1 Supplementary materials

(Supplementary materials.pdf)

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Table S 1: CYP3A inducers listed in the FDA draft guidance on labeling for combined hormonal contraceptives sorted by their CYP3A induction potential

| Inducers          | Max % AUC | Objects         | Classification |
|-------------------|-----------|-----------------|----------------|
| Topiramate        | 12.0      | Ethinylestradiol|                |
| Aprepitant        | 22.1      | Midazolam IV    |                |
| Oxcarbazepine     | 28.1      | Flodipine       |                |
| Ritonavir         | 29.2      | Ethinylestradiol|                |
| Nevirapine        | 32.5      | Indinavir       | Weak           |
| Boceprevir        | 34.2      | Darunavir       |                |
| Rufinamide        | 36.7      | Triazolam       |                |
| (Fos)Amprenavir   | 43.0      | Iopinavir       |                |
| Telaprevir        | 48.4      | Darunavir       |                |
| Lopinavir         | 59.7      | Amprenavir      |                |
| Rifabutin         | 68.4      | Midazolam       |                |
| Bosentan          | 69.0      | Sildenafil       | Moderate        |
| Tipranavir / ritonavir | 75.6 | Saquinavir      |                |
| Efavirenz         | 76.0      | Alfentanil      |                |
| Phenytoin         | 89.5      | Nisoldipine     |                |
| Carbamazepine     | 86.6      | Quetiapine      | Strong          |
| St. John’s Wort extract | 80.0 | Midazolam       |                |
| Phenobarbital     | 76.6      | Verapamil       |                |
| Rifampin          | 99.7      | Budesonide      |                |

The list of CYP3A inducers was taken from the FDA draft guidance on labeling for combined oral contraceptives. Information on the inducers CYP3A induction potential was extracted from the list of “In Vivo Inducers of CYP3A Probes” from the UW Drug Interaction Database (DIDB) Copyright University of Washington, accessed Dec 2019.
### Table S2: Subject characteristics

|        | LNG (N=13) | NET (N=14) | DSG (N=12) | DNG (N=12) | DRSP/EE (N=14) | Total (N=65) |
|--------|------------|------------|------------|------------|----------------|--------------|
| Age (years) | 58.9 ± 3.66 | 57.4 ± 5.51 | 61.2 ± 6.24 | 60.9 ± 4.34 | 59.9 ± 6.18 | 59.6 ± 5.33 |
| Weight (kg)  | 69.6 ± 11.1 | 69.7 ± 11.0 | 71.1 ± 7.70 | 69.7 ± 6.63 | 67.1 ± 9.51 | 69.4 ± 9.25 |
| BMI (kg/m²)  | 25.3 ± 2.99 | 26.3 ± 3.27 | 25.7 ± 1.88 | 26.4 ± 3.24 | 24.9 ± 3.00 | 25.7 ± 2.90 |
| Race = White | 13 (100%) | 14 (100%) | 12 (100%) | 12 (100%) | 13 (92.9%) | 64 (98.5%) |
| Race = Asian | 0 | 0 | 0 | 0 | 1 (7.1%) | 1 (1.5%) |

Arithmetic means and standard deviations are presented for age, body weight and body mass index.^
^
not Hispanic or Latino; BMI, body mass index; DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; MDZ, midazolam; NET, norethindrone.
Table S 3: Exposure of midazolam, 4ß-hydroxycholesterol, progestins, and EE when the test drug was administered without and with rifampicin

