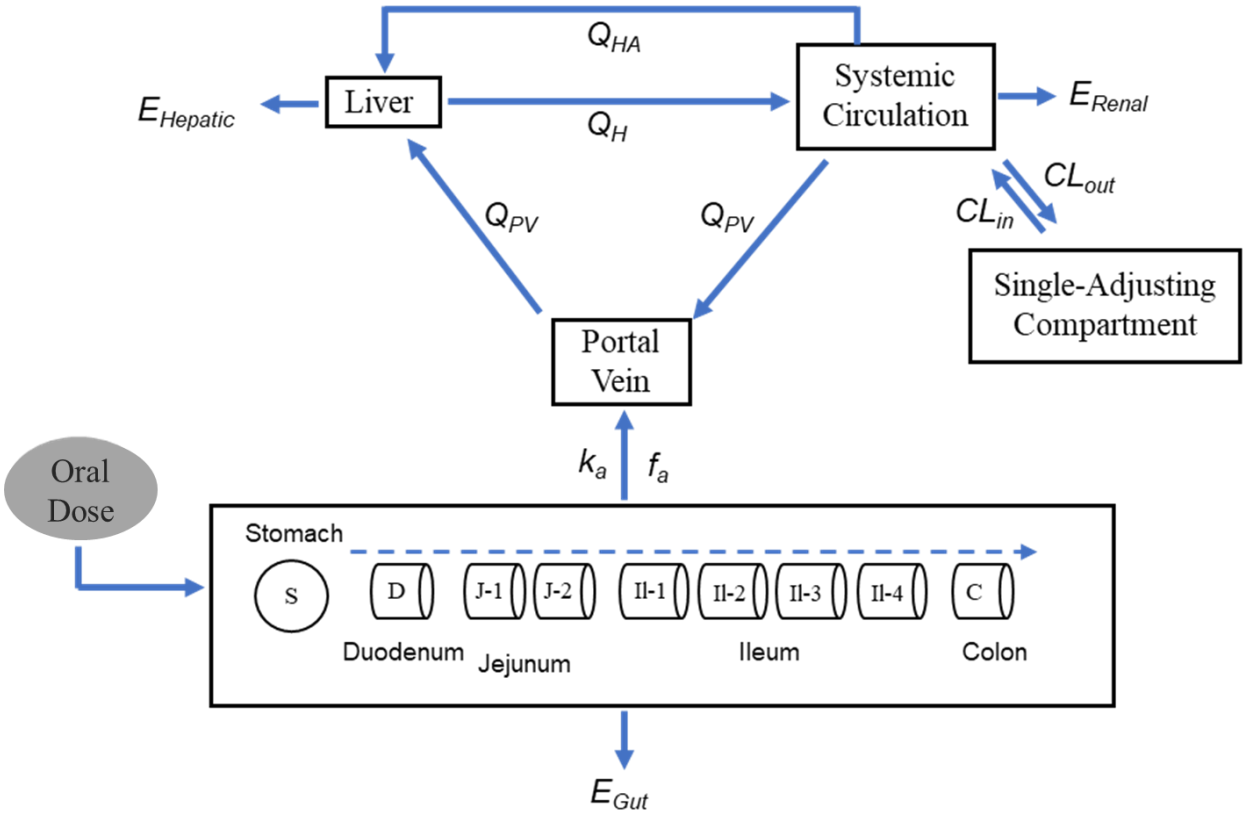
pharmaceutics

# Supplementary Materials: Physiologically Based Pharmacokinetic Model Development and Verification for Bioequivalence Testing of Bempedoic Acid Oral Suspension and Reference Tablet Formulation

**Figure S1.** Bempedoic acid physiologically based pharmacokinetic (PBPK) model schematic.




$CL_{in}$, $CL_{out}$, intercompartmental clearance; C, colon; D, duodenum; $E_{Gut}$, $E_{Hepatic}$, $E_{Renal}$, extraction by the gut, liver and kidney, respectively; $f_a$, fraction of dose absorbed; Il, ileum; J, jejunum; $k_a$, absorption rate constant; $Q_H$, $Q_{HA}$, $Q_{PV}$, blood flow in liver, hepatic artery and portal vein, respectively; S, stomach.

**Table S1.** Summary of bempedoic acid pharmacokinetic parameters after single 180 mg bempedoic acid administration and statistical analysis for the comparison of formulation 2 to formulation 1 (Study 004).

| | Geometric LS Mean | | Ratio of Geometric LS Means (90% CI) |
|---|---|---|---|
| PK Parameter | Formulation 2 (n=59) | Formulation 1 (n=58) | Formulation 2 to Formulation 1 |
| $C_{max}$, µg/mL | 18.4 | 18.7 | 0.983 (0.9421–1.0263) |
| $AUC_{inf}$, µg·h/mL | 269 | 265 | 1.016 (0.9876–1.0454) |
| $AUC_{last}$, µg·h/mL | 263 | 260 | 1.012 (0.9855–1.0398) |

$AUC_{inf}$, area under the concentration-time curve from time zero to infinity; $AUC_{last}$, area under concentration-time curve from time zero to last timepoint; CI, confidence interval; $C_{max}$, maximum concentration; LS, least square; PK, pharmacokinetics. $C_{max}$, $AUC_{last}$, $AUC_{inf}$ estimates are rounded to 3 significant figures.

The log-transformed PK parameters ($AUC_{last}$, $AUC_{inf}$ and $C_{max}$) were analyzed using a linear mixed model, with fixed effects for treatment, period and sequence, subject within sequence as random effect.

Formulation 1, immediate release tablet used during clinical development; Formulation 2, commercial immediate release tablet.

**Table S2**. Dissolution of bempedoic acid 180 mg immediate release tablets.

| Buffer | Average % Dissolved (Released), n=12 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 min | 10 min | 15 min | 20 min | 30 min | 45 min | 60 min | 75 min |
| 0.1N HCl pH 1.2 | 0 | 1 | 1 | 2 | 2 | 2 | 3 | 3 |
| 50 mM Acetate pH 4.5 | 0 | 3 | 3 | 4 | 5 | 5 | 5 | 5 |
| 50 mM Phosphate pH 6.6 | 26 | 69 | 93 | 99 | 101 | 101 | 101 | 101 |
| 50 mM Phosphate pH 6.8 | 33 | 82 | 101 | 103 | 104 | 104 | 104 | 104 |

Dissolution of bempedoic acid tablet (Lot 99743-07D) was determined using USP apparatus II operated at 50 rpm in 900 mL media volume.

**Table S3**. Dissolution of bempedoic acid 180 mg oral suspension (20 mg/mL).

| Buffer | Average % Dissolved (Released), n=12 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 min | 10 min | 15 min | 20 min | 30 min | 45 min | 60 min | 75 min |
| 0.1N HCl pH 1.2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 |
| 50 mM Acetate pH 4.5 | 2 | 3 | 4 | 4 | 4 | 4 | 4 | 4 |
| 50 mM Phosphate pH 6.6 | 75 | 87 | 90 | 91 | 92 | 93 | 93 | 96 |
| 50 mM Phosphate pH 6.8 | 88 | 91 | 92 | 92 | 93 | 93 | 94 | 95 |

Dissolution of bempedoic acid suspension formulation (Lot 0000091928) was determined using USP apparatus II operated at 50 rpm in 900 mL media volume.