# Synopsis of study report: 226/2004
# Location in Module 5:

**Study Protocol No.:**
BY217/CP-061

**Report Version:**
Version 2.0

**Title of the study:**

Pharmacokinetic and clinical safety interaction study between roflumilast 500 µg repeated dose and midazolam (MDZ, single dose, i.v. 1 mg, oral 2 mg alone and with roflumilast) in healthy male subjects; open, randomized, five periods cross-over study with interspersed fixed treatment periods

**Study center:**

SocraTec R&D GmbH, Median Klinik 1, Turnweg 2a, 99438 Bad Berka (Germany)

**Publication (reference):**

Not applicable

**Studied period (years):**

23 March 2004 – 16 May 2004

**Clinical phase:** I

**Objectives:**

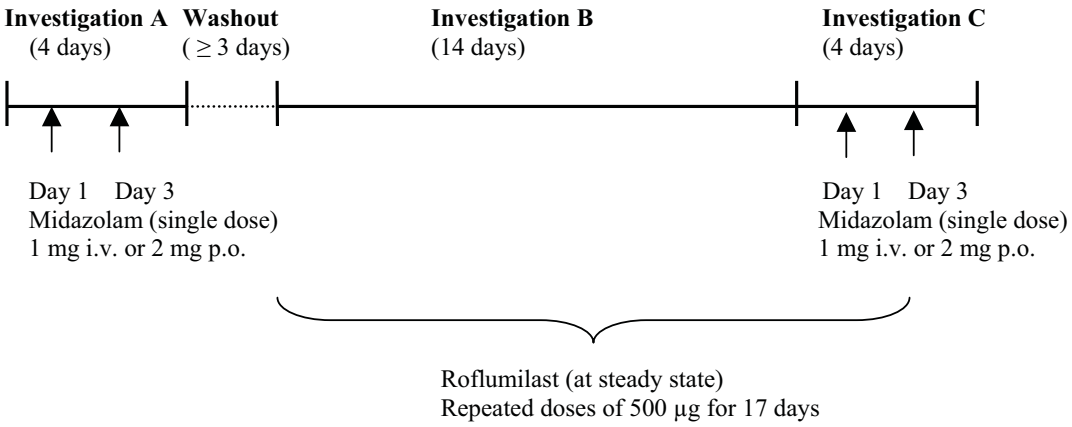
- To investigate the effects of steady-state roflumilast on the pharmacokinetics of MDZ following single-dose MDZ (1 mg i.v. and 2 mg p.o.) upon co-administration
- To use MDZ as in vivo probe for the assessment of cytochrome P450 3A4 (CYP3A4) activity by measuring clearance of MDZ*

*Apparent oral clearance (CL/F, where F denotes the fraction of the dose absorbed) is calculated after MDZ p.o. administration to estimate intestinal CYP3A activity, whereas systemic clearance (CL) is calculated after MDZ i.v. to estimate hepatic CYP3A activity.

- To study the pharmacokinetic parameter estimates of 1-hydroxy MDZ and 4-hydroxy MDZ after single-dose MDZ (1 mg i.v. and 2 mg p.o.) administered alone or with roflumilast
- To investigate the effects of single-dose MDZ (1 mg i.v. and 2 mg p.o.) on the pharmacokinetics of steady-state roflumilast and roflumilast N-oxide upon co-administration
- To evaluate whether a potential interaction would affect the safety and tolerability of single-dose MDZ and steady-state roflumilast

**Methodology:**

This study was conducted according to an open, randomized, five period cross-over design with interspersed fixed treatment periods. It consisted of a screening examination, Investigation A (4 days), a washout period (at least 3 days), Investigation B (14 days), Investigation C (4 days), and a post-study examination. Subjects were randomly allocated to i.v. or p.o. MDZ treatment in Investigation A (MDZ administered alone). The same treatment sequence was then used in Investigation C in which single-dose MDZ was administered together with steady-state roflumilast. Repeated daily doses of 500 µg roflumilast were administered for 17 days (within Investigation B and C):




Blood samplings for pharmacokinetic purposes were performed on:

- Study Days 1 and 3 of Investigation A at pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 h after study drug administration (MDZ 1 mg i.v. or 2 mg p.o.)
- Study Day 13 of Investigation B at pre-dose, 15 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 h after study drug administration (500 µg roflumilast)