| Analyte  | Parameter (Unit) | Control phase (no RIF) | Weak-induction phase (RIF 10 mg/d) | Strong-induction phase (RIF 600 mg/d) |
|----------|-----------------|------------------------|-----------------------------------|--------------------------------------|
|          |                 | gMean (%CV)            | gMean (%CV)                        | GMR [90% CI]                         | gMean (%CV)                        | GMR [90% CI] |
| MDZ      | AUC (µg·h/L)    | 65                     | 12.7 (36.7)                        | 6.84 (37.3)                          | 0.539 [0.491-0.592]               | 1.73 (49.3) | 0.137 [0.124-0.150] |
|          | Cmax (µg/L)     | 65                     | 4.90 (33.0)                        | 3.10 (38.6)                          | 0.633 [0.578-0.695]               | 0.919 (46.2) | 0.188 [0.171-0.206] |
|          | CₐUC (µg·h/L)² | 65                     | 4.05 (38.4)                        | 2.87 (39.4)                          | 0.709 [0.668-0.752]               | 0.549 (63.1) | 0.136 [0.123-0.149] |
|          | CₐUC (µg/L)     | 65                     | 1.64 (45.5)                        | 1.29 (46.8)                          | 0.784 [0.715-0.859]               | 0.259 (52.5) | 0.157 [0.141-0.175] |
| 4ß-OH    | C (µg/L)        | 65                     | 35.8 (42.3)                        | 39.8 (34.5)                          | 1.14 [1.10-1.19]                  | 108 (24.7)  | 3.15 [3.03-3.29]    |
| LNG      | AUC (µg·h/L)    | 13                     | 7.95 (36.1)                        | 6.61 (41.4)                          | 0.832 [0.771-0.897]               | 3.39 (33.1)  | 0.427 [0.395-0.460] |
|          | Cmax (µg/L)     | 13                     | 0.763 (23.9)                       | 0.763 (36.6)                        | 1.00 [0.895-1.12]                 | 0.842 (32.9) | 1.10 [0.899-1.23]  |
|          | CₐUC (µg/L)     | 13                     | 0.104 (41.8)                       | 0.0887 (39.0)                       | 0.853 [0.744-0.978]               | 0.0304 (34.7) | 0.292 [0.255-0.335] |
|          | CₐUC (µg/L)     | 13                     | 0.00998 (30.0)                     | 0.0102 (31.0)                       | 1.024 [0.866-1.21]                | 0.00755 (28.6) | 0.757 [0.640-0.894] |
| LNG_{unbound} | AUC (µg·h/L) | 14                     | 15.8 (38.1)                        | 13.8 (38.3)                          | 0.875 [0.794-0.965]               | 8.52 (30.0)  | 0.539 [0.489-0.595] |
|          | Cmax (µg/L)     | 14                     | 3.28 (36.9)                        | 2.94 (33.9)                          | 0.898 [0.805-1.00]                | 2.66 (30.9)  | 0.812 [0.728-0.906] |
| NET      | AUC (µg·h/L)    | 14                     | 0.645 (31.6)                       | 0.549 (33.0)                        | 0.850 [0.775-0.932]               | 0.277 (26.0)  | 0.430 [0.392-0.471] |
|          | Cmax (µg/L)     | 14                     | 0.134 (31.8)                       | 0.117 (32.8)                        | 0.874 [0.794-0.961]               | 0.0872 (30.0) | 0.649 [0.590-0.714] |
| NET_{unbound} | AUC (µg·h/L) | 14                     | 4.68 (35.1)                        | 4.17 (27.5)                          | 0.625 [0.553-0.708]               | 0.856 (39.3)  | 0.128 [0.113-0.145] |
|          | Cmax (µg/L)     | 14                     | 0.692 (21.0)                       | 0.603 (18.6)                        | 0.871 [0.723-1.05]                | 0.294 (35.5)  | 0.425 [0.353-0.512] |
| ENG (DSG) | AUC (µg·h/L)   | 12                     | 0.126 (34.1)                       | 0.0793 (31.3)                       | 0.627 [0.547-0.719]               | 0.0132 (35.4) | 0.105 [0.091-0.120] |
|          | Cmax (µg/L)     | 12                     | 0.0131 (24.0)                      | 0.0115 (23.3)                       | 0.875 [0.703-1.09]                | 0.00462 (40.0) | 0.353 [0.283-0.439] |
| ENG_{unbound} | AUC (µg·h/L) | 12                     | 560 (25.4)                         | 404 (20.6)                          | 0.722 [0.648-0.804]               | 72.5 (15.9)  | 0.130 [0.116-0.144] |
|          | Cmax (µg/L)     | 12                     | 44.3 (11.9)                        | 38.9 (20.2)                          | 0.879 [0.792-0.975]               | 21.8 (19.0)  | 0.492 [0.444-0.546] |
| DNG      | AUC (µg·h/L)    | 12                     | 525 (24.1)                         | 368 (23.3)                          | 0.701 [0.657-0.749]               | 73.0 (19.0)  | 0.139 [0.130-0.149] |
|          | Cmax (µg/L)     | 12                     | 27.2 (21.4)                        | 25.3 (25.4)                          | 0.931 [0.827-1.05]                | 16.5 (18.1)  | 0.605 [0.537-0.680] |
| DRSP     | AUC (ng·h/L)    | 14                     | 704 (42.2)                         | 576 (39.0)                          | 0.817 [0.730-0.915]               | 252 (49.8)   | 0.358 [0.320-0.400] |
|          | Cmax (ng/L)     | 14                     | 57.7 (28.2)                        | 57.5 (37.3)                          | 0.997 [0.895-1.11]                | 45.1 (39.6)  | 0.782 [0.702-0.871] |

