CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022522Orig1s000

<u>CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)</u>

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	022522	*Submission Dates*	0029 (08/30/2010) 0036 (12/21/2010)
Brand Name		Daxas® (proposed)	
Generic Name		Roflumilast	
Reviewer		Ping Ji, Ph.D.	
Team Leader		Yun Xu, Ph.D.	
OCP Division		Division of Clinical Pharmacology-II	
OND Division		Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)	
Sponsor		Forest Research Institute	
Relevant IND(s)		57,883	
Submission Type; Code		505 (b) (1)	
Formulation; Strength(s)		Tablet, 500 mcg	
Indication		Maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.	
Proposed Dosing Regimen		One tablet of 500 mcg per day	

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**1		Executive Summary**

**1.1		Recommendations**

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

**1.2		Phase IV Commitments**

None.

**1.3		Summary of Clinical Pharmacology and Biopharmaceutics Findings**

Background

Daxas® (roflumilast) is an anti-inflammatory agent indicated for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.   Roflumilast is a phosphodiesterase-4 (PDE4) inhibitor. In response to FDA's complete respone letter dated May 17, 2010, Forest Laboratory submitted this resubmission of NDA22522 on Aug 30, 2010.

In this new submission, Daxas was evaluated to assess its potential as P-gp substrate *in vitro.* Included in this review are the *in vitro* study and the labeling recommendation. The proposed dosing regimen for COPD patients is one oral table of 500 μg per day, with or without food.

**2		Question-Based Review**

**2.1		General Attributes**

**2.1.1		What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?**

Daxas® (roflumilast) is an anti-inflammatory agent indicated for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. Roflumilast is a phosphodiesterase-4 (PDE4) inhibitor. On May 17, 2010, a complete response letter was send to the sponsor, and the following clinical pharmacology related deficiencies were identified in the letter:

(b) (4)

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2. The proposed dose of 500 mcg of roflumilast once daily is the maximal tolerated chronic dose of the drug. Because roflumilast has significant dose-related adverse reactions, the increased exposure to roflumilast, if it is a P-glycoprotein (P-gp) substrate, when taken concomitantly with other drugs that are P-gp inhibitors (e.g. ketoconazole) is a safety concern. Therefore, conduct an in vitro evaluation of the potential of roflumilast as a substrate for P-gp.

In response to FDA's complete respone letter dated May 17, 2010, Forest Laboratory submitted this resubmission of NDA22522 on Aug 30, 2010.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In this new submission, Daxas was evaluated to assess its potential as P-gp substrate *in vitro*. Included in this review are the *in vitro* study and the labeling recommendation. Sponsor proposes to designate the drug product formulation used in the pivotal clinical trials as the commercial drug product. This is acceptable. The proposed dosing regimen for COPD patients is one oral table of 500 μg per day, with or without food.

2.4 Extrinsic Factors

2.4.1. Drug-Drug Interactions

a) Is the drug a substrate of P-glycoprotein transport processes?

Neither Roflumilast nor its N-oxide metabolite was found to be a substrate of P-gp.

The potential role of roflumilast as P-gp substrate was evaluated in an *in vitro* study 10FOREP1S2GLPS134. Determination of the P-gp substrate potential of Roflumilast was carried out using Caco-2 cell monolayers, and the determination was performed at four different concentration of Roflumilast: 0.05, 0.25, 2, and 4 μM (0.0201, 0.101, 0.806, and 1.61 μg/mL). Functional P-gp activity was observed in the same batch of Caco-2 cells. Because the

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efflux ratios of Roflumilast were less than 2 at all tested concentrations, Roflumilast is not a P-gp substrate.

Table 4. Permeability and Recovery of Roflumilast and Digoxin in Caco-2 Cells

Treatments	$P_{app\ (AP\text{-to-}BL)}$	$P_{app\ (BL\text{-to-}AP)}$	Total Recovery (%)[3]	Efflux ratio
0.05 µM (0.0201 µg/mL) Roflumilast[1]	42.1 ± 3.1	30.4 ± 3.6	118 ± 15 (AP-to-BL) 116 ± 5.8 (BL-to-AP)	0.721
0.25 µM (0.101 µg/mL) Roflumilast[1]	48.9 ± 8.0	23.9 ± 5.2	115 ± 4.8 (AP-to-BL) 101 ± 1.4 (BL-to-AP)	0.488
2 µM (0.806 µg/mL) Roflumilast[1]	34.2 ± 1.6	25.7 ± 1.7	111 ± 2.4 (AP-to-BL) 101 ± 4.1 (BL-to-AP)	0.751
4 µM (1.61 µg/mL) Roflumilast[1]	32.5 ± 3.8	17.9 ± 1.8	88.7 ± 1.2 (AP-to-BL) 86.2 ± 1.4 (BL-to-AP)	0.551
10 µM Digoxin[2]	0.972 ± 0.08	16.7 ± 1.2	93.6 ± 7.0 (AP-to-BL) 97.7 ± 4.2 (BL-to-AP)	17.2
10 µM Digoxin + 5 µM CsA[2]	4.70 ± 0.50	4.44 ± 0.74	102 ± 5.5 (AP-to-BL) 107 ± 7.7 (BL-to-AP)	0.945

[1] All data are shown as average ± standard deviation (n=3). The results of each individual replicate are listed in Appendix 2.
[2] All data are shown as average ± standard deviation (n=4). The results of each individual replicate are listed in Appendix 2.
[3] For Roflumilast, the total recovery values included the compound accumulated in the receiver, donor, cells, and inserts by the end of the experiment. For digoxin, the reported recovery values included the compound accumulated in the receiver and donor by the end of the experiment.

