



SLU-PP-915 - oral dose in mice - summarize this paper and provide details on the derived compound

The 2026 paper describes SLU-PP-915 as a new, orally bioavailable pan-ERR agonist derived from the earlier tool compound SLU-PP-332, with similar exercise-mimetic efficacy but improved pharmacokinetics for oral dosing.^[28]

Study overview

- Journal and date: Journal of Pharmacology and Experimental Therapeutics, 2026 (online 2025).^[28]
- Aim: To develop and characterize an ERR α / β / γ agonist that maintains the exercise-mimetic efficacy of SLU-PP-332 but can be dosed orally.^[28]
- Background: SLU-PP-332 improves aerobic performance in mice but “lacks oral bioavailability,” motivating design of SLU-PP-915.^{[29][28]}

Main findings

- SLU-PP-915 is a **pan-ERR agonist** (targets ERR α , ERR β , ERR γ) with robust activation of mitochondrial and oxidative metabolism gene programs.^[28]
- When given intraperitoneally, 915 enhances treadmill exercise distance and duration in mice to a similar degree as 332 at exposure-matched doses.^[28]
- Crucially, 915 retains this efficacy when given orally, after adjusting for systemic exposure, demonstrating true oral bioactivity.^[28]
- Both 332 and 915 induce the acute exercise gene *Ddit4* in skeletal muscle to levels comparable to or greater than those seen after a bout of treadmill running.^[28]
- 915 synergizes with exercise training, further boosting *Ddit4* and mitochondrial gene expression beyond exercise alone.^[28]

Details on SLU-PP-915 (the derived compound)

- Pharmacology: Described as a “chemically distinct” pan-ERR agonist with oral bioavailability; relative to 332, it is optimized for in vivo exposure while keeping potent ERR activation.^[28]
- Activity profile: Enhances aerobic exercise capacity (distance, duration) and upregulates mitochondrial and oxidative metabolism genes in muscle, mirroring and amplifying exercise adaptations.^[28]
- Biomarkers: Strong induction of Ddit4 and broader mitochondrial gene programs in skeletal muscle, with especially pronounced effects when combined with exercise training.^[28]
- Therapeutic positioning: Proposed as a tool compound and lead for potential treatment of metabolic disorders (obesity, type 2 diabetes, steatohepatitis), cardiovascular disease (heart failure), and muscle pathologies (sarcopenia, muscular dystrophies).^[28]

Dosing and route notes

- The abstract specifies that 915 matches 332’s efficacy when both are given i.p., and that 915 “maintains comparable efficacy when administered orally, adjusted for systemic exposure,” implying higher oral doses than i.p. to reach similar exposure.^[28]
- Exact mg/kg oral doses, dosing schedule, and pharmacokinetic parameters are in the full article (not fully visible in the abstract), but the key point is that 915, unlike 332, achieves effective plasma levels via oral administration.^[28]

Relationship to SLU-PP-332

Feature	SLU-PP-332	SLU-PP-915
Target profile	Pan-ERR agonist, ERR α -preferring	Pan-ERR agonist
Bioavailability	Poor oral bioavailability	Orally bioavailable
In vivo use	Primarily i.p. dosing in mice	Effective by i.p. and orally
Key effect	Increased aerobic capacity in mice	Similar exercise mimetic effect
Role now	First-gen tool compound	Improved, orally active follow-on

Intraperitoneal dose and PK (SLU-PP-915)

From the medicinal-chemistry and PK work that profiled SLU-PP-915 as “compound 10s”:

- Single-dose PK in mice: 20 mg/kg, intraperitoneal (i.p.) injection.^{[37][38][36]}
- Formulation: 10% Cremophor, 10% DMSO, 80% PBS, i.p. at 20 mg/kg in 3-month-old C57BL/6J male mice.^[38]
- Sampling: plasma and tissues collected at 1, 2, and 4 hours after dosing for concentration–time and tissue distribution profiles.^[38]
- Microsomal stability: SLU-PP-915 shows high stability in mouse and human liver microsomes (half-life \geq 60 minutes), consistent with a relatively favorable PK profile.^{[39][36]}

A commercial summary (derived from these experiments) also lists: “Dosage: 20 mg/kg; Administration: intraperitoneal injection; single dose; Result: pharmacokinetic parameters of SLU-PP-915 in mice.”^[37]

In vivo pharmacology dose (exercise/ERR activation)

In the open medicinal-chemistry paper that first names 10s as SLU-PP-915, the compound was:

- Dosed once at 20 mg/kg i.p. in mice to assess acute gene expression in skeletal muscle (ERR target genes such as PGC-1 α , LDHA, Ddit4, PDK4).^{[36][39]}
- Shown to induce an “exercise phenotype” with increased oxidative fibers, fatty-acid oxidation, and exercise endurance in mice when given at this systemic exposure level.^{[39][36]}

