

An sFlt1-Targeted Degradar for Early-Onset Preeclampsia

Phil Graham, Effie Tozzo, Jeni Sideris, Rene Lemieux, Anthony Monti, Hu Liu, Hanlan Liu

Avilar Therapeutics, Inc., 480 Pleasant Street, Suite C120, Watertown, MA 02472,USA

Avilar’s sFlt1 degrader is investigational and not approved by any regulatory authority

THE CLINICAL PROBLEM

- Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality typically arising after 20 weeks of gestation affecting 2–8% of pregnancies. The only definitive treatment is delivery of the fetus and placenta
- Early-onset preeclampsia (EOP), arising <34 weeks gestational age, accounts for ~12% of the ~200,000 U.S. preeclampsia cases annually (~25,000 patients) and carries significantly higher maternal and fetal risks than later-onset disease. In the EU ~0.4% of births are affected by EOP¹
- Standard-of-care focuses on maternal stabilization with antihypertensive medications, seizure prophylaxis with magnesium sulfate, and corticosteroids to accelerate fetal lung maturation when delivery is anticipated <34 weeks
- When possible, patients are managed expectantly by hospital admission and careful monitoring in an effort to prolong pregnancy
- The clinical dilemma in EOP balances maternal safety against established consequences of fetal immaturity

RATIONALE FOR TARGETING sFlt1

- **Mechanistic rationale:** sFlt1 acts as a decoy receptor — binds/sequesters VEGF and PlGF, lowering their bioavailability. Disrupted angiogenic signaling results in endothelial dysfunction and vascular injury²
- **Pharmacologic evidence:** Blocking VEGF (bevacizumab) reproduces PE-like symptoms³; supplying PlGF attenuates them⁴ — both point to angiogenic-factor depletion as the driver
- **Genetic support:** GWAS⁵, gene-dosage (trisomy 13)⁶, and epigenetic studies link *FLT1* variants to elevated sFlt1 and Preeclampsia (PE) risk⁷
- **Preclinical data:** exogenous sFlt1 alone induces PE (hypertension, proteinuria, glomerular endotheliosis, FGR) in rodents^{1,8}, lowering sFlt1 reverses/prevents PE manifestations, including in NHPs⁹
- **Temporal relationship:** sFlt1 rises weeks before clinical symptoms.¹⁰ Drops within 72 h of delivery, tracking symptom resolution¹¹
- **Approved diagnostic test:** sFlt1/PlGF ratio allows identification of patients who may benefit from sFlt1 reduction. The ratio strongly correlates to the risk of early delivery^{12, 13, 14}

