**Supplementary methods**

**Analysis of plasma concentration of probe drugs and metabolites**

**Chemical reagents**

 LPZ and 5OH-LPZ were obtained from Tokyo Chemical Industry (Tokyo, JAPAN) and Toronto Research (Toronto, Ontario, CANADA), respectively. NIF and DNIF were obtained from FUJIFILM Wako Pure Chemical Corporation (Osaka, JAPAN) and Sumika Chemical Analysis Service (Osaka, JAPAN), respectively. Nitrendipine (NTR) is an internal standard (IS) for LPZ, 5OH-LPZ, NIF, and DNIF and was purchased from FUJIFILM Wako Pure Chemical Corporation. Mobile phase and stock solutions were prepared using methanol (LC/MS grade), formic acid, ammonium acetate, and dimethyl sulfoxide that were purchased from FUJIFILM Wako Pure Chemical Corporation.

**Preparation of stock solutions and calibration**

 Primary stock solutions of LPZ, NIF, and DNIF were dissolved in methanol, and 5OH-LPZ was dissolved in dimethyl sulfoxide. The IS of NTR stock solution was dissolved in methanol. All stock solutions were obtained by dissolving the appropriate amounts to achieve the final concentration of 10 mM.

 Calibration ranges were 0.05-0.1 µM for LPZ and 5OH-LPZ, and 0.005-0.1 µM for NIF and DNIF. The coefficients of correlation (r2) values were >0.997 for LPZ and 5OH-LPZ and >0.999 for NIF and DNIF. Variations in coefficients of lower limit of quantification and high-concentration were less than 10%.

**Blood sample preparation**

 After the blood sampling test, plasma was collected to measure the concentration of substrate drugs and their metabolites. The plasma samples were labeled and kept frozen at -20 ℃ until analysis.

i) LPZ and 5OH-LPZ

 The aliquot of plasma (250 µL) was mixed with 150 µL of IS and 100 µL of 50% methanol. The aliquot sample (500 µL) was extracted with 500 µL acetonitrile by vortex-mixing for 1 min. The mixture was centrifuged at 15,000×g for 10 min at 5 ℃. The supernatant was injected into the ultraperformance liquid chromatography in combination with triple quadrupole mass spectrometry (UPLC-MS/MS) system 26).

ii) NIF and DNIF

 NIF and DNIF were extracted by Oasis HLB Extraction Cartridges© (Waters Corp., Milford, Massachusetts, USA). The aliquot of sample consisted of 200 µL of patient’s plasma, 50 µL of IS, 200 µL of 50% methanol, and 600 µL of ultrapure water 27).

**UPLC-MS/MS conditions**

 Liquid chromatography was performed on an ACQUITY UPLC/Xevo TQ-S (Waters Corp.) and Quaternary Solvent Manager (Waters Corp.), with an ACCQUITY UPLC BEH C18 (50 mm×2.1 mm, i.d. 1.7 µm (Waters Corp.)), ACQUITY UPLC 0.2 µm stainless filter (Waters Corp.).

 A gradient elution program for LPZ and 5OH-LPZ was used for chromatographic separation with a mobile phase A (methanol) and a mobile phase B (0.2% ammonium acetate and 0.1% formic acid) as follows: 0-0.5 min (95% B), 0.5-3 min (95→5% B), 3-5 min (5% B), 5-7 min (5→95% B), 7-10 min (95% B). The flow rate was 0.5 mL/min. The total run time was 10 min. The detection was operated in the multiple reaction monitoring (MRM) mode under unit mass resolution in the mass analyzers. The MRM transitions were *m/z* 370.12→251.98 for LPZ, *m/z* 386.09→252.03 for 5OH-LPZ, and *m/z* 361.0→315.0 for NTR. Mass spectrometry was operated with the capillary voltage set at 4.0 kV, the cone voltage was 35 V, and collision voltage was 11 eV for LPZ and 20 eV for 5OH-LPZ. The desolvation temperature for LPZ and 5OH-LPZ was 400 ℃.

 A gradient elution program for NIF and DNIF was used or the chromatographic separation with a mobile phase A (methanol) and a mobile phase C (2% formic acid) as follows: 0-0.5 min (95% C), 0.5-3 min (95→20% C), 3-4 min (20% C), 4-5 min (10% C), 5-6 min (40% C), 6-6.5 min (30% C), 6.5-7 min (30→95% C), 7-8 min (95% C). The flow rate was 0.2 mL/min. The total run time was 8 min. The MRM transitions were *m/z* 347.1→315.0 for NIF, *m/z* 345.1→284.3 for DNIF, and *m/z* 361.0→315.0 for NTR. Mass spectrometry was operated with the capillary voltage set at 3.0 kV, the cone voltage was 30 V for NIF and 25 V for DNIF, and collision voltage was 4 eV for NIF and 28 eV for DNIF. The desolvation temperature for NIF and DNIF was 350 ℃.

 The Masslynx 4.1 software (Waters Corp.) was used for data acquisition, instrument control, and data analysis.