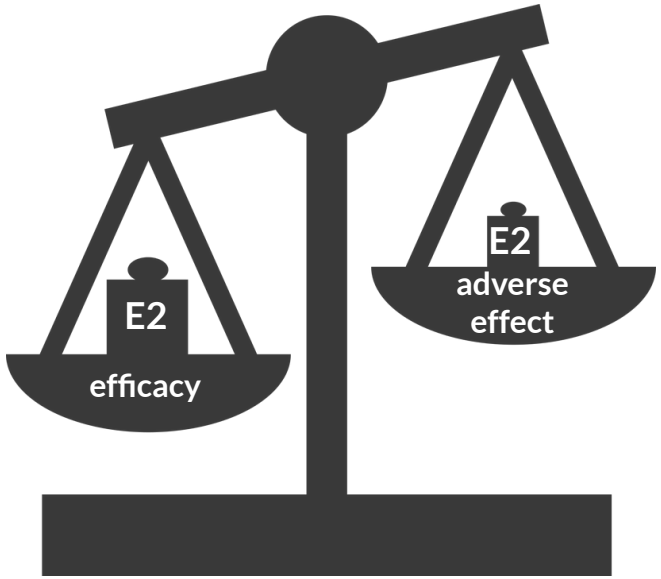
Model-based Dose Selection for a GnRH Receptor Antagonist in Endometriosis and Uterine Fibroids (UF) to Reduce Symptoms While Preventing Lumbar Spine Bone Mineral Density (BMD) Loss



Kyle Baron[1], Oliver Pohl[2], Matthew Riggs[1], Jonathan French[1], Jean-Pierre Gotteland[2], Ramon Garcia[1]

[1]Metrum Research Group, [2]ObsEva SA

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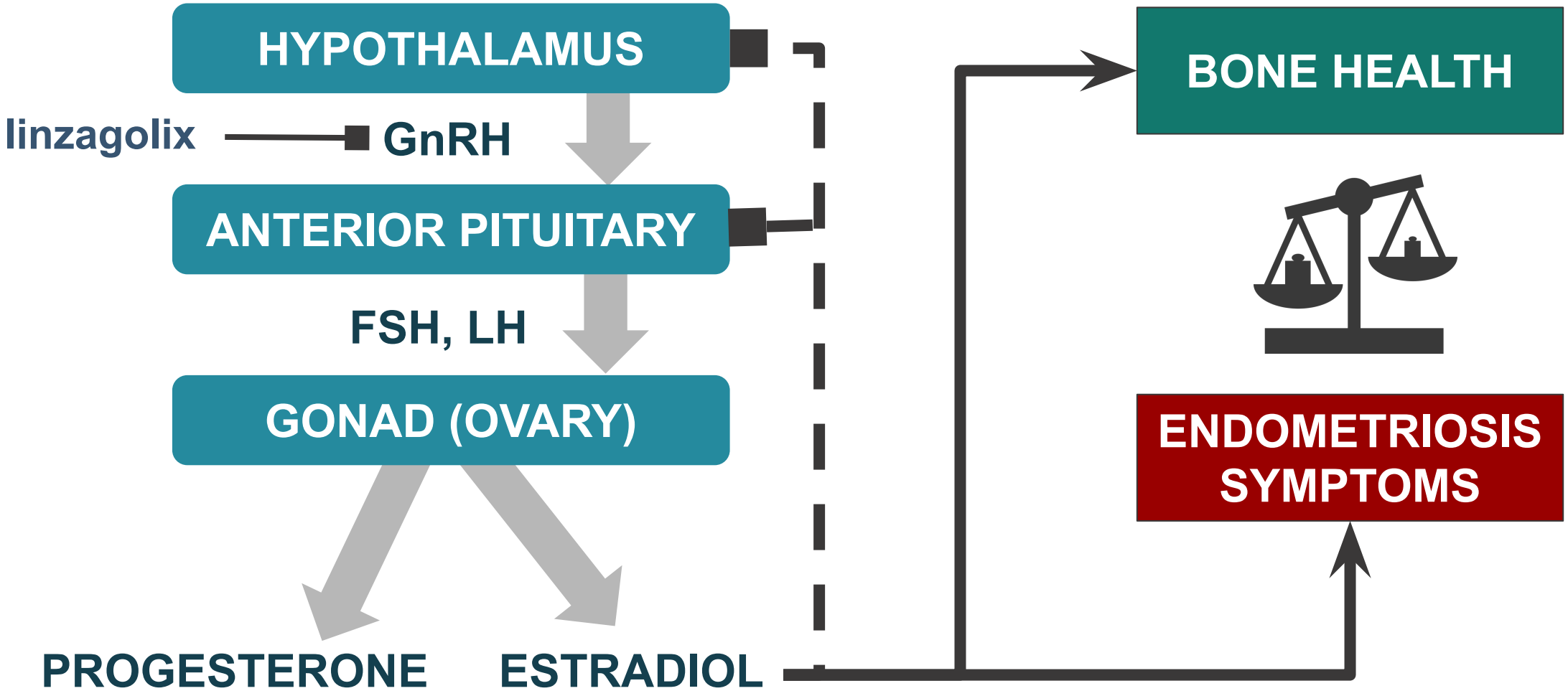
HPG Axis, Endometriosis, and Bone Health