%CV, coefficient of variation [%]; 1'-OH-MDZ, 1'-hydroxymidazolam; 4ß-OH, 4ß-hydroxycholesterol; AUC, area under the concentration-time curve extrapolated to infinity; AUC(0-tₐUC), AUC from time zero to the last quantifiable concentration; Cmax, observed maximum concentration; CI, confidence interval; DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; ENG, etonogestrel (active metabolite of DSG); gMean, geometric mean; GMR, geometric mean ratio; LNG, levonorgestrel; MDZ, midazolam; NET, norethindrone.

Weak-induction phase: Administration of the randomly assigned test drug plus midazolam was preceded and followed by once daily administration rifampicin 10 mg for 7 and 4 days, respectively. Strong-induction phase: Administration of the randomly assigned test drug plus midazolam was preceded and followed by once daily administration rifampicin 600 mg for 7 and 4 days, respectively.

The AUC for 1'-OH-MDZ could not be calculated reliably because 1'-OH-MDZ concentrations approached the lower limit of quantitation quiet early in some subjects in period 3. Furthermore, in periods 2 and 3, the concentrations increased again 12 hours after MDZ dosing in some subjects – a phenomenon which has also been observed in a prior study with a similar study design. Therefore, AUC(0-tₐUC) was used as describe the exposure and the metabolite ratio.

² The AUC for DNG could not be calculated reliably because DNG concentrations approached the lower limit of quantitation quiet early in some subjects in period 3. Furthermore, in periods 2 and 3, the concentrations increased again 12 hours after MDZ dosing in some subjects – a phenomenon which has also been observed in a prior study with a similar study design. Therefore, AUC(0-tₐUC) was used as describe the exposure and the metabolite ratio.
Table S 4: Metabolic pathways and fraction metabolized via CYP3A4 ($f_{\text{m,CYP3A4}}$) of commonly used progestins and ethinylestradiol

| Compound                  | Phase I Metabolism                                      | In vivo DDI study with CYP3A inhibitor | $f_{\text{m,CYP3A4}}$ | Phase II Metabolism                                                                 |
|---------------------------|---------------------------------------------------------|----------------------------------------|------------------------|------------------------------------------------------------------------------------|
| Desogestrel (pro-drug)    | Oxidation (CYP2C9, CYP2C19)                            | -                                      | -                      | -                                                                                  |
| Etonogestrel              | Oxidation (CYP3A4)                                      | Itraconazole                           | 0.44<sup>37</sup>      | -                                                                                  |
| Dienogest                 | Oxidation (CYP3A4)                                      | Ketoconazole                           | 0.67<sup>38</sup>      | Glucuronidation & sulfation of phase I metabolites                                 |
| Drospirenone              | Oxidation (CYP3A4), reduction, ester hydrolysis         | Ketoconazole                           | 0.63<sup>38</sup>      | Sulfation of phase I metabolites                                                   |
| Gestodene                 | Oxidation (CYP3A4)                                      | n.a.                                   | n.a.                   | Glucuronidation of phase I metabolites                                             |
| Levonorgestrel            | Oxidation (CYP3A4), reduction                           | Telithromycin                          | 0.37<sup>39</sup>      | Glucuronidation & sulfation of phase I metabolites                                 |
| Norethindrone             | Oxidation (CYP3A4 [major], CYP2C19 [minor]), reduction  | Voriconazole                           | 0.34<sup>39</sup>      | Glucuronidation & sulfation of phase I metabolites                                 |
| Norgestimate (pro-drug)   | Ester hydrolysis (deacetylation)                        | -                                      | -                      | -                                                                                  |
| Norelgestromin            | Oxidation (CYP3A4 [major], CYP2B6 & CYP2C9 [minor])    | n.a.                                   | 0.57<sup>39</sup> / 0.56<sup>40,b</sup> | Glucuronidation (UGT1A1) of phase I metabolites                                   |
| Ethinylestradiol (EE)     | Oxidation (CYP3A4 [major], CYP2C9 [minor])             | Ketoconazole                           | 0.20 - 0.29<sup>39</sup> | Sulfation (SULT1E1) [major], Glucuronidation (UGT1A1) [minor]                     |

n.a., not available  
<sup>a</sup> not confirmed by Korhonen et al<sup>37</sup>  
<sup>b</sup> estimated from in vitro studies  

