Clinical Pharmacokinetics

Quantitative Assessment of Elagolix Enzyme-Transporter Interplay and Drug-Drug Interaction Using Physiologically-Based Pharmacokinetics Modeling

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**Supplemental Table 1**: Demographic information of the population representative used for the simulations.

|                          |                |
|--------------------------|----------------|
| **Sex**                  | Male           |
| **Age (Years)**          | 20             |
| **Weight (kg)**          | 81             |
| **Height (cm)**          | 177            |
| **BSA (m²)**             | 1.98           |
| **BMI (kg/m²)**          | 25.9           |
| **Haematocrit (%)**      | 43.0           |
| **HSA (g/L)**            | 47.3           |
| **Serum Creatinine (µmol/L)** | 76.5       |
| **GFR (mL/min/1.73m²)**  | 136            |
| **Renal Function**       | 1.13           |
| **OATP1B1 Status**       | Extensive transporter |
| **CYP P450 Status**      | Extensive metabolizer |
### Supplemental Table 2: Simulation Design for PK and DDI studies

| Study                        | Drug               | Rout e | Dose | Time of Administration | Fasting/Fed | Duration | Simulation Population |
|-----------------------------|--------------------|--------|------|------------------------|-------------|----------|-----------------------|
| Multiple Ascending Dose     | Elagolix (Victim)  | PO     | 150 mg | QD for 21 days          | Fasting     | 23 days  | Population Representative |
| Multiple Ascending Dose     | Elagolix (Perpetrator) | PO     | 200 mg | BID for 21 days         | Fasting     | 23 days  | Population Representative |
| Rifampin DDI Study          | Elagolix (Victim)  | PO     | 150 mg | SD on Day 1 and Day 10 | Fasting     | 13 days  | Population Representative |
| Rifampin DDI Study          | Rifampin (Perpetrator) | PO     | 600 mg | QD 12 days              | Fasting     | 13 days  | Population Representative |
| Ketoconazole DDI Study      | Elagolix (Victim)  | PO     | 150 mg | SD on Day 4             | Fasting     | 8 days    | Population Representative |
| Ketoconazole DDI Study      | Ketoconazole (Perpetrator) | PO     | 400 mg | QD for 6 days           | Fasting     | 8 days    | Population Representative |
| Midazolam DDI Study         | Midazolam (Victim) | PO     | 5 mg  | SD Day 14               | Fasting     | 17 days  | Population Representative |
| Midazolam DDI Study         | Elagolix (Perpetrator) | PO     | 150 mg | QD for 16 days          | Fasting     | 17 days  | Population Representative |
| Digoxin DDI Study           | Digoxin (Victim)   | PO     | 0.5 mg | QD Day 1 and Day 10     | Fasting     | 13 days  | Population Representative |
| Digoxin DDI Study           | Elagolix (Perpetrator) | PO     | 200 mg | BID for 13 days         | Fasting     | 13 days  | Population Representative |
| Midazolam DDI Study         | Midazolam (Victim) | PO     | 5 mg  | SD Day 14               | Fasting     | 17 days  | Population Representative |
| Midazolam DDI Study         | Elagolix (Perpetrator) | PO     | 200 mg | BID for 16 days         | Fasting     | 17 days  | Population Representative |
| Digoxin DDI Study           | Digoxin (Victim)   | PO     | 0.5 mg | QD Day 1 and Day 10     | Fasting     | 13 days  | Population Representative |
| Digoxin DDI Study           | Elagolix (Perpetrator) | PO     | 150 mg | QD for 13 days          | Fasting     | 13 days  | Population Representative |

BID twice daily, DDI drug-drug interaction, PO orally, QD once daily, SD single dose.
Supplemental Figure 1: Sensitivity Analysis to assess the impact of choice of OATP1B1 Jmax parameter on the predicted elagolix AUC ratio following co-administration with single dose of rifampin.
Supplemental Figure 2: Sensitivity Analysis to assess the impact of choice of CYP3A4 CLint parameter on the predicted elagolix AUC ratio following co-administration with single dose of ketoconazole.
Supplemental Figure 3: Sensitivity Analysis to identify the P-gp fold induction that captures the observed DDI of Digoxin with Rifampin.

Impact of Pgp Induction on Digoxin AUCR and CmaxR

Shaded regions (blue and red) indicate the range of acceptance criteria based on Guest et al.