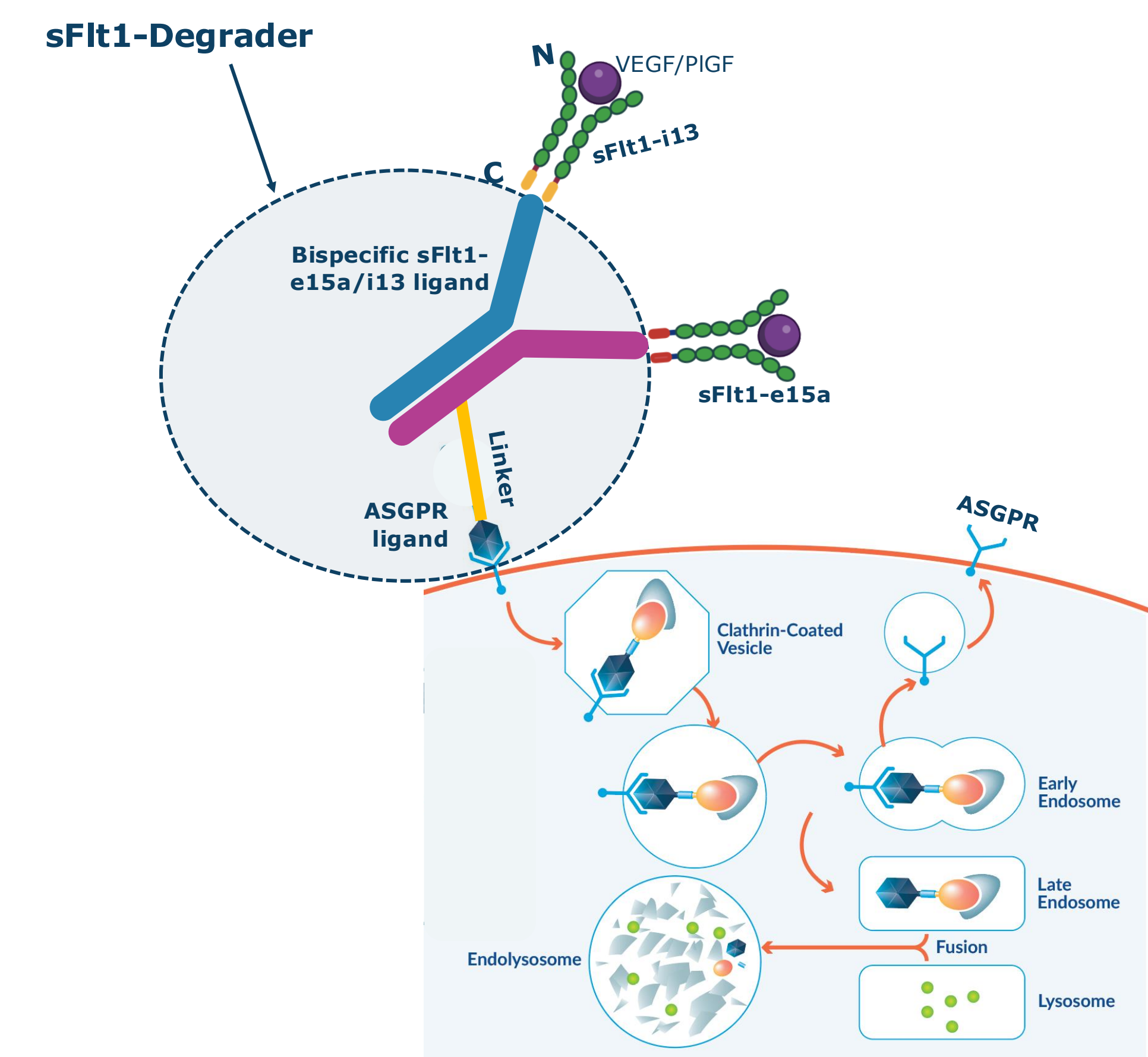
HOW THE sFlt1-DEGRADER WORKS

Molecular design

- The sFlt1 Degradar comprises a bispecific antibody that binds the two major circulating sFlt1 isoforms in preeclampsia, e15a and i13, connected to an ASGPR ligand via a chemical linker
- Binds sFlt1 at C-terminus, avoiding membrane VEGFR1 engagement; contains mutations to prevent placental crossing

In-vivo action

1. The Degradar binds sFlt1 in the maternal circulation
2. The complex of sFlt1 with the Degradar travels to the liver
3. The ASGPR ligand engages hepatocyte ASGPR; the complex is then internalized and degraded in the endolysosome



APHERESIS: PROXY FOR DEGRADATION

- Apheresis and plasma exchange physically remove sFlt1 providing the closest clinical precedent for a degrader
- Transient reductions of sFlt1 up to ~50% without any reported adverse consequences¹⁵. Blood pressure falls only modestly and is likely procedure-related¹⁴
- sFlt1 returns to baseline in ~2 days (estimated $t_{1/2}$ ~15 h)¹⁶
- Gestation was prolonged when given every few days, compared to contemporaneous controls, suggesting even intermittent sFlt1 reduction can provide a benefit^{16,17}
- Degradation can achieve the effect of an apheresis session in a small-volume injection and avoids the procedure risks, the specialized infrastructure, and limits on dosing frequency

ANTICIPATED CLINICAL PROFILE OF THE sFlt1-DEGRADER

"An apheresis session in a single small-volume injection"

The goal is to safely extend gestational age at delivery by at least 1 week, on top of standard-of-care expectant management