- Study Days 1 and 3 of Investigation C at pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 h after study drug administration (MDZ 1 mg i.v. or 2 mg p.o. together with 500 µg roflumilast)

Analytical Method:
Plasma concentrations of MDZ and its hydroxy metabolites (1-OH and 4-OH) were determined by using a validated High Performance Liquid Chromatography (HPLC) assay with fluorescence detection. The limit of quantitation in plasma (LLOQ) was 0.505 ng/mL for MDZ and 0.252 ng/mL for 1-hydroxy MDZ and 4-hydroxy MDZ using a sample volume of 0.5 mL. The plasma concentrations of roflumilast and roflumilast N-oxide were determined by using a validated High Performance Liquid Chromatography with tandem Mass Spectrometry (HPLC-MS/MS) assay. The LLOQ was 0.10 ng/mL using a sample volume of 0.4 mL.

**No. of subjects:**

A total of 18 healthy male subjects met the inclusion criteria and were included in this study performed in a single center.

**Diagnosis and criteria for inclusion:**

Eligible subjects were healthy male Caucasians, aged 18 to 45 years, with a normal body weight, who were non-smokers for at least one year and gave their written informed consent.

**Study medication, Dose, Mode of administration, Batch No.:**

- Roflumilast: 500 µg tablets, oral administration with 240 mL of water in the morning; batch No. 320200, manufactured by ALTANA Pharma Oranienburg GmbH
- Midazolam (MDZ): 5 mg/5mL ampoules, batch No. F004501, Dormicum® V 5mg/5mL, commercially available from Hoffmann-La Roche AG

  Dose and Mode of administration: solution of 1 mg i.v. MDZ infused over 1 min.; solution of 2 mg MDZ administered orally with 240 mL water. Solutions were prepared by diluting MDZ (1 mg for i.v. administration and 2 mg for p.o. administration) in a total of 5 mL sodium chloride solution

MDZ was used as in vivo CYP3A4 probe and roflumilast as test drug.

**Duration of treatment:**

- Roflumilast: administered for 14 days in Investigation B and continued for 3 days in Investigation C, i.e. a total treatment duration of 17 days (steady-state)
- MDZ: 2 days in Investigation A and 2 days in Investigation C (single dose of 1 mg i.v. MDZ and single dose of 2 mg p.o. MDZ on Study Days 1 and 3, respectively)

**Criteria for evaluation:**

- Primary pharmacokinetic parameter estimates: Clearance (CL and CL/F), area under the plasma concentration-time curve (AUC), and maximum plasma concentration (Cmax) of MDZ (single dose i.v. and p.o. administered alone and with roflumilast at steady state), roflumilast and roflumilast N-oxide at steady state
- Secondary pharmacokinetic parameter estimates: AUC, Cmax, tmax, and t1/2 for 1-hydroxy MDZ and 4-hydroxy MDZ on Study Days 1 and 3 of Investigation A and Study Days 1 and 3 of Investigation C (i.v. and p.o.), as well as tmax, and t1/2 for MDZ (single dose i.v. and p.o.), roflumilast and roflumilast N-oxide at steady state

  **Safety variables:** Adverse events (AEs), laboratory work-up (including blood chemistry, hematology, urinalysis), physical examination, blood pressure (BP), pulse rate, body temperature, and 12-lead ECG (including heart rate, PR, QRS, QT, and QTc parameters)

**Statistical methods:**

The primary pharmacokinetic parameter estimates (AUC, $C_{max}$, CL and CL/F) of analytes were compared between treatments with the WinNonLin linear mixed effects modeling (bioequivalence wizard) to perform an analysis of variance (ANOVA) using the 90% confidence interval (CI) for the ratio of the least-squares means (LSM). Each pharmacokinetic parameter estimate was then log-transformed prior to analysis and a 90% CI was computed for the difference (Test-Reference) between the means. The endpoints of the intervals were then exponentiated resulting in approximate 90% CIs in the natural scale for the ratios of geometric means.

Percentage ratios of geometric means for clearance, AUC and $C_{max}$ of MDZ, roflumilast and its N-oxide of Investigation C/Investigation A for the respective MDZ treatments and Investigation C/Investigation B for the respective roflumilast and roflumilast N-oxide treatments were calculated as stated above. No interaction was concluded if the 90% CI was within the equivalence range of 0.80-1.25 for clearance and AUC, and within the equivalence range of 0.70-1.43 for $C_{max}$.

