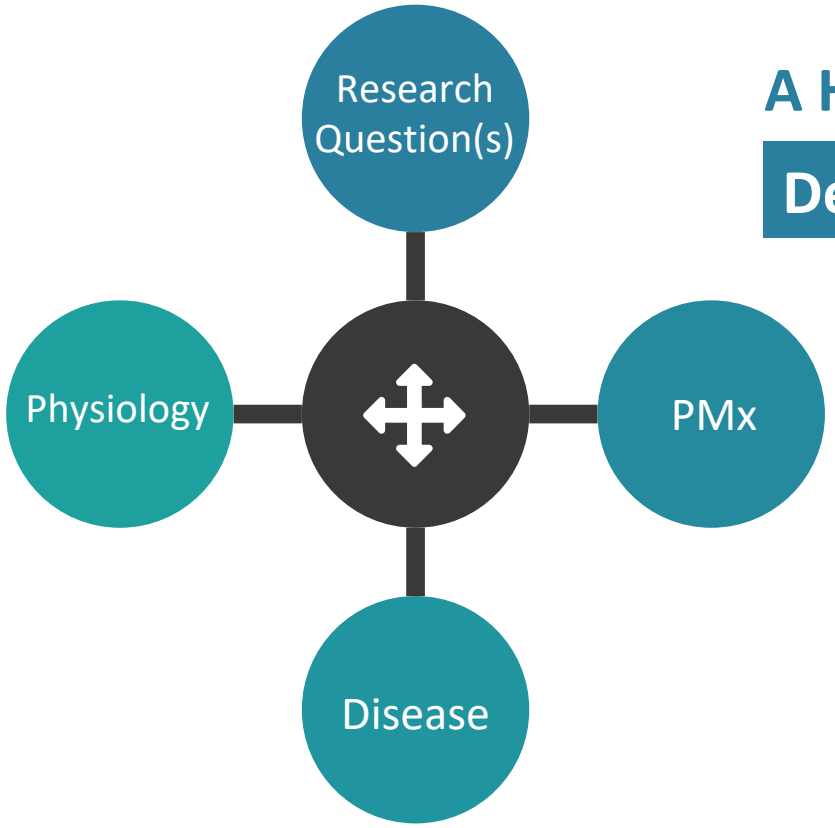
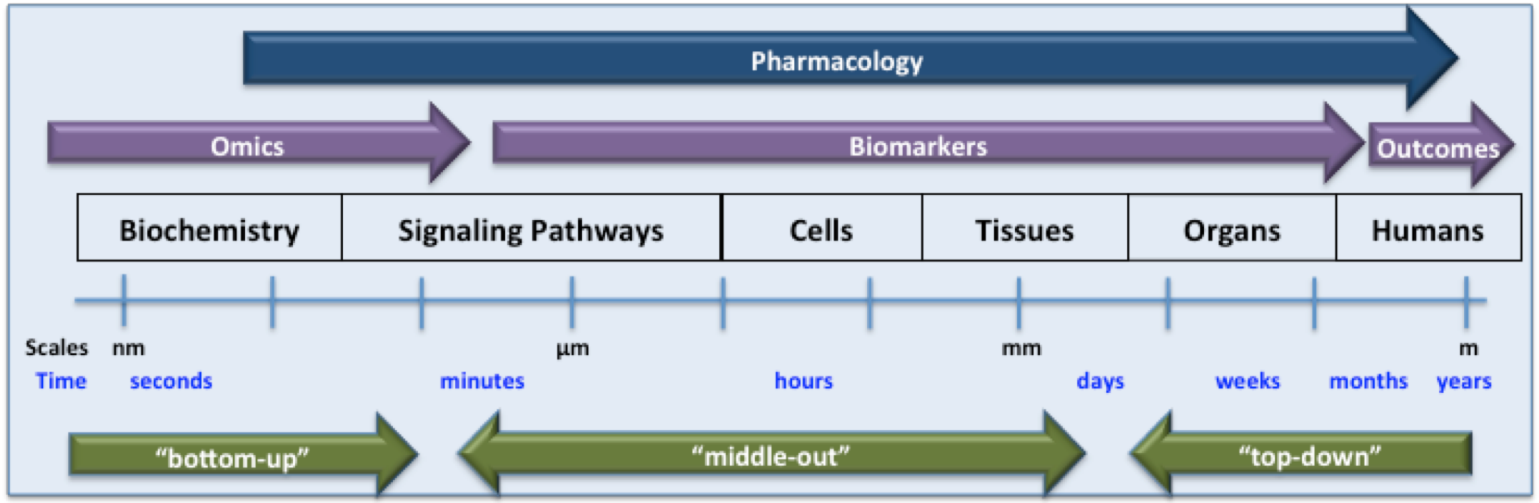
Systems Pharmacology: Mineral and Bone Health

Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63



A History of Model Evaluations

Define Needs: Time, Space, Precision



From Figure 1 of Riggs M. Multiscale Systems Models as a Knowledge Bridge Between Biology, Physiology and Pharmacology. *AAPS Newsmagazine (December, 2011)*

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Acknowledgements Collaborating Authors/Researchers

It has been my privilege to work with so many brilliant researchers

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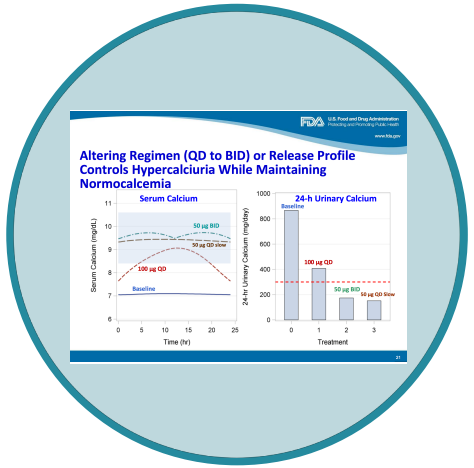
Model Evaluation First, Understand the Question

Open science opens doors



PTH for Hypoparathyroidism

Clinical data

FDA suggested BID or sustained release likely to retain efficacy while minimizing risk of hypercalciuria

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Outline

- Highlight important mechanistic aspects of PTH
- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of Natpara in patients with hypoparathyroidism
  - ➢ Relevance of PD effects on urinary calcium excretion to clinical data
- Can we obtain better control on hypercalciuria?
  - ➢ Is different dosing regimen a solution?
- Summary

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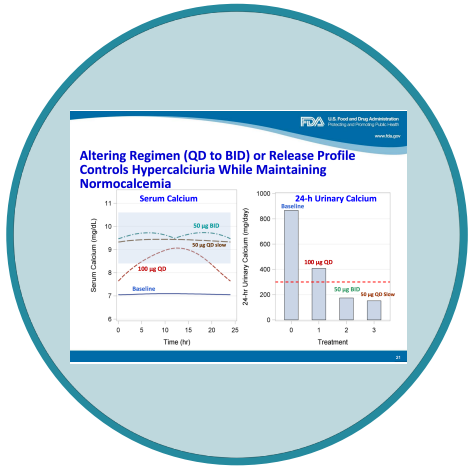
Model Evaluation Using Open, Public Source Model

Open science opens doors



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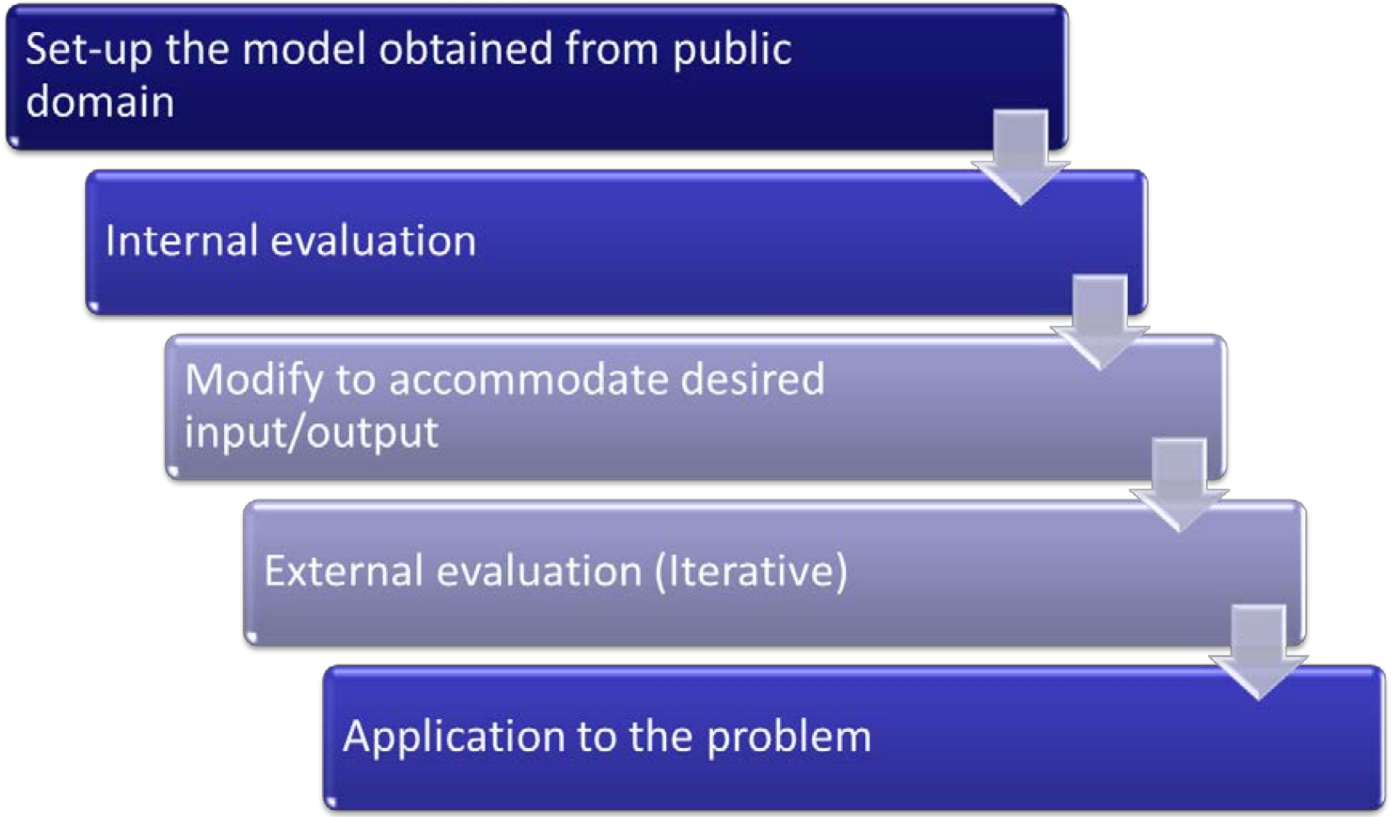

Figure 14 Schematic of the fit for purpose model validation strategy

Simulation for Hypoparathyroidism state:

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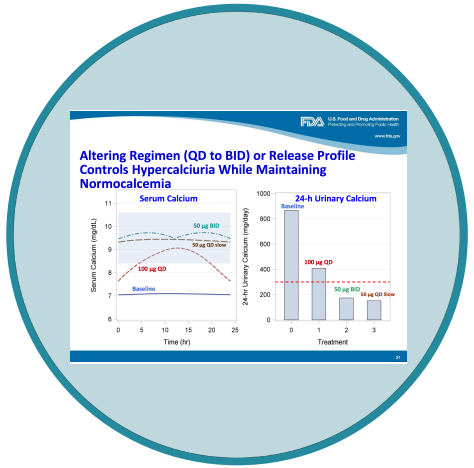

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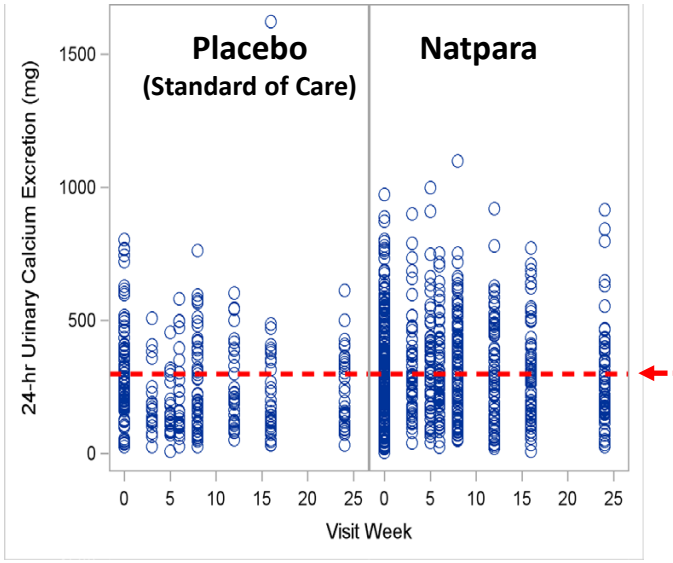
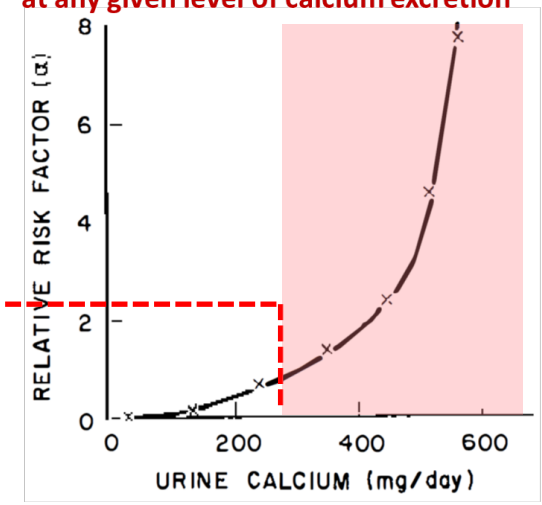
Control on 24-hour Urinary Calcium was Not Apparent with Natpara – Long-term Risk?



Relative risk of calcium stone formation at any given level of calcium excretion*



*Andrew F. Stewart and Arthur E. Broadus. Ann Rev Med. 32: 457-73 (1981).

3

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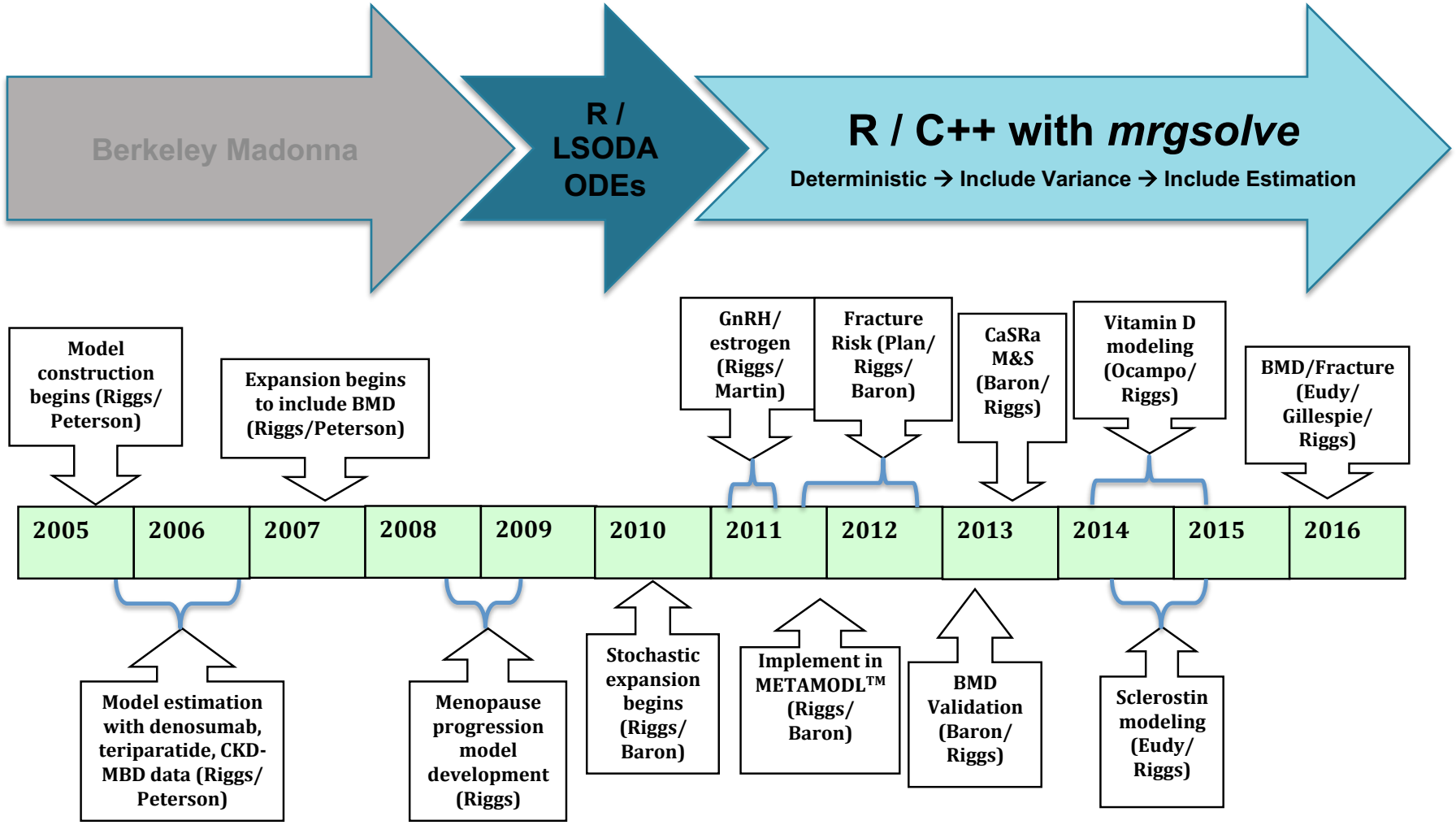
Time Scale: An Evolution in the Model, Too!



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iPSP: Integrated Outputs

Balancing act: minimized risk for AE (bone loss) while providing therapeutic response

Endometriosis: GnRH modulation → Estrogen Loss

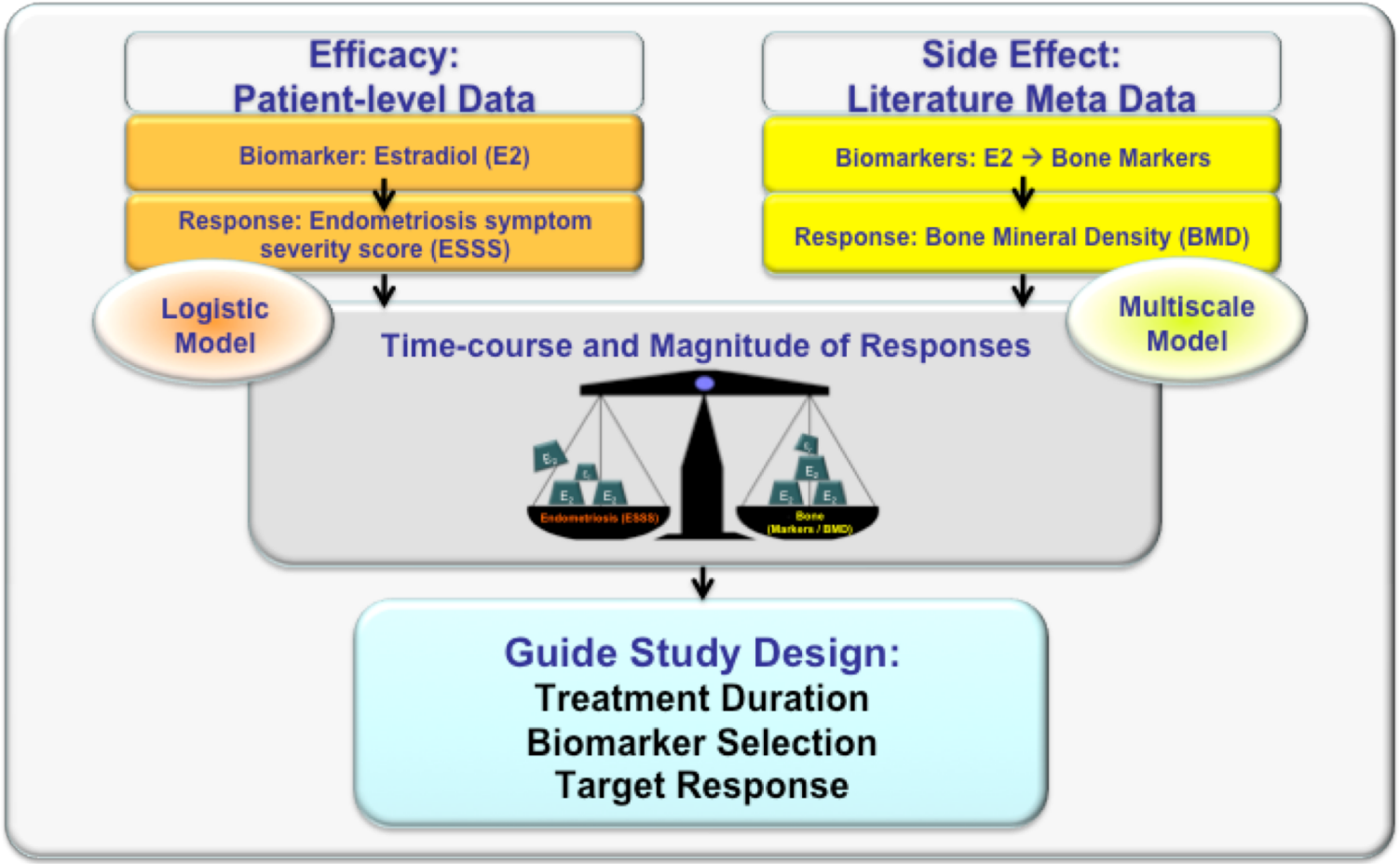

Figure 1 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f1.html#figure-title

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iPSP: Integrated Outputs

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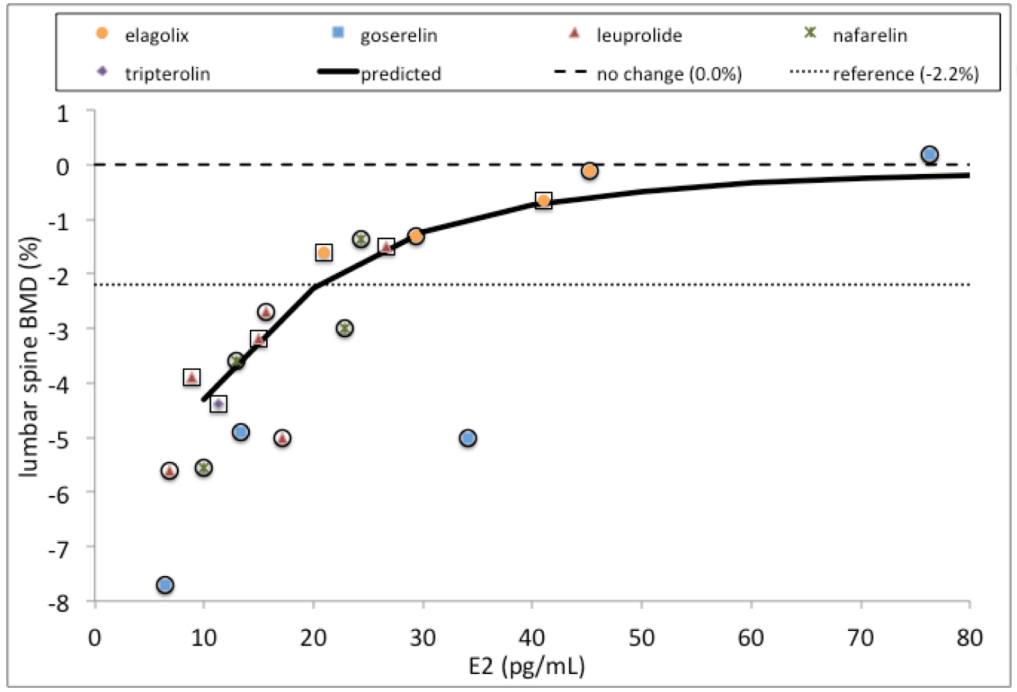
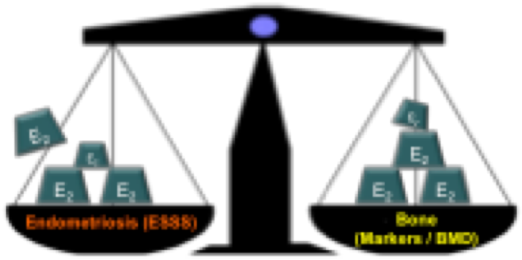
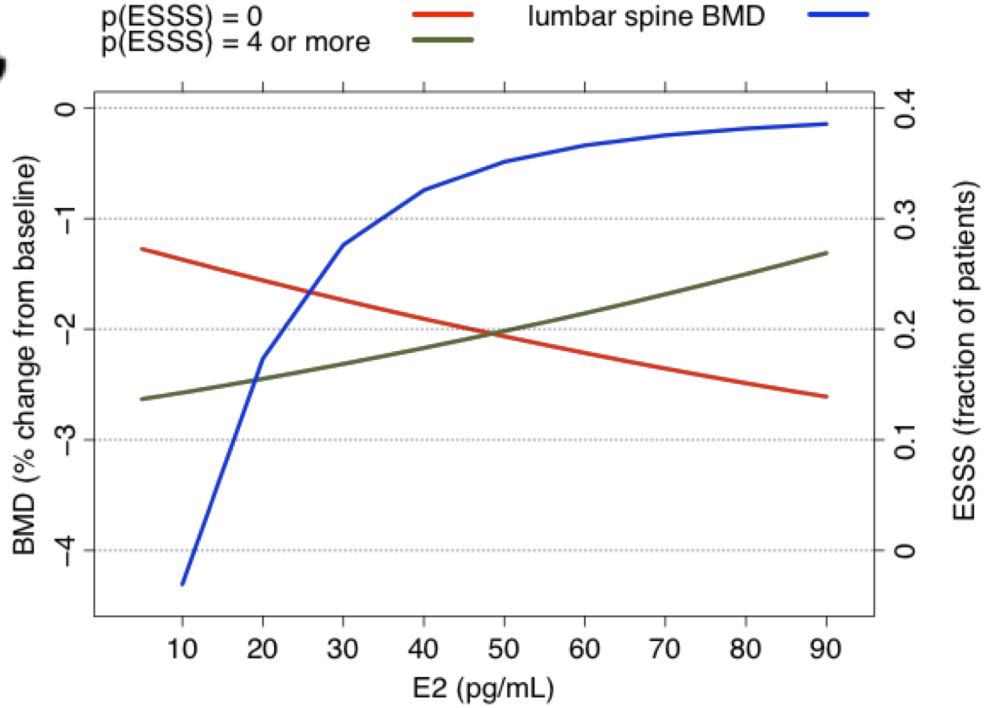
Endometriosis: GnRH modulation → Estrogen Loss

External Evaluation of BMD Response





Overlay of BMD and Symptom Severity



Figs 4, 6 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f1.html#figure-title

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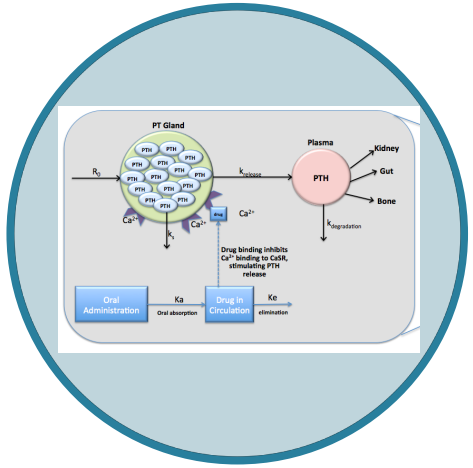
iPSP Same SP Model, More iPSP Examples

Open science opens doors

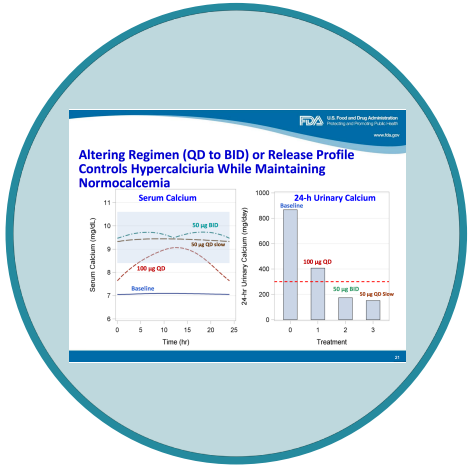


Calcilytic

Translational, clinical, literature data

Threshold / Maximum Release of PTH from PT gland: ceiling effect for BMD response well below teriparatide clinical data

Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Baltimore, MD; October 6, 2013 (Abstract# SU0407)



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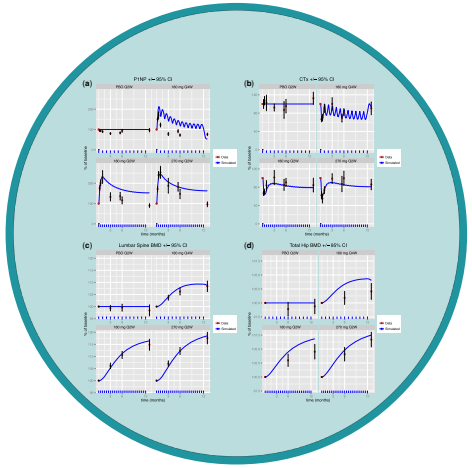
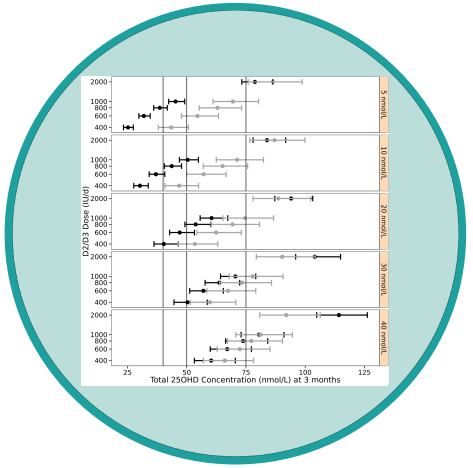


Sclerostin Inhibition

Clinical literature data

Explored dose and dosing interval responses and provided descriptive responses of bone markers changes over time

Eudy R, Gastonguay M, Baron K, and Riggs M. Connecting the dots. CPT: Pharmacometrics Syst Pharmacol, 2015



Vitamin D

Clinical literature data

Included pharmacokinetic conversion of Vitamin D in liver (calcidiol) and kidney (calitriol) with link into system model to evaluate dose-response on Ca and BMD response

Ocampo-Pelland, Gastonguay, and Riggs. J Pharmacokinet Pharmacodyn, 44(4):375–388, Aug 2017.

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