- **Rapid acting** — Reduces circulating sFlt1 within hours of dosing
- **Fast clearing** — Clears quickly from the circulation ($t_{1/2}$ ~3 h in cynomolgus monkeys)
- **Titratable** — Rapid depletion of sFlt1 combined with rapid clearance of the degrader enable individual titration of dose to optimize efficacy and safety
- **Selective** — Reduces sFlt1 only; does not engage membrane VEGFR1
- **Simple administration** — Small-volume IV bolus injection — no apheresis circuit or specialist center required
- **No placental transfer** — Engineered not to cross the placenta; undetectable in fetal cord blood

PRECLINICAL NHP DATA DEMONSTRATE KEY sFlt1-DEGRADER PROPERTIES

Degradation of Human sFlt1 in Cynos

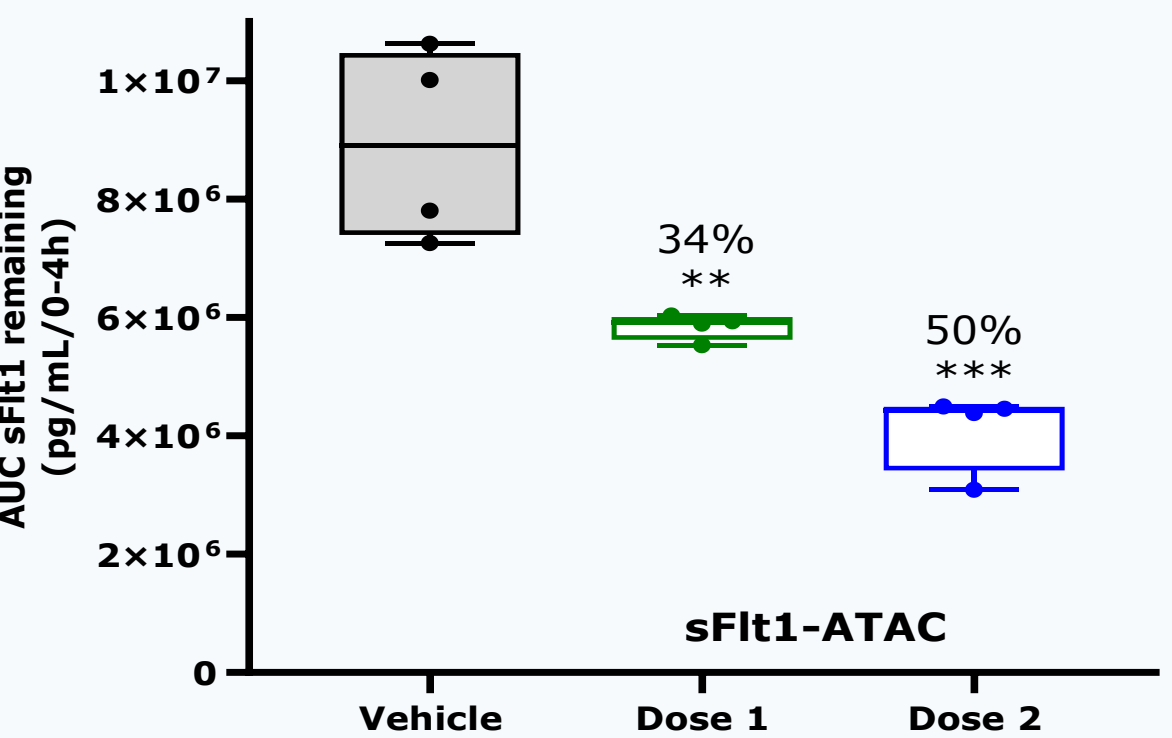


Figure 1. Rapid, dose-dependent sFlt1 degradation (female cynos).