The safety variables were analyzed descriptively, including summary statistics (e.g. median, min and max, 68%-range, mean, SD) where appropriate.

## SUMMARY – CONCLUSIONS

**Demographic data:**

All 18 healthy male subjects who entered the study were analyzed and used for the evaluation of pharmacokinetic parameter estimates. All subjects were of Caucasian origin. Median [min-max] value for age was 34 [19-44] years, for body weight was 78 [60-98] kg, and for height was 180 [166-194] cm.

**Pharmacokinetic results:**

**MDZ i.v. and p.o.**

Data on CL (MDZ i.v.), CL/F (MDZ p.o.), AUC, and $C_{max}$ show that steady-state roflumilast (500 µg once daily) does not alter the pharmacokinetics of MDZ following i.v. and p.o. administration.

**Pharmacokinetic parameter estimates of MDZ after single dose (1 mg i.v. or 2 mg p.o.) administered alone (MDZ Reference) and together with 500 µg roflumilast at steady state (MDZ $Test_{iv}$, MDZ $Test_{po}$); geometric means, 68%-range**

| | Midazolam i.v. (N=18) | | Midazolam p.o. (N=18) | |
|---|---|---|---|---|
| | alone | with roflumilast | alone | with roflumilast |
| **$AUC_{(0-\infty)}$** | **36.342** | **35.247** | **17.932** | **17.551** |
| (hr*µg/L) | 26.075, 50.652 | 29.588, 41.988 | 12.776, 25.168 | 12.924, 23.834 |
| **$AUC_{last}$** | **33.615** | **32.866** | **16.144** | **15.928** |
| (hr*µg/L) | 24.606, 45.923 | 27.315, 39.545 | 11.275, 23.117 | 11.647, 21.782 |
| **CL or CL/F[a]** | **27.516** | **28.372** | **111.53** | **113.952** |
| (L/hr) | 19.742, 38.351 | 23.817, 33.798 | 79.463, 156.537 | 83.913, 154.745 |
| **$C_{max}$** | **22.035** | **22.934** | **8.976** | **8.722** |
| (µg/L) | 17.438, 27.844 | 19.042, 27.622 | 6.597, 12.214 | 6.391, 11.904 |

[a]CL: systemic clearance calculated for MDZ i.v. only; CL/F: apparent oral clearance calculated for MDZ p.o. only

Comparison of the primary pharmacokinetic parameter estimates after i.v. and p.o. administration of MDZ alone and with roflumilast at steady state revealed no significant differences in MDZ pharmacokinetic parameter estimates and met the predefined equivalence criteria. For $C_{max}$, not only the equivalence range of 0.7 to 1.43 postulated in the study protocol was met but also the standard equivalence range of 0.80 to 1.25.

**Point estimates and 90%-confidence interval for the Test/Reference ratios of the primary pharmacokinetic parameter estimates for MDZ after single dose (1 mg i.v. or 2 mg p.o.) administered alone (Reference) and together with 500 µg roflumilast at steady state (Test)**

| | Midazolam i.v. (N=18) | | Midazolam p.o. (N=18) | |
|---|---|---|---|---|
| | **Ratio (% Ref)** | **90% CI** | **Ratio (% Ref)** | **90% CI** |
| **$AUC_{(0-\infty)}$** | **96.985** | 83.505, 112.64 | **97.874** | 81.592, 117.406 |
| **$AUC_{last}$** | **97.771** | 84.627, 112.956 | **98.659** | 81.609, 119.273 |
| **CL or CL/F[a]** | **103.109** | 88.778, 119.754 | **102.172** | 85.175, 122.561 |
| **$C_{max}$** | **104.078** | 92.382, 117.255 | **97.164** | 81.618, 115.67 |

[a]CL: systemic clearance calculated for MDZ i.v. only; CL/F: apparent oral clearance calculated for MDZ p.o. only

**1-hydroxy and 4-hydroxy MDZ**

The pharmacokinetic parameter estimates AUC, $C_{max}$, $t_{max}$, and $t_{1/2}$ of 1-hydroxy and 4-hydroxy MDZ following single i.v. or p.o. dose of MDZ administered alone or in combination with roflumilast also remained similar. Ratio analysis did not reveal any change in AUC and $C_{max}$ of 1-hydroxy MDZ following single dose MDZ (1 mg i.v. and 2 mg p.o.) co-administered with steady-state roflumilast as compared with MDZ administered alone.