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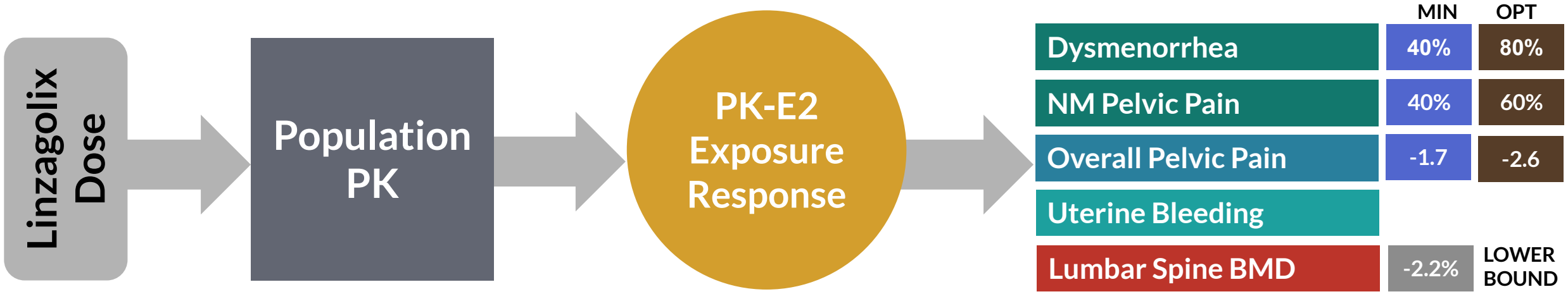
Decision Informatics Model-Based Workflow



dosing regimen

once daily
25 to 200 mg

daily exposure

metric
24-hr AUC

decrease estradiol

confirm target
20-50 pg/mL

decrease pain bleeding — maximize

possible BMD losses — minimize

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PK and PK/PD Data Set

	PK	E2	NMPP VRS	DYS VRS	OPP NRS	UTERINE BLEEDING	LS BMD
Healthy Volunteers **MAD/SAD (C09070)** **PK/PD Trial 1 and 2 [1,2]**	✓	✓				✓ PK/PD Trials Only	
Patients **EDELWEISS** **Phase 2 Trial**	✓	✓	✓	✓	✓	✓	✓

- **Patients**: 25 - 200 mg QD x 24 w
- **Healthy Volunteers:** 100 - 200 mg QD x 42 - 70 d
- **SAD** 12.5 - 400 mg
- **MAD**: 100 - 400 QD x7d

- **E2**: modeling used sparse measurements
- **NMPP/DYS - VRS**: responder rate
- **OPP - NRS**: raw score, 0-10
- **Bleeding**: fraction of days / month
- **BMD**: lumbar spine

[1] Pohl O et al. Reproductive Sciences (in press)
[2] Pohl O et al. (2018) J Clin Endocrinol Metab. **PMID: 29216361**