Exogenous human sFlt1 e15a/i13 (3:1) IV, then a 15-min IV infusion of sFlt1-Degradar; total human sFlt1 by ELISA up to 4 h. Median AUC_{0-4h} fell 34% ($p<0.01$) and 50% ($p<0.001$) vs vehicle ($n=4$ /group). Comparable sFlt1 degradation in mice and rats.

sFlt1-ATAC in Maternal and Cord Blood

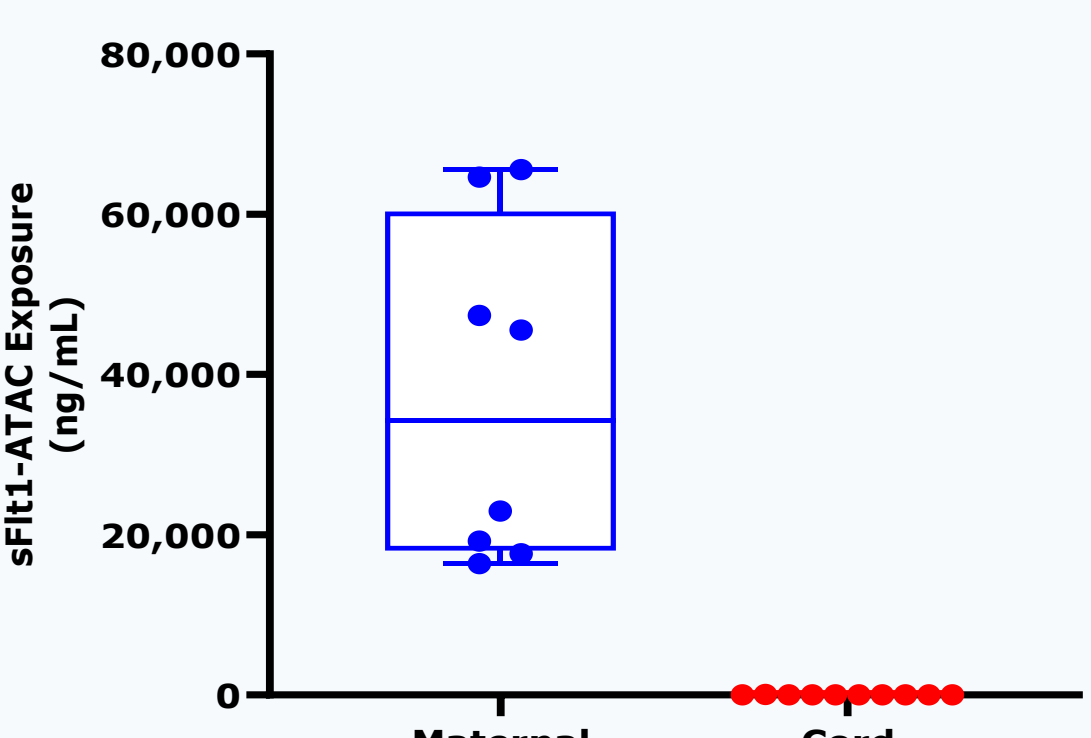


Figure 2. No placental transfer (pregnant cynos).

Four animals in late third trimester dosed for 4 days; maternal and umbilical cord blood sampled 1-3h after cesarean section. sFlt1-Degradar undetectable in cord blood in all 4 fetuses despite maternal exposure ~6x required for 50% sFlt1 degradation based on studies described in Fig1.