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The potential role of roflumilast N-oxide as P-gp substrate was evaluated in an *in vitro* study 10FOREP2. Determination of the P-gp substrate potential of Roflumilast N-oixde was carried out using Caco-2 cell monolayers, and the determination was performed at four different concentration of Roflumilast: 0.1, 0.5, 2, and 4 µM (0.042, 0.21, 0.838, and 1.68 µg/mL). Functional P-gp activity was observed in the same batch of Caco-2 cells. Because the efflux ratios of Roflumilast N-oxide were less than 2 at all tested concentrations, Roflumilast N-oxide is not a P-gp substrate.

Table 10. Permeability and Recovery of Roflumilast N-oxide and Digoxin in Caco-2 Cells

Treatments	$P_{app\ (AP\text{-to-}BL)}$	$P_{app\ (BL\text{-to-}AP)}$	Total Recovery (%)[3]	Efflux ratio
0.1 µM (0.042 µg/mL) Roflumilast N-oxide[1]	27.6 ± 4.1	40.9 ± 5.4	112 ± 1.4 (AP-to-BL) 113 ± 1.7 (BL-to-AP)	1.48
0.5 µM (0.210 µg/mL) Roflumilast N-oxide[1]	38.8	50.0 ± 2.1	105 ± 1.8 (AP-to-BL) 97.8 ± 2.0 (BL-to-AP)	1.29
0.5 µM (0.210 µg/mL) Roflumilast N-oxide + 5 µM CsA[1]	29.0 ± 1.1	40.6 ± 1.2	108 ± 7.1 (AP-to-BL) 97.5 ± 1.6 (BL-to-AP)	1.40
0.5 µM (0.210 µg/mL) Roflumilast N-oxide + 20 µM Ketoconazole[1]	48.7 ± 4.9	40.8 ± 1.6	108 ± 3.6 (AP-to-BL) 98.1 ± 3.8 (BL-to-AP)	0.838
2 µM (0.838 µg/mL) Roflumilast N-oxide[1]	57.5 ± 6.5	40.0 ± 3.0	128 ± 3.5 (AP-to-BL) 88.3 ± 4.5 (BL-to-AP)	0.696
4 µM (1.68 µg/mL) Roflumilast N-oxide[1]	24.6 ± 5.0	39.9 ± 2.7	101 ± 2.5 (AP-to-BL) 92.5 ± 1.9 (BL-to-AP)	1.62

[1] All data are shown as average ± standard deviation (n=3) if applicable. The results of each individual replicate are listed in Appendix 2.
[2] The total recovery values included the compound accumulated in the receiver, donor, cells, and inserts by the end of the experiment.

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2.6   Analytical Section

2.6.1   How are the active moieties identified and measured in the plasma in the clinical pharmacology studies?

Roflumilast and its N-oxide metabolite were identified via high performance liquide chromatography (HPLC) coupled with tandem mass spectrometry (HPLC-MS/MS) method.

Analytical measurements of roflumilast used HPLC-MS/MS method (10FOREP1S2GLPS134 Validation Report).

2.6.3   Howe was the assay performed for roflumilast?

The analytical methods performed for roflumilast and roflumilast N-oxide were validated.

Characteristics of relevant HPLC-MS/MS methods used in clinical studies for the determination of roflumilast concentrations are summarized in the following table:

Table: Characteristics of most important analytical HPLC-MS/MS methods used in clinical studies for the determination of roflumilast concentrations in plasma

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Validation Summary

Compound:	Roflumilast (reference standard, mfr lot#: R03285)
	Roflumilast-d5 (IS, lot#: FH5/49)
Sample Matrix:	1:1 ACN (with IS)/HBSSg pH 7.4 (v/v);
	1:1 cell lysate (with IS)/HBSSg pH 7.4 (v/v);
Instrument Platform:	API 4000
Ionization:	ESI (+)
Range:	1-250 nM (0.403 ng/mL-101 ng/mL)
Curve Fit:	Linear, $1/x^2$
Sample Volume:	20 µL
Matrix Stability of Roflumilast:	48 hours at room temperature and 48 hours at 2-8 °C
Dilution integrity:	40X
Post Preparative Stability:	3 days for samples in 1:1 ACN (with IS)/HBSSg pH 7.4 (v/v);
	1 day for samples in 1:1 cell lysate (with IS)/HBSSg pH 7.4 (v/v);
Stock Solution Stability in DMSO:	17 days
Working Solution stability (in 1:1 ACN/dH$_2$O (v/v)):	17 days

Source: Page 3 of 32 in the validation report 10FOREP1S2GLPS134

Characteristics of relevant HPLC-MS/MS methods used in clinical studies for the determination of roflumilast N-oxide concentrations are summarized as follows:

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Appendix 3. Analytical Conditions of Roflumilast N-oxide

Equipment

The LC-MS/MS system was an Applied Biosystems API 4000 LC-MS/MS with Perkin Elmer Series 200 MicroPumps, CTC Analytics autosampler, and a Perkin Elmer Mixer.