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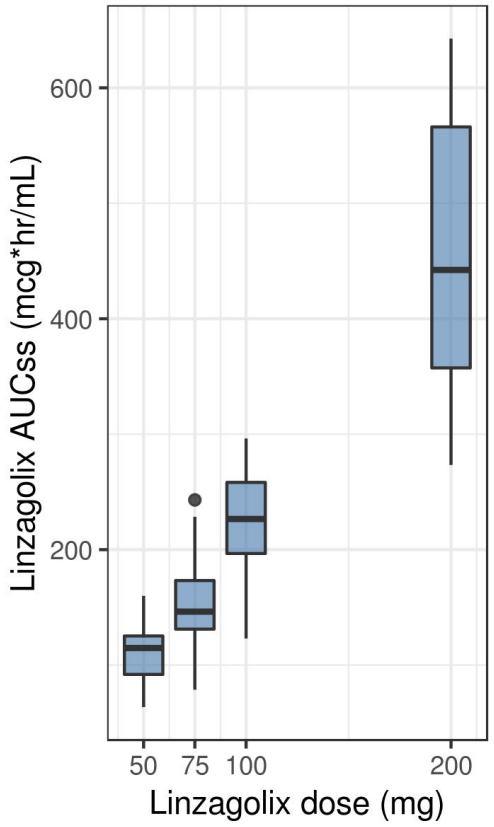
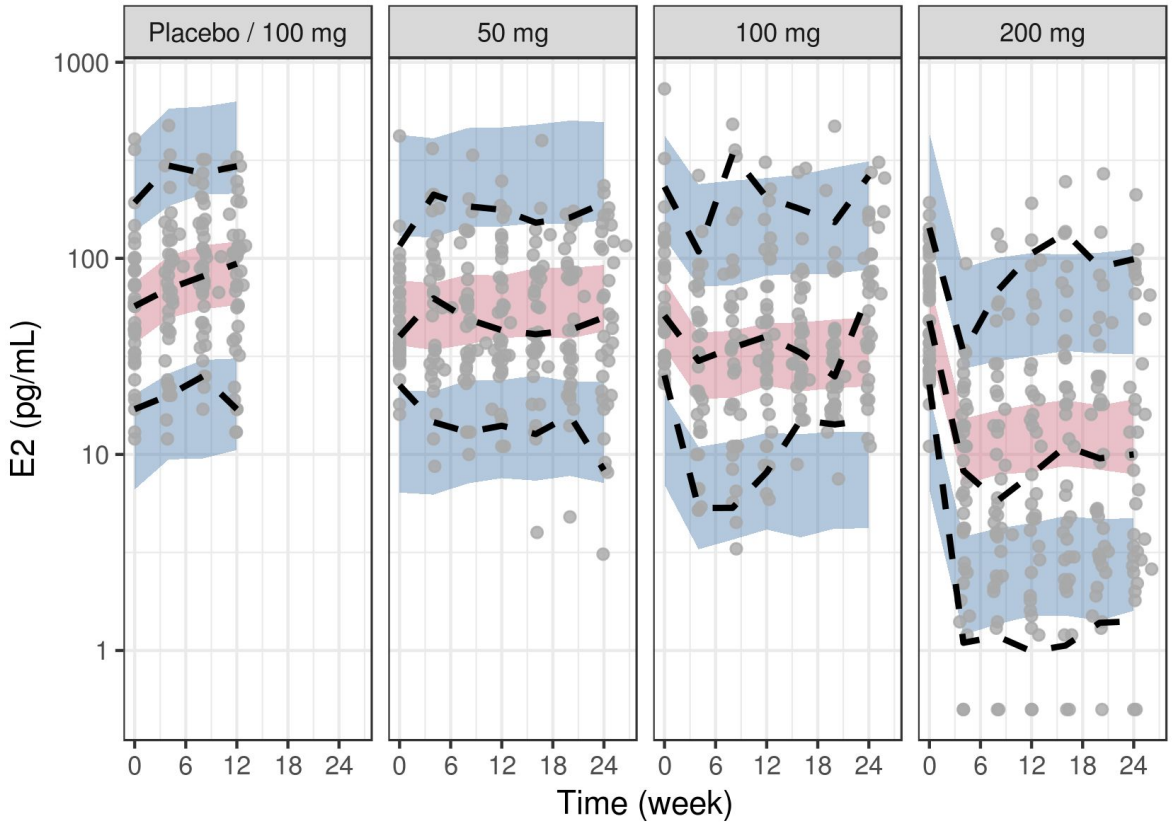
PK/PD Modeling PK and PK-E2