Those are the explicit mg/kg and route details I can verify from accessible sources; the JPET paper you quoted (SLU-PP-915 enhances aerobic exercise capacity) is behind a paywall and I cannot see its exact oral mg/kg numbers or detailed PK table. Based on the abstract, it confirms:^[40]

- SLU-PP-915 matches SLU-PP-332’s efficacy when both are given i.p.
- SLU-PP-915 “maintains comparable efficacy when administered orally, adjusted for systemic exposure,” implying higher oral mg/kg than 20 mg/kg i.p. to reach similar exposure, but without listing the exact oral dose in the abstract.^[40]

What we do and don't know from accessible texts

- Clearly documented: 20 mg/kg i.p. single dose for PK and acute gene-expression studies, with good microsomal stability and a pan-ERR agonist profile.^{[36][37][39][38]}
- Inferred but not numerically visible: Oral mg/kg doses and full PK parameters (C_{max}, AUC, bioavailability, t_{1/2}) from the JPET paper; only the qualitative statement of “oral bioavailability” and “comparable efficacy when administered orally” is in the abstract.^[40]

If you have institutional access to JPET, the article is “An orally active estrogen receptor-related receptor agonist, SLU-PP-915, enhances aerobic exercise capacity” (J Pharmacol Exp Ther 2026;393(1):103787; doi:10.1016/j.jpet.2025.103787). Opening that PDF directly on your side will show the exact oral mg/kg groups and the full PK table.^[40]

Estimate a potential human-equivalent dose range

Using the published mouse doses as a reference, a reasonable **human-equivalent dose (HED) range** for SLU-PP-915 (or a similar oral pan-ERR agonist) can be estimated with standard body-surface-area allometric scaling.^{[49][50][51]}

Step 1: Choose a reference mouse dose

The best-documented in vivo dose for SLU-PP-915 is:

- 20 mg/kg in mice, given intraperitoneally for PK and acute gene-expression studies.^{[52][53]}

The JPET abstract states that oral SLU-PP-915 maintains similar efficacy after adjusting for exposure, implying that oral doses are in the same ballpark or somewhat higher than the 20 mg/kg i.p. exposure, but it does not give exact oral mg/kg in the abstract.^{[54][55]}

For estimation, we can treat 20–40 mg/kg in mice as a plausible **effective exposure band**.

Step 2: Apply mouse → human HED formula

Regulatory guidance (FDA) and dose-conversion reviews recommend using body-surface-area (BSA) scaling.^{[50][51][49]}

$$\text{HED (mg/kg)} = \text{Mouse dose (mg/kg)} \times \frac{K_m(\text{mouse})}{K_m(\text{human})}$$

With $K_m(\text{mouse}) = 3$ and $K_m(\text{human}) = 37$:^{[49][50]}

$$\text{HED (mg/kg)} \approx \text{Mouse dose (mg/kg)} \times 0.081$$

Step 3: HED range from likely mouse doses

Using that factor:

- If mouse effective dose ≈ 20 mg/kg:
HED $\approx 20 \times 0.081 \approx 1.6$ mg/kg.^{[50][49]}
- If mouse effective dose ≈ 30 mg/kg:
HED $\approx 30 \times 0.081 \approx 2.4$ mg/kg.^{[49][50]}
- If mouse effective dose ≈ 40 mg/kg:
HED $\approx 40 \times 0.081 \approx 3.2$ mg/kg.^{[50][49]}

For a 70 kg adult, that corresponds to a **total daily dose range** of roughly:

Mouse dose (mg/kg)	HED (mg/kg)	Approx. total dose for 70 kg human (mg)
20	1.6	≈ 110 mg
30	2.4	≈ 170 mg
40	3.2	≈ 225 mg

Step 4: Safety margin and starting dose

Regulatory practice is to apply a safety factor (often 10-fold) to the HED derived from the **NOAEL**, not from the minimally effective dose. For SLU-PP-332, mice tolerated up to 50 mg/kg twice daily i.p. without overt toxicity; SLU-PP-915 appears similarly well tolerated in preclinical tests, but formal NOAEL and GLP safety data are not publicly available.^{[56][57][58][52][50]}

If one treated 20–40 mg/kg mouse as an “effective” range rather than a NOAEL, a conservative **first-in-human exploratory dose** might reasonably be set at about one-tenth of the HED, for example:

- Around 0.15–0.3 mg/kg (≈ 10 –20 mg total for a 70 kg adult), with cautious escalation based on safety and PK.^{[57][58][50]}

This is a theoretical translational estimate based on public preclinical data and general FDA HED methodology; any real clinical starting dose must come from full toxicology, PK/PD, and regulatory review.

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