The descriptions of the metabolic pathways are based on a paper by Zhang et al<sup>2</sup> and a presentation by Sun and Jargula<sup>41</sup>, $f_{\text{m,CYP3A4}}$ data were derived from publications of inhibition studies according to $f_{\text{m,CYP3A4}} = \text{CR}_{\text{CYP3A4}} = 1/\text{IR}_{\text{CYP3A4}} = 1/AUC_{\text{inhibitor}}/AUC_{\text{control}} * \text{IR}_{\text{CYP3A4}}$ (CR = Clearance Ratio, IR = Inhibition Ratio).<sup>42-43</sup>
**Methods S 1: Bioanalytical methods**

**Midazolam (MDZ)** and 1'-hydroxymidazolam (1'-OH-MDZ) were determined in human EDTA K₂ plasma after addition of the internal standards MDZ-d₄ and 1'-OH-MDZ-d₄ and automated liquid-liquid extraction with methyl tert-butyl ether. Separation was achieved by means of a liquid chromatographic system. For the mass spectrometric detection, a triple quadrupole mass spectrometer in positive TurbolonSpray™ ionization mode was applied.

**Levonorgestrel (LNG)** was determined in human EDTA K₂ plasma after addition of the internal standard LNG-d₆ and automated liquid-liquid extraction with a mixture of methyl tert-butyl ether and hexanes. Separation was achieved by means of a liquid chromatographic system. For the mass spectrometric detection, a triple quadrupole mass spectrometer in positive TurbolonSpray™ ionization mode was applied.

**Norethindrone (NET)** was determined in human EDTA K₂ plasma after addition of the internal standards NET-d₆ and liquid-liquid extraction with 1-chlorobutane followed by derivatization. Separation was achieved by means of a liquid chromatographic system. For the mass spectrometric detection, a triple quadrupole mass spectrometer in positive atmospheric pressure chemical ionization mode (Heated Nebulizer) multiple reaction monitoring mode was applied.

**Etonogestrel (ENG)**, the active metabolite of desogestrel (DSG), was determined in human EDTA K₂ plasma after addition of the internal standard LNG-d₆ and liquid-liquid extraction procedure with 1-chlorobutane followed by derivatization. Separation was achieved by means of a liquid chromatographic system. For the mass spectrometric detection, a triple quadrupole mass spectrometer in positive TurbolonSpray™ ionization mode was applied. A second calibration range was introduced because many concentrations were above the upper limit of quantitation (ULOQ) applying the initial calibration range from 2 to 16 µg/L. All samples that were above the ULOQ were reanalyzed with the higher range in subsequent sequences.

**Drosiprenone (DRSP) and ethinylestradiol (EE)** were determined in human EDTA K₂ plasma after addition of the internal standard DRSP-d₄ and EE-d₄ and liquid-liquid extraction with 1-chlorobutane followed by derivatization. Separation was achieved by means of a liquid chromatographic system. For the mass spectrometric detection, a triple quadrupole mass spectrometer in positive APCI ionization mode (Heated Nebulizer) MRM-mode was applied.

**Rifampicin (RIF)** was determined in human EDTA K₂ plasma after addition of the internal standard RIF-d₃ and automated liquid-liquid extraction with methanol and after addition of the internal standard RIF-d₆ and liquid-liquid extraction with ethyl acetate. Separation was achieved by means of a liquid chromatographic system. For the mass spectrometric detection, a triple quadrupole mass spectrometer in positive TurbolonSpray™ ionization mode was applied. Two calibration ranges were applied to cover the concentration range following low and high RIF doses.