**Roflumilast and roflumilast N-oxide**

There was no change in primary pharmacokinetic parameter estimates of roflumilast with or without MDZ treatment, neither for p.o. nor for i.v. administration of MDZ. Similarly, no change in primary pharmacokinetic parameter estimates of roflumilast N-oxide was observed after roflumilast administration with or without MDZ (p.o. or i.v.).

**Point estimates and 90%-confidence interval for the $Test_{iv}$/Reference and $Test_{po}$/Reference ratios of the primary pharmacokinetic parameter estimates for roflumilast and roflumilast N-oxide after repeated once-daily doses of roflumilast (500 µg) administered with MDZ (1 mg i.v. or 2 mg p.o.)**

| | $Test_{iv}$ | | $Test_{po}$ | |
|---|---|---|---|---|
| | **Ratio (% Ref)** | **90% CI** | **Ratio (% Ref)** | **90% CI** |
| **Analyte: Roflumilast, Reference: Roflumilast alone (N=18)** | | | | |
| **$AUC_{last}$** | **93.806** | 83.041, 105.965 | **95.881** | 84.879, 108.310 |
| **CLss_F[a]** | **106.603** | 94.371, 120.422 | **104.296** | 92.328, 117.815 |
| **$C_{max}$** | **92.859** | 81.463, 105.848 | **98.016** | 85.988, 111.727 |
| **Analyte: Roflumilast N-oxide, Reference: Roflumilast alone (N=18)** | | | | |
| **$AUC_{last}$** | **94.722** | 82.801, 108.358 | **94.995** | 83.040, 108.670 |
| **$C_{max}$** | **92.761** | 81.170, 106.007 | **94.162** | 82.396, 107.608 |

[a]CLss_F: apparent oral clearance at steady state for roflumilast

Note: Point estimate and 90%-confidence limits are not reported for CLss_F in the case of roflumilast N-oxide because this would be based on various unreliable assumptions as documented in Section 9.8 of the study report

Data indicate that single intravenous or oral doses of MDZ (1 mg i.v. or 2 mg p.o.) has no effect on the steady-state pharmacokinetics of roflumilast and roflumilast N-oxide.

**Safety results:** During treatment, a total of 50 AEs were reported by 16 subjects (89% of all subjects). The reported AEs were either mild or moderate in intensity, and they resolved completely in all cases. The most frequently reported AE was headache, which occurred in 44% of the subjects. None of the AEs led to study discontinuation, and no serious or unexpected AEs or deaths were reported.

Laboratory values did not show any clinically relevant changes between the screening and post-study examination. Repeated measurements of pulse rate, blood pressure, and ECG parameters throughout the study did not show clinically relevant alterations.

**Conclusions:**

Based on CL (MDZ i.v.), CL/F (MDZ p.o.), AUC, and $C_{max}$, steady-state roflumilast (500 µg once daily) does not alter the pharmacokinetics of single-dose MDZ following i.v. and p.o. administration. As MDZ was used as standard probe for CYP3A4 interactions, the finding

suggests that roflumilast may be co-administered with substrates of CYP3A4 (single dose) without any need for dose adjustment of the CYP3A4 substrate.

The pharmacokinetic parameter estimates AUC, $C_{max}$, $t_{max}$, and $t_{1/2}$ of 1-hydroxy MDZ and 4-hydroxy MDZ were similar following administration of MDZ (i.v. and p.o.) alone or with concomitant roflumilast. Ratio analysis did not reveal any change in AUC and $C_{max}$ of 1-hydroxy MDZ following single dose MDZ (1 mg i.v. and 2 mg p.o.) co-administered with steady-state roflumilast as compared with MDZ administered alone.

Consequently, the findings regarding CL (MDZ i.v.) and CL/F (MDZ p.o.) also show that there is no change in CYP3A4 activity whether the study drugs (MDZ and roflumilast) are administered alone or in combination with each other.

Overall, the safety data obtained in the present study indicate that repeated doses 500 µg roflumilast/day and single doses of MDZ (1 mg i.v. and 2 mg p.o.) administered alone or with 500 µg roflumilast were safe.