linzagolix dose → **linzagolix AUC** → **decrease estradiol**





Linzagolix PK

- 2-compartment, zero + first-order absorption
- fixed allometric scaling
- **CL: 0.422 L/hr** (58 kg)

PK-E2

- direct sigmoid Imax model
- exposure: daily AUC
- **AUC_{50}: 168 μg*hr/mL**

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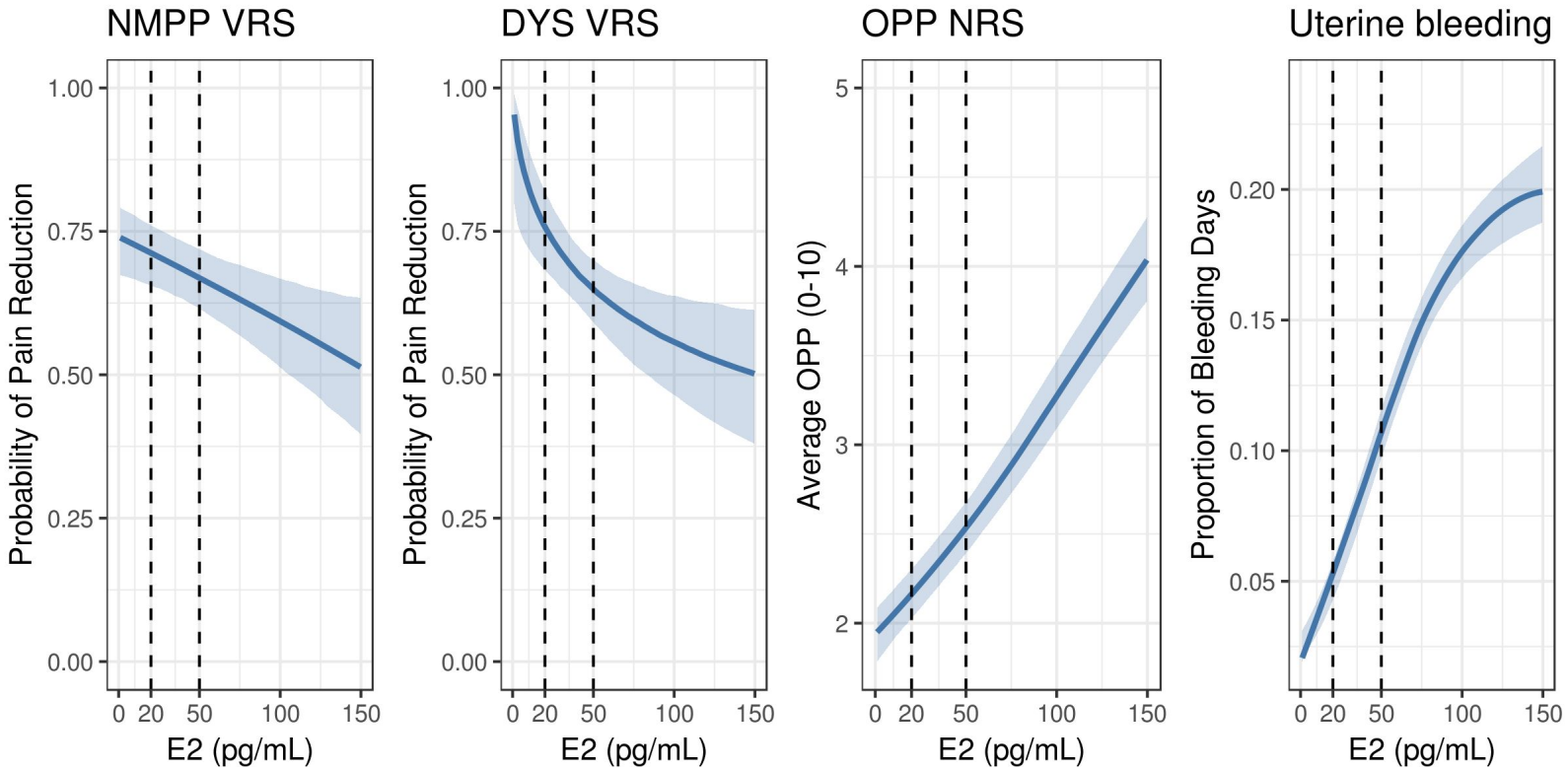
Efficacy OPP, NMPP, DYS, Uterine Bleeding