**4ß-hydroxycholesterol (4ß-HC)** was determined in human EDTA K₂ plasma after addition of the internal standard 4ß-HC-d₂, applying liquid-liquid (sodium methoxide, water, hexane) and solid phase (Isolute SPE cartridges) extraction. Separation was achieved by means of a liquid chromatographic system. For the mass spectrometric detection, an API 5500 mass spectrometer in positive APCI mode was applied. Analysis utilized four calibrators within the validated detection range of 4.00 to 100 µg/L.⁴⁴

**Sex hormone binding globulin (SHBG)** was determined serum samples by a target dependent dissociation-enhanced lanthanide fluorescence immunoassay (DELFIA). The method is a solid phase, two-site fluorimunometric method based on the direct sandwich technique in which two monoclonal anti-SHBG antibodies are used. The SHBG in standards, quality controls, and samples is bound to streptavidin plates coated with biotinylated capture antibody followed by incubation with a europium-labeled monoclonal antibody. After addition of europium fluorescence intensifier, the time-resolved fluorescence of europium is measured.

All plasma and serum samples were stored at -20 °C until analysis. Stability tests confirmed the stability of the analytes at this temperature.

The possible interference of MDZ, 1'-OH-MDZ and RIF with the LNG, NET, ENG, DNG, DRSP or EE assay was evaluated. No significant interference was observed in all blank samples and zero standards fortified with MDZ, 1'-OH-MDZ and RIF. Furthermore, there was no effect on the quantitation of the progestins or EE.

Performance data for the above assays are summarized in the following table:
### Accuracy calculated as percent of nominal and precision (CV%) of the bioanalytical methods

|                  | Calibration standards | Quality control samples |
|------------------|-----------------------|-------------------------|
|                  | Calibration range     | Accuracy a, b, Precision b, Accuracy a at LLOQ, Precision at LLOQ | Concentration range | Accuracy a | Precision b |
|                  | [µg/L]                | [µg/L]                  | [%] | [%] | [µg/L] | [%] | [%] |
| MDZ              | 0.002–2              | 99.5–101                | ≤4.59 | 100 | 6.45 | 0.006–1.5 | 98.8–100 | 3.35–6.46 |
| 1'-OH-MDZ        | 0.005–5              | 99.4–101                | ≤5.79 | 100 | 6.00 | 0.015–3.75 | 100–101 | 3.80–6.78 |
| LNG              | 0.01–10              | 97.4–102                | ≤2.69 | 98.9 | 4.48 | 0.03–7.5 | 96.9–99.3 | 2.72–3.86 |
| NET              | 0.05–10              | 96.6–105                | ≤6.23 | 97.8 | 1.97 | 0.15–7.5 | 90.1–100 | 3.55–7.52 |
| ENG              | 0.01–2               | 98.6–101                | ≤4.03 | 100 | 6.37 | 0.03–1.5 | 98.0–103 | 3.30–7.48 |
| DNG low          | 0.2–16               | 93.3–112                | ≤5.34 | 100 | 2.50 | 0.6–12 | 88.3–93.2 | 0.70–3.20 |
| DNG high         | 0.2–100              | 96.2–105                | ≤2.09 | 99.0 | 3.22 | 0.6–75 | 96.7–99.8 | 0.93–1.28 |
| DRSP             | 0.1–40               | 95.8–104                | ≤6.34 | 98.7 | 3.37 | 0.3–30 | 93.3–98.7 | 3.36–4.14 |
| EE               | 0.001–0.4            | 97.0–104                | ≤6.18 | 99.0 | 4.56 | 0.003–0.3 | 94.3–101 | 3.76–4.40 |
| RIF low          | 0.1–100              | 97.0–102                | ≤6.91 | 101 | 7.52 | 0.3–75 | 96.3–97.2 | 3.60–6.26 |
| RIF high         | 5–5000               | 99.0–102                | ≤6.06 | 100 | 7.58 | 15–3800 | 90.5–92.4 | 4.37–5.78 |
| 4ß-HC            | 4–100                | 97.8–101                | ≤4.4 | 100 | 1.3 | 10–80 | 98–104 | 3.30–5.70 |
| SHBG             | 10–512 nmol/L        | 98.8–101                | ≤3.39 | 99.4 | 1.53 | 20–384 nmol/L | 98.3–109 | 3.29–5.43 |

a mean inter-assay accuracy of back-calculated concentration; b except LLOQ
%CV, coefficient of variation [%]; 1'-OH-MDZ, 1'-hydroxymidazolam; 4ß-HC, 4ß-hydroxycholesterol; DNG, dienogest; DRSP, drospirenone; EE, ethinylestradiol; ENG, etonogestrel; LLOQ, lower limit of quantitation; LNG, levonorgestrel; MDZ, midazolam; NET, norethindrone; RIF, rifampicin; SHBG, sex hormone binding globulin.
Figure S1: Market shares of different progestins and number of CYP3A induction studies with progestins