LC-MS/MS Conditions

LC Conditions

Column: Phenomenex Synergi 4μ Polar-RP 80A 50 × 2.0 mm i.d., 4 micron
Guard Column: IDEX-Frit 0.5 μm 0.062x0.65x0.2485

Mobile Phase: A: 0.2% formic acid in dH_2O
                    B: 0.2% formic acid in MeOH

Gradient Program:

Time (min)	%A	%B	TE#1	TE#2
0.0	70	30	close	open
0.1	70	30	open	open
1.0	28	72	open	close
1.5	5	95	open	open
3.0	5	95	open	open
3.5	70	30	close	open
4.5	70	30	open	open

Flow Rate: 300 μL/minute

Run Time: 4.5 minutes

Retention Times: Roflumilast N-oxide: ~2.48 minutes
                    D5-Roflumilast N-oxide: ~2.48 minutes

Injection Volume: 20 μL

Autosampler Temp: ~ 4ºC

Autosampler Wash #1: acetonitrile: isopropyl alcohol: water: formic acid = 40:30:30:1 (v/v/v/v)
Autosampler Wash #2: 0.2% formic acid in water

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MS Conditions

Mass Spectrometer: Applied Biosystems API 4000 Mass Spectrometer

Source: TurboIonsprayTM

Scan Type: Multiple Reaction Monitoring (MRM)

Polarity: Positive

MRM Transition:

Analyte	Precursor Ion	Product Ion	Declustering Potential (V)	Collision Energy (V)	Entrance Potential (V)	Exit Collision Potential (V)	Dwell (msec)
Roflumilast N-oxide	419.4	187.0	95	37	10	10	150
D5-Roflumilast N-oxide	424.4	190.0	95	37	10	10	150
Roflumilast	404.2	187.0	53	39	10	7	150

Instrument Settings:

Gas 1:   40.00
Gas 2:   40.00
Curtain Gas: 10.00
CAD Gas: 12.00
IonSpray V: 5500.00
Temp: 500.0

Test Items

Identity/Chemical: Roflumilast N-oxide
Description: White powder
Supplier/Manufacturer: Forest Laboratories
Batch/Lot Number: FMD-ROF-005
Purity: 100%
M.W.:   419.2
Storage Conditions: 4 °C refrigerator
Safety Precautions: Standard laboratory precautions

Identity/Chemical: Roflumilast
Description: White powder
Supplier/Manufacturer: Forest Laboratories
Batch/Lot Number: FMD-ROF-007
Purity: 75%
M.W.:   424.2
Storage Conditions: 4 °C refrigerator
Safety Precautions: Standard laboratory precautions

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Table A3.1. Accuracy and Precision Summary Results for Standard Samples

Roflumilast N-oxide (nM)	1	2.5	10	25	50	100	200	250
Measured Concentration (nM)	1.00	3.13	10.0	25.2	50.3	99.3	189	246
	0.853	2.80	10.0	23.9	48.9	95.6	203	234
Mean (nM)	0.927	2.97	10.0	24.6	49.6	97.5	196	240
Accuracy	92.7%	119%	100%	98.2%	99.2%	97.5%	98.0%	96.0%
n	2	2	2	2	2	2	2	2

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Table A3.2. Intra-assay Accuracy Results for QC Samples in 50/50 ACN/HBSSg

Nominal Concentration of Roflumilast N-Oxide (nM)	2.5	25	200
Measured Concentration (nM)	2.76	30.0	197
	3.26	26.5	194
	2.69	26.0	200
	2.24	24.0	195
	2.53	25.1	194
	3.08	196[1]	194
Mean (nM)	2.76	26.3	196
Accuracy	110%	105%	97.8%
RSD	13.4%	8.61%	1.24%
n	6	5	6

[1] The sample might be misplaced with the sample for bench-top stability (Table A3.5), and the value was excluded from the calculation of the average.

Table A3.3. Intra-assay Precision Results in Cell Lysate

Nominal Concentration of Roflumilast N-oxide (nM)	2.5
Measured Concentration (nM)	2.69
	2.64
	2.53
	3.04
	2.70
	3.01
Mean	2.77
Accuracy	111%
RSD	7.51%
n	6

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Table A3.6. Post-Preparative Stability of Roflumilast N-oxide

Nominal Concentration of Roflumilast N-oxide (nM)	2.5	25	200
Measured Concentration (nM)	2.59	26.4	188
	2.67	26.3	206
	2.71	25.6	202
Mean (nM)	2.66	26.1	199
Accuracy	106%	104%	99.3%
RSD	2.30%	1.67%	4.76%
n	3	3	3

Source: page 25 of 34 in the report 10FOREP2.