decrease estradiol ⇒ **reduce pain & bleeding**



Efficacy modeling

- Outcome average daily pain & bleeding per month at 6 months
- Model logistic & zero-inflated beta regression models for repeated measures
- Controlled for baseline pain / bleeding, race, weight, & health status

Lower E2 associated with

- Increased non-menstrual & dysmenorrhea **pain reduction**
- Decreased overall pelvic pain & % of bleeding days

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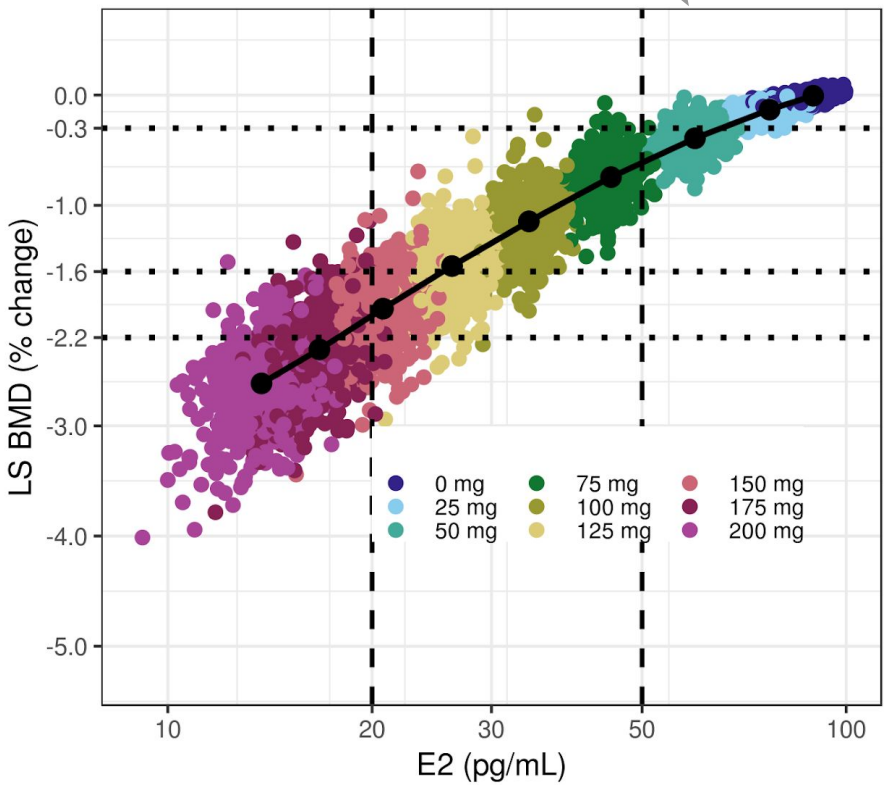
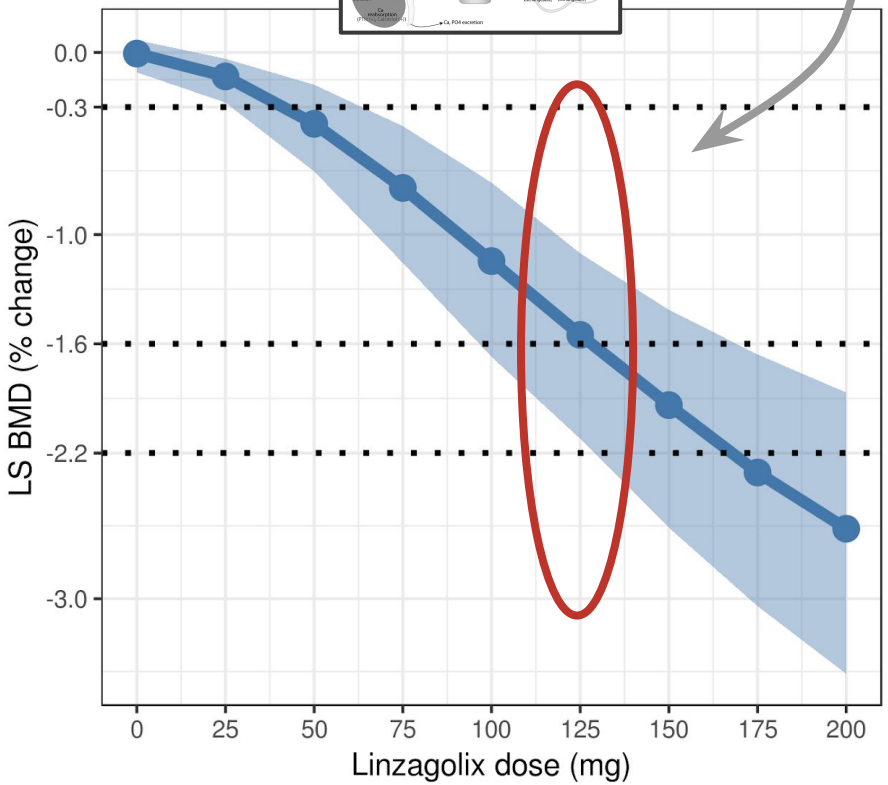
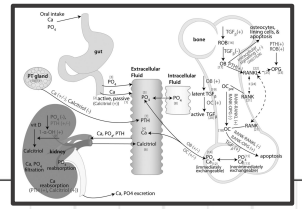
Linzagolix Doses to Control BMD Loss at 6 months