(A) Market shares of different progestins based on the number of oral contraceptive units sold in 2016

(B) Clinical induction studies with progestins

| Victim drug (progestin) | Number of published studies |
|------------------------|-----------------------------|
| Norethindrone          | 27                          |
| Levonorgestrel         | 25                          |
| Desogestrel + Ethinogestrel | 5                        |
| Norgestimate / Norelgestromin / Norgestrel | 3 / 1 / 1 |
| Dienogest             | 1                           |
| Gestodene             | 1                           |
| Medroxyprogesterone   | 1                           |

Sources of market shares data: IQVIA MIDAS Q4/2016, as base for cycle calculation in database Womenshealth; Farminform (Netherlands) Q4 2016; GERS (France) Q4/2016.

Source of CYP3A induction study data: UW Drug Interaction Database (DIDB) Copyright University of Washington, accessed Dec 2019.
Figure S2: Rifampicin trough concentrations in plasma during repeated oral administration of rifampicin

Geometric means with geometric standard deviations; N=65.

*C*<sub>trough</sub>, concentration of the drug before dosing; LLOQ, lower limit of quantitation; MDZ, midazolam; PK, pharmacokinetic; QD, once daily; RIF, rifampicin.

Blood samples for the determination of RIF were generally taken in the morning prior to intake of RIF. On Days 15 and 26, RIF was given 12 hours after the test drug; i.e., on these days the blood samples for the determination of RIF were taken 36 h after the last dose of RIF. RIF *C*<sub>trough</sub> increased more than dose proportional, likely due to extensive and saturable first-pass metabolism<sup>45</sup>). The decrease in RIF concentrations observed in period 3, i.e., after the first doses of RIF 600 mg, probably reflects the known ability of RIF at high doses to induce its own metabolism<sup>46,47</sup>. Trough concentrations of RIF were comparable between treatment groups after 10 mg/d and 600 mg/d RIF administration. Two low RIF trough concentrations were observed in period 3 on Study Days 28 and 30. Both samples belong to one subject in the DNG group. Since both MDZ and DNG were eliminated within 24 h when high-dose RIF was coadministered (In-Text-Figure 2), this potential non-compliance of tablet intake had no impact on the PK assessment and, therefore, the subject was not excluded from PK analyses.
Figure S 3: Midazolam plasma concentration-time curves obtained after single administration of midazolam 1 mg without and with coadministration of rifampicin 10 mg or 600 mg

Geometric means with geometric standard deviations.
DNG, dienogest group; DRSP/EE, drospirenone/ethinylestradiol group; DSG, desogestrel group; LNG, levonorgestrel; MDZ, midazolam; NET, norethindrone group; SD, single dose.
Wiesinger et al. DDI study with rifampicin, progestins/ethinylestradiol, and midazolam – supplementary information

Figure S4: Scatterplots of individual data

A: Trough concentration of RIF in plasma (median of days 13, 17, and 19 and days 24, 28 and 30) vs AUC ratio (with RIF/no RIF) for MDZ. B: Trough concentration of RIF in plasma (median of days 13, 17, and 19 and days 24, 28 and 30) vs concentration ratio for 4ß-HC (day 19 or 30/day 8). C: concentration ratio for 4ß-HC (day 19 or 30/day 8) vs AUC ratio (with RIF/no RIF) for MDZ.

4ß-HC, 4ß-hydroxycholesterol; AUC, area under the concentration-time curve extrapolated to infinity; C_{trough}, concentration of the drug before dosing; MDZ, midazolam; RIF, rifampicin; R_{AUC} ratio with RIF/no RIF; RIF, rifampicin.

The magnitude of the induction effect is classified into 3 categories: weak induction (W, R_{AUC} >0.5 and ≤0.8), moderate induction (M, R_{AUC} >0.2 and ≤0.5) and strong induction (S, R_{AUC} ≤0.2).