Table A3.7. Working Solution Stability of Roflumilast N-oxide (7 days)

Roflumilast N-oxide	Peak Area (Counts)	Mean	RPD
Fresh Working solution	5.85E+05	5.58E+05	8.11%
	5.94E+05		
	5.16E+05		
	5.60E+05		
	5.30E+05		
	5.62E+05		
Old Working solution	4.97E+05	5.14E+05	
	5.58E+05		
	4.71E+05		
	4.65E+05		
	5.65E+05		
	5.30E+05		

Source: page 26 of 34 in the report 10FOREP2.

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Appendix 1 Individual Study Review

Study No.: 10FOREP1S2GLPS134

Study Title: Determination of the P-gp Substrate Potential of Roflumilast in Caco-2 Cell Monolayers

Purpose: To determine the potentiali of roflumilast is the P-gp substrate.

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Results:

The results of the permeability and recovery of roflumilast and digoxin in caco-2 cells are shown in the table below:

Table 4. Permeability and Recovery of Roflumilast and Digoxin in Caco-2 Cells

Treatments	$P_{app\ (AP\text{-}to\text{-}BL)}$	$P_{app\ (BL\text{-}to\text{-}AP)}$	Total Recovery (%)[3]	Efflux ratio
0.05 µM (0.0201 µg/mL) Roflumilast[1]	42.1 ± 3.1	30.4 ± 3.6	118 ± 15 (AP-to-BL) 116 ± 5.8 (BL-to-AP)	0.721
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10 µM Digoxin[2]	0.972 ± 0.08	16.7 ± 1.2	93.6 ± 7.0 (AP-to-BL) 97.7 ± 4.2 (BL-to-AP)	17.2
10 µM Digoxin + 5 µM CsA[2]	4.70 ± 0.50	4.44 ± 0.74	102 ± 5.5 (AP-to-BL) 107 ± 7.7 (BL-to-AP)	0.945

[1] All data are shown as average ± standard deviation (n=3). The results of each individual replicate are listed in Appendix 2.
[2] All data are shown as average ± standard deviation (n=4). The results of each individual replicate are listed in Appendix 2.
[3] For Roflumilast, the total recovery values included the compound accumulated in the receiver, donor, cells, and inserts by the end of the experiment. For digoxin, the reported recovery values included the compound accumulated in the receiver and donor by the end of the experiment.

• At the tested concentrations (0.05 ~ 4 µM), Papp (AP-to-BL) values ranged from 32.5 to 48.9 × 10-6 cm/s, and Papp (BL-to-AP) values ranged from 17.9 to 30.4 × 10-6 cm/s; the efflux ratios ranged from 0.488 to 0.751 (Table 4).

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• Because the efflux ratios of Roflumilast were less than 2 at all tested concentrations, Roflumilast is very unlikely a P-gp substrate.1

• Digoxin, a known P-gp substrate, showed efflux ratios of 17.2 and 0.945 in the absence and presence of 5 μM CsA (Table 4) in Caco-2 cells. The results confirmed the functionality of P-gp in this test system.

Conclusion: Determination of the P-gp substrate potential of Roflumilast was carried out using Caco-2 cell monolayers, and the determination was performed at four different concentration of Roflumilast: 0.05, 0.25, 2, and 4 μM (0.0201, 0.101, 0.806, and 1.61 μg/mL). Functional P-gp activity was observed in the same batch of Caco-2 cells. Because the efflux ratios of Roflumilast were less than 2 at all tested concentrations, Roflumilast is not a P-gp substrate.

Reference ID: 2901331

Addendum to Clinical Pharmacology review for NDA 22522 on March 23, 2010

Date: April 22, 2010
NDA: 22522
Drug name: Roflumilast

The following information reflects update on PMC/R (Post Marketing Commitment/Requirement) in clinical pharmacology review for NDA 22522, which was finalized in Darrts on March 23, 2010.

In the original review, the following PMC/R were proposed:

1. *In vitro* evaluation of the potential of roflumilast being a substrate of P-gp (PMC).
2. Quantify the potentially carcinogenic epoxide metabolite of ADCP N-oxide, by way of measuring hydroxy-ADCP N-oxide, in rodents and in humans following multiple doses of roflumilast (PMR).
3. Assess whether human CYP2A7, 2F1 and 2C18 are capable of converting ADCP N-oxide to the epoxide metabolite (by measuring hydroxy-ADCP N-oxide) *in vitro* (PMC).
4. Re-evaluate QT effect in a randomized clinical trial (PMC).

After the Advisory Committee (AC) meeting on April 07, 2010 and further discussion with the review team on April 21, 2010, PMC/R 2, 3 and 4 are no longer needed based on the following rationales.

a). Although deficiencies were identified in the thorough QT study, the review team determined there are sufficient clinical data to conclude that QT prolongation is not an issue for this drug based on the safety profile of the large patient population exposed in clinical development program with cardiac monitoring. Therefore, PMC 4 of re-evaluating QT effect is no longer necessary.

b). PMC/R 2 and 3 above were recommended to evaluate the potential for human carcinogenicity of epoxy ADCP N-oxide, which is formed following roflumilast metabolism. Since then, the review team has concluded that roflumilast can produce carcinogenic metabolite(s) (see addendum to the Minutes of May 10, 2005 ECAC [Executive Carcinogenicity Assessment Committee] Meeting placed in Darrts on January 22, 2010). PMC/R 2 and 3 above are therefore no longer necessary.

c). Since this application will receive a complete response (CR), instead of PMC, comment to evaluate the potential of roflumilast being a substrate of P-gp *in vitro* will be included in the CR letter to the sponsor.

In conclusion, PMC/R 2, 3 and 4 are no longer necessary based on current available data. The Agency will ask the sponsor in the CR letter to evaluate the potential of roflumilast being a substrate of P-gp *in vitro* from a clinical pharmacology perspective.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	022522	*Submission Dates*	0000 (05/13/2009) 0011 (1/29/2010)
Brand Name	Daxas® (proposed)		
Generic Name	Roflumilast		
Reviewer	Ping Ji, Ph.D., Agrawal Arun, Ph.D.		
Team Leader	Yun Xu, Ph.D.		
Pharmacometrics Reviewer	Venkatesh Bhattaram, Ph.D.		
Pharmacometrics Team Leader	Yaning Wang, Ph.D.		
Genomics Reviewer	Mike Pacanowski, Pharm.D., M.P.H.		
Genomics Team Leader	Issam Zineh, Pharm.D., M.P.H.		
OCP Division	Division of Clinical Pharmacology-II		
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)		
Sponsor	Forest Research Institute		
Relevant IND(s)	57,883		
Submission Type; Code	505 (b) (1)		S
Formulation; Strength(s)	Tablet, 500 mcg		
Indication	Chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations		
Proposed Dosing Regimen	One tablet of 500 mcg per day		

Table of Contents

Appears This Way On Original

1 Executive Summary

1.1 Recommendations

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

- *In vitro* evaluation of the potential of roflumilast being a substrate of P-gp (PMC).
- Quantify the potentially carcinogenic epoxide metabolite of ADCP N-oxide, by way of measuring hydroxy-ADCP N-oxide, in rodents and in humans following multiple doses of roflumilast (PMR).
- Assess whether human CYP2A7, 2F1 and 2C18 are capable of converting ADCP N-oxide to the epoxide metabolite (by measuring hydroxy-ADCP N-oxide) *in vitro* (PMC).
- Re-evaluate QT effect in a randomized clinical trial (PMC).

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Daxas® (roflumilast) is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. Roflumilast is a phosphodiesterase-4 (PDE4) inhibitor.

Daxas was evaluated in 19 *in vitro* studies in human biomaterials and 75 Phase 1 & II studies. These studies were designed to evaluate the pharmacokinetics, pharmacodynamics, intrinsic and extrinsic factors, and dose-response relationship of rolumilast. Included in this review are the fifteen *in vitro* studies and 65 Phase 1 and II studies and reports. The remaining studies were not reviewed because they were either exploratory or did not provide additional information. The proposed dosing regimen for COPD patients is one oral table of 500 µg per day, with or without food.

Pharmacokinetics in Healthy Subjects

Absorption
The absolute bioavailability of roflumilast following a 500 µg oral dose is 79%. The median time to reach maximum plasma concentrations of roflumilast (t_{max}) is one hour, while t_{max} of roflumilast N-oxide (the major active metabolite of roflumilast) is eight hours in the fasted state. Food intake delays t_{max} of roflumilast by one hour and reduces C_{max} by 40%; however, C_{max} and t_{max} of roflumilast N-oxide are unaffected. The exposure (AUC and Cmax) of roflumilast and roflumilast N-oxide is dose-proportional over the roflumilast dose range of 250 to 1000 µg.

Distribution
Plasma protein binding of roflumilast and its N-oxide metabolite is 99% and 97%, respectively.

Metabolism and Excretion
Roflumilast is extensively metabolized via Phase 1 (cytochrome P450) and Phase II (conjugation) reactions. Roflumilast N-oxide is the major metabolite observed in human plasma. The plasma AUC of roflumilast N-oxide, on average, is about 10-fold greater than that of roflumilast. *In vitro* studies and clinical drug-drug interaction studies suggested that the metabolism of roflumilast to roflumilast N-oxide was mediated by CYP1A2 and CYP3A4. Following an oral dose of roflumilast, the median plasma effective half-lives of roflumilast and roflumilast N-oxide were 17 and 30 hours, respectively. Steady-state plasma concentrations were reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing of roflumilast. Following once daily oral administration of roflumilast at 500 μg in healthy subjects, the accumulation index was about 1.8 for roflumilast and 2.0 for roflumilast N-oxide. After intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Pharmacokinetics in COPD Patients

The PK of roflumilast in COPD patients was evaluated in studies IN108 and M2-110. As compared to healthy subjects, roflumilast exposure in COPD patients based on mean observed data was about 60% higher for AUC (up to 9 hours) and 6% higher for C_{max}; roflumilast N-oxide exposure in COPD patients was about 30% higher for AUC (up to 9 hours) and 37% higher for C_{max}. Based on a population PK analysis, COPD patients have a 65% higher AUC for roflumilast and about 8% higher AUC for roflumilast N-oxide compared to healthy subjects.

Pharmacokinetics in Special Populations

Age
The age effect on the PK of roflumilast and roflumilast N-oxide was evaluated in study CP-050. The exposure between young (18-45 years old) and middle-aged (45-65 years old) subjects was comparable for both roflumilast and roflumilast N-oxide. However, the exposure in elderly (>65 years old) was 27% higher for AUC and 16% higher for C_{max} for roflumilast and 19% higher for AUC and 13% higher for C_{max} for roflumilast-N-oxide than that in young subjects.

Gender
Women exhibited higher exposures of both roflumilast and roflumilast N-oxide when compared with men (Study CP-050). As compared to male subjects, the AUC of roflumilast was increased by 40%, 79%, and 28%, respectively, for young, middle-aged, and elderly female subjects. The C_{max} of roflumilast was comparable between male and female subjects. As compared to male subjects, the AUC of roflumilast N-oxide was increased by 33%, 52%, and 45%, respectively, for young, middle-aged, and elderly female subjects; the C_{max} of roflumilast N-oxide was

increased by 30%, 53%, and 47%, respectively, for young, middle-aged, and elderly female subjects.

Race

The exposure difference between Caucasians and Japanese was assessed in study CP-048. African American, Hispanic, and Caucasian healthy subjects were enrolled in several drug-drug interaction studies (CP-044, CP-066, CP-067, and CP-068). The impact of subjects being African American and Hispanic on exposure was assessed using the combined dataset from these four studies.

As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 25%, 47%, and 15% higher AUC, respectively, for roflumilast, and 69%, 51%, and 16% higher AUC, respectively, for roflumilast N-oxide. As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 15%, 31%, and 17% higher C_{max}, respectively, for roflumilast, and 17%, 9%, and 5% higher C_{max}, respectively, for roflumilast N-oxide.

Renal Impairment

The effect of renal impairment on the exposure of roflumilast and roflumilast N-oxide was examined after a single dose of 500 µg roflumilast to patients with severe renal impairment as compared to healthy subjects (Study FHP020). As compared to healthy subjects, the roflumilast exposure in severe renal impairment patients was 21% lower for AUC and 16% lower for Cmax. The roflumilast N-oxide exposure in severe renal impairment patients was 7% lower for AUC and was 13% lower for Cmax as compared to healthy subjects.

Hepatic Impairment

The effect of hepatic impairment on the exposure of roflumilast and roflumilast N-oxide was examined after 14 days of oral administration of roflumilast at 250 µg once daily in 16 subjects with mild to moderate hepatic impairment (Child-Pugh category A (n=6) and Child-Pugh category B (n=6)) and compared to healthy subjects (Study CP-062). As compared to healthy subjects, the AUC and C_{max} of roflumilast were 51% and 3% higher for patients with Child-Pugh A, respectively; and 92% and 26% higher for patients with Child-Pugh B, respectively. As compared to healthy subjects, the AUC and C_{max} of roflumilast N-oxide were 24% and 26% higher for patients with Child-Pugh A, respectively; and 42% and 40% higher for patients with Child-Pugh B, respectively.

The effect of intrinsic factors on the exposure of roflumilast and roflumilast N-oxide is shown in the Figures 1 and 2, respectively.

Drug-Drug Interactions

In vitro metabolism studies using human liver microsomes and *in vivo* drug-drug interaction studies indicated that roflumilast is mainly metabolized by CYP3A4 and CYP1A2 and did not inhibit or induce the activity of the major CYP P450 enzymes. *In vitro* study showed that roflumilast did not inhibit P-gp transport.

Drug-drug interaction studies were conducted with the following drugs: midazolam, erythromycin, ketoconazole, rifampicin, fluvoxamine, digoxin, Maalox, salbutamol, formoterol, budesonide, theophylline, cimetidine, warfarin, enoxacin, sildenafil, minulet, montelukast. No significant interactions were observed with midazolam, salbutamol, formoterol, budesonide, warfarin, Maalox, digoxin and montelukast. Coadministration of roflumilast with the rest compounds significantly changed the exposure of roflumilat and/or roflumilst N-oxide (Figures 3 and 4).

Figure 1. The effect of intrinsic factors on roflumilast exposure.
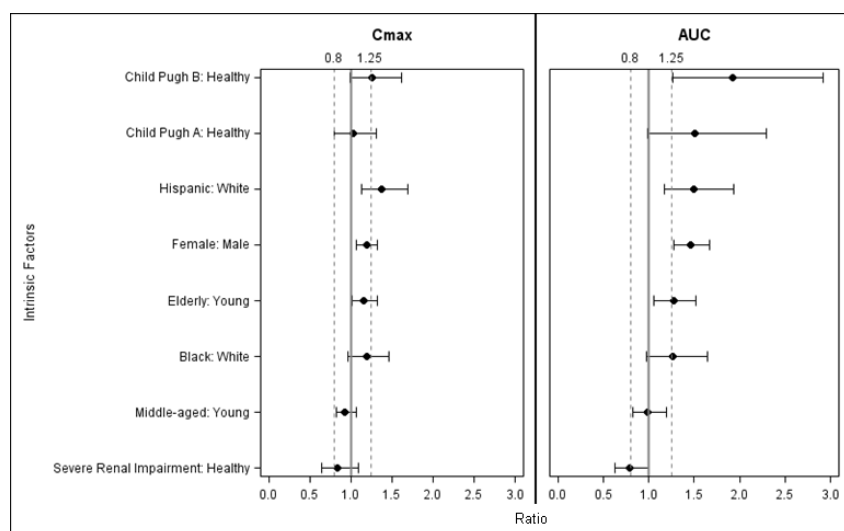
Figure 2. The effect of intrinsic factors on roflumilast N-oxide exposure.
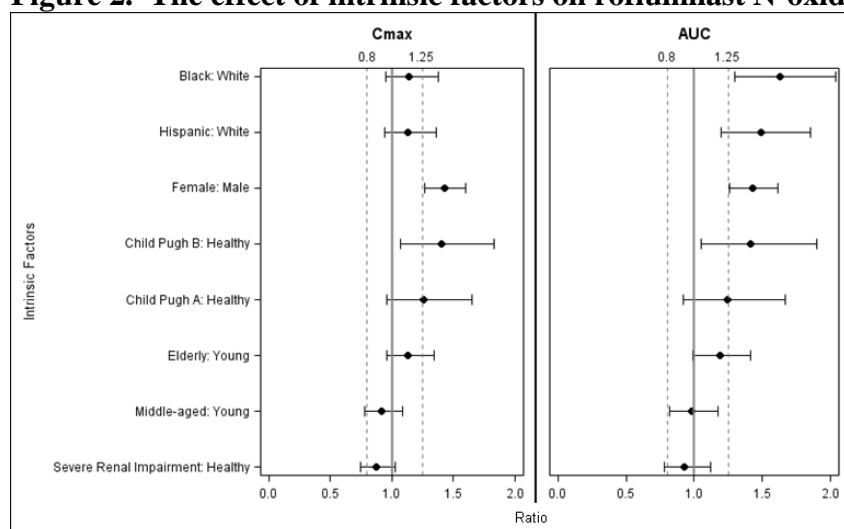
Figure 3. The effect of extrinsic factors on roflumilast exposure.
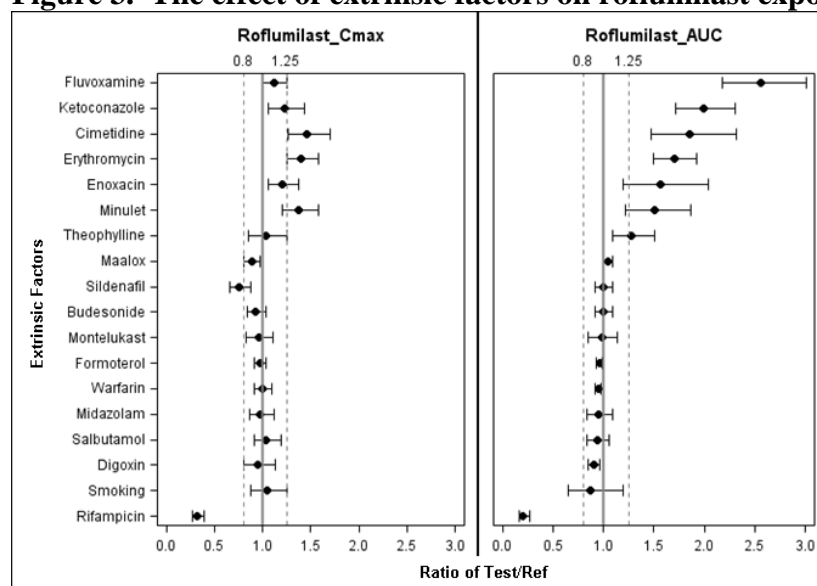
Figure 4. The effect of extrinsic factors on roflumilast N-oxide exposure.
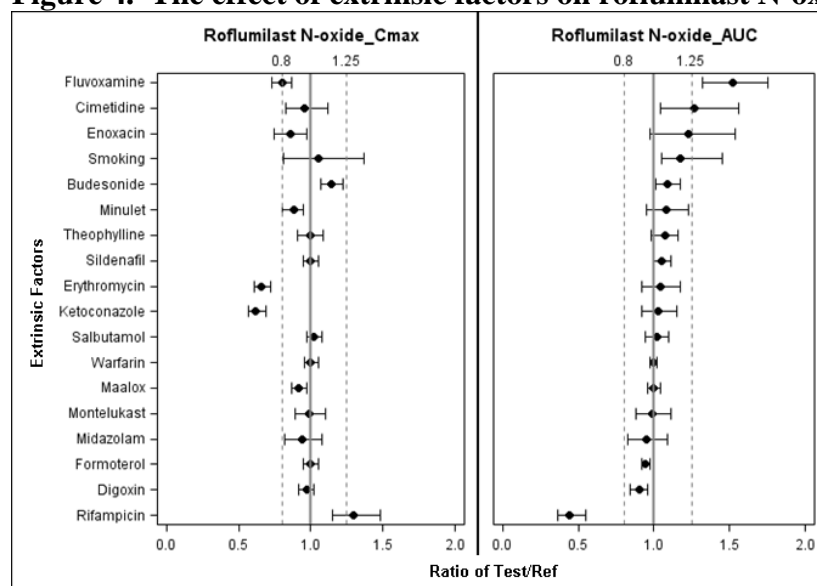
Exposure-response relationship

Exposure-response relationship for effectiveness
The pivotal studies used lung function (pre-bronchodilator FEV1) and a symptomatic benefit endpoint (rate of COPD exacerbations) as primary endpoints. The relationship between exposure (AUC, Cmax of roflumilast, roflumilast N-oxide) and primary endpoints in the registration trials was not characterized. The concentrations of roflumilast and roflumilast N-oxide were not measured in registration trials.

The observed mean change from baseline pre-bronchodilator FEV1 in placebo, 250 and 500 mcg groups from registration trials (M2-124, M2-125), 1 year studies (M2-111, M2-112) and early dose finding studies (M2-107, FK1-101) are shown in Tablebelow.

Table 1. Pre-bronchodilator FEV1 [L] in placebo and treatment groups.

Study	Dose	Mean change from baseline pre-bronchodilator -FEV1 (L)	Mean change from baseline pre-bronchodilator FEV1 (L)- Placebo Corrected
M2-124 (52 wks)	Placebo	0.008	0.039[*]
	500 mcg	0.046	
M2-125 (52 wks)	Placebo	-0.025	0.058[*]
	500 mcg	0.033	
M2-111 (52 wks)	Placebo	-0.012	0.042[*]
	500 mcg	0.030	
M2-112 (52 wks)	Placebo	-0.008	0.057[*]
	500 mcg	0.049	
M2-110 (24 wks)	Placebo	-0.027	0.086[*]
	500 mcg	0.059	
M2-107 (24 wks)	Placebo	-0.039	
	250 mcg	0.024	0.064[*]
	500 mcg	0.049	0.088[*]
FK1 101 (26 wks)	Placebo	0.029	
	250 mcg	0.064	0.035
	500 mcg	0.069	0.041

*- P<0.05
Source:
M2-107; FK1 101- Table 2.73.-68, Page 117 of 124 from summary-clin-efficacy-copd.pdf
M2-124; M2-125- Table 2.5-6, Page 24 of 56 from clinical-overview.pdf
M2-110- Table 2.7.3-42, Page 87 of 214 from summary-clin-efficacy-copd.pdf

Exposure-response relationship for safety
A clear dose-response relationship was observed for diarrhoea, nausea and weight loss. The percentage of patients with safety events such as diarrhoea, nausea and weight loss in pivotal studies pool and COPD safety pool are shown in the following table.

Table 2. Percentage of patients with safety events such as diarrhoea, nausea and weight loss in pivotal studies pool and COPD safety pool.

Dose (µg)	% patients with		
	Diarrhoea	Nausea	Weight loss
Pivotal Studies Pool[a]			
0 (N=1545)	3.2	1.9	2.8
500 (N=1547)	8.4	4.0	10.1
COPD Safety Pool[b]			

0 (N=5491)	2.6	1.4	1.8
250 (N=797)	4.9	2.3	0.8
500 (N=5766)	10.1	5.2	6.8

Source: Table 20 on Page 58 in Report No: iss-iss.pdf
a Includes studies M2-124, M2-125.
b Includes studies FK1 101, FK1 103, IN-108, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128.

Biopharmacuetics

2 Question-Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Roflumilast is a new chemical entity developed by Nycomed for the indication of maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations. The sponsorship of NDA22522 was transferred from Nycomed to Forest Research Institute, Inc. (Forest) effective 4 December 2009. Roflumilast is a PDE4 inhibitor submitted for review. The review status is standard for this NDA.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The active ingredient in Daxas film-coated tablets is roflumilast. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22.

The chemical structure is:
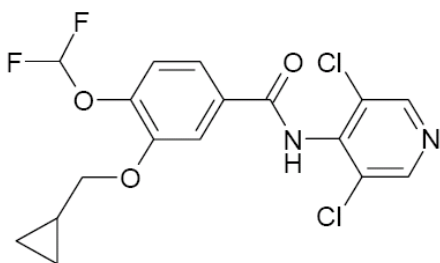
The drug substance is poorly soluble in water. Daxas is supplied as a yellow, D-shaped film-coated tablet, embossed with "D" on one side that contains 500 mcg of roflumilast. Each film-coated tablet of Daxas for oral administration contains the following inactive ingredients: lactose monohydrate, maize starch, povidone and magnesium stearate. In addition, the film-coat contains: hypromellose, Macrogol 4000, titanium dioxide and yellow iron oxide.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

Phosphodiesterases are a large family of intracellular enzymes that hydrolyze the cyclic nucleotides adenosine 3',5'-cyclic monophosphate (cAMP) and/or guanosine 3',5'-cyclic monophosphate (cGMP). Phosphodiesterase 4 (PDE4) is specific for cAMP and is the predominant PDE isoenzyme in many inflammatory cells. Inhibition of PDE4