linzagolix dose → decrease estradiol → possible BMD losses → controlled BMD loss







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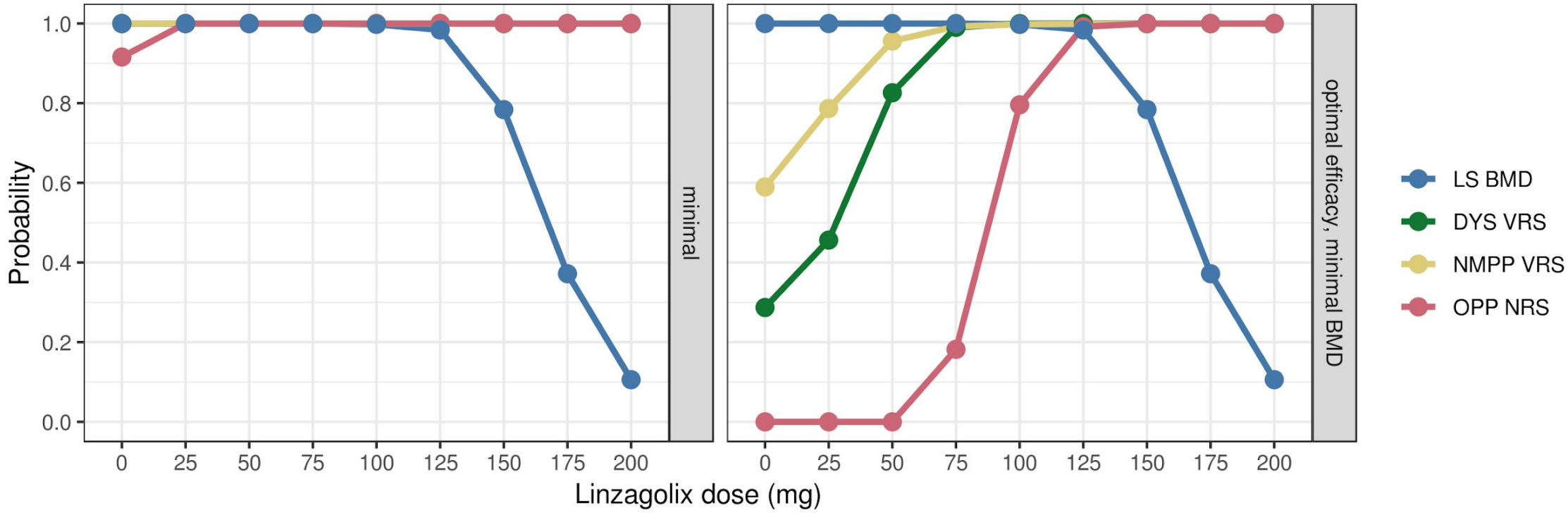
Riggs MM, et al. CPT PSP (2012)
PMID: 23887363