sFlt1-ATAC PK Profile in Cynomolgus Monkeys

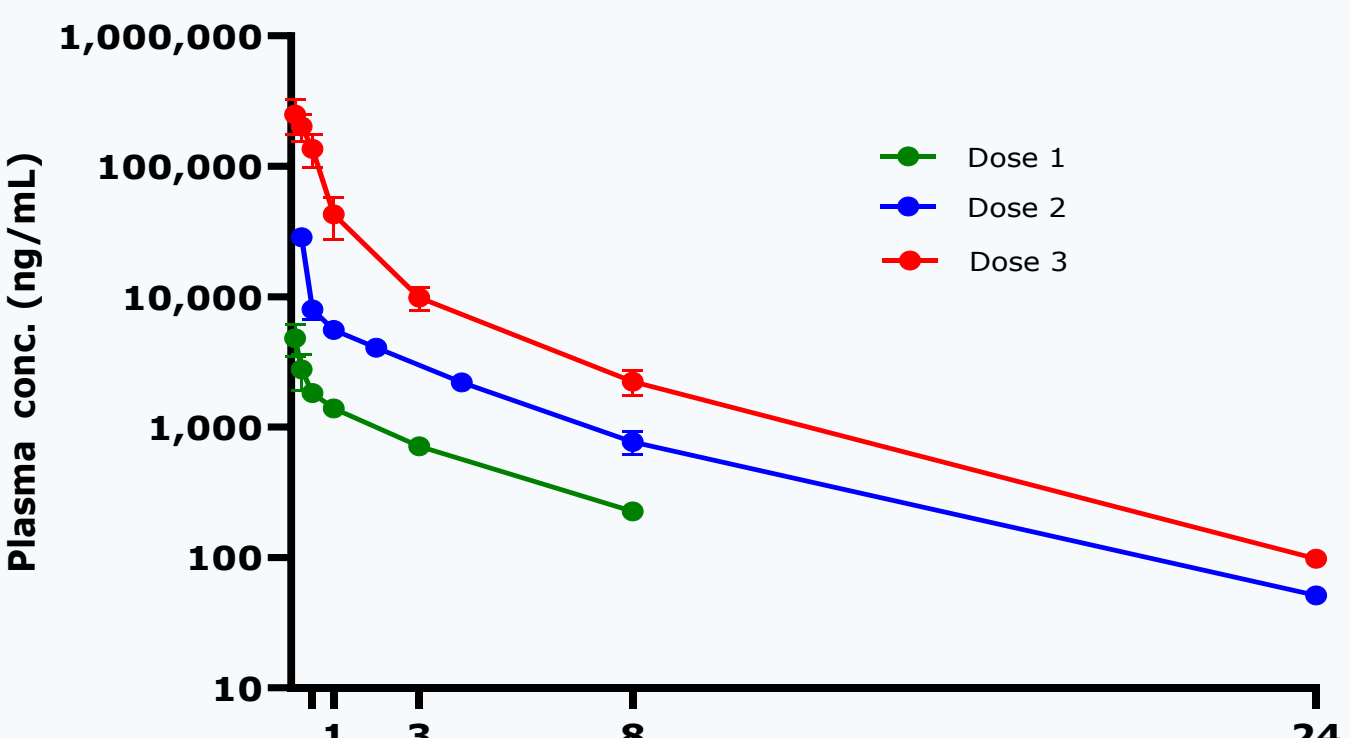


Figure 3. Fast-clearing PK profile (female cynos).

Half-life ~3 h at efficacious doses 1 and 2 and at 6x higher exposure (dose 3), driven by the engineered antibody mutations and ASGPR-mediated hepatocyte internalization. Profiles similar in pregnant and non-pregnant animals, supporting Phase 1 to Phase 2 dose translation.

PROGRAM STATUS

- Manufacturing and IND-enabling studies underway; first-in-human study in healthy non-pregnant female volunteers expected to start in 2027
- An open-label Phase 2 study in early-onset PE patients will include dose individualization

References: 1. Roberts BMJ (2011); 2. Maynard JCI (2003); 3. Cross Rev. Obstet. Gynecol (2012); 4. Spradley, F. T. et al.; 5. The FINNPEC Consortium et al. Nat. Genet. (2017); 6. Silasi, M. et al. AJOG (2011); 7. Kusuma Indones Biomed (2025); 8. Murphy Hypertension (2010); 9. Turanov Nat. Biotech (2018); 10. Levine NEJM (2004); 11. Wathen Human Reproduction (2011); 12. Verlohren et al. 2022 Pregnancy Hypertension; 13. Zeisler et al. NEJM (2016); 14. Thadhani R, et al. NEJM Evid (2022); 15. Gubensek J. Clin Apheresis (2021); 16. Thadhani, R. et al. J. Am. Soc. Nephrol. (2016); 17. Thadhani R, et al Nat. Med. (2026);

Disclosures: all authors are employees or shareholders of Avilar Therapeutics, Inc.