Dose Selection Balance Efficacy & Safety at 6 months

linzagolix dose ⇒ decrease pain bleeding ↓ ⚖ controlled BMD losses ⇔



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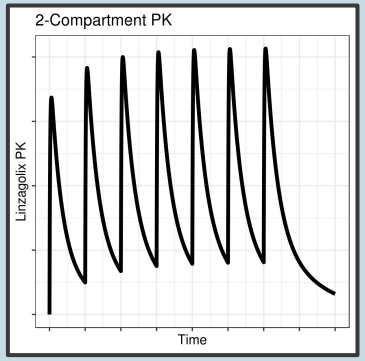
Model-Based Dose Selection for Phase 3 Trials

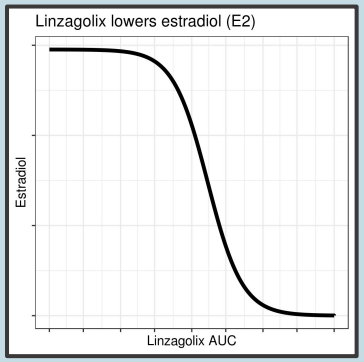
2-compartment PK, fixed allometric scaling

CL: 0.422 L/hr at 58 kg



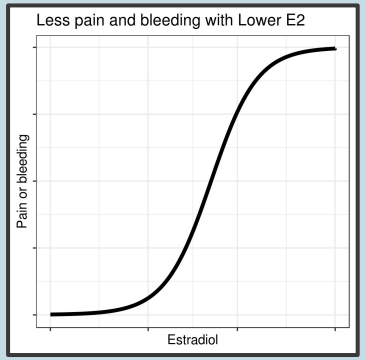
PK-E2 model - direct sigmoidal Imax model

AUC_{50}: 168 μg*hr/mL



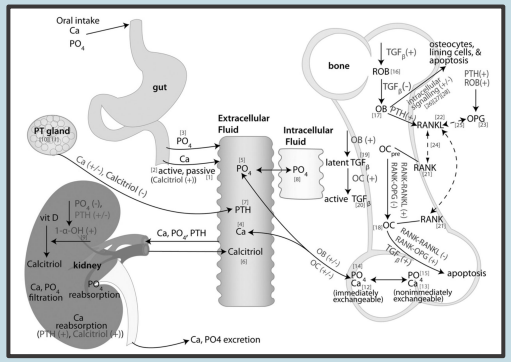
Optimal efficacy targets likely with doses ≥ 75 - 100 mg QD

Model: logistic and zero-inflated beta regression



Doses ≤ 125 mg QD with 90% CI lower bound not exceeding -2.2% Δ LS BMD at 24 weeks

Model: OpenBoneMin QSP



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24-hr AUC

decrease estradiol

target window
20-50 pg/mL

decrease pain bleeding

maximize

E2 in 20 - 50 pg/mL window a reasonable target

Doses for pivotal Phase 3 trials

- Endometriosis - 75 mg daily
- Uterine Fibroids - 100 mg daily

controlled BMD loss at week 24

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Thank You

- **E2 in 20 - 50 pg/mL window a reasonable target for balancing efficacy and safety**

- **Doses for pivotal Phase 3 trials**

Endometriosis	75 mg QD	EDELWEISS 2 & 3
Uterine Fibroids	100 mg QD	PRIMROSE 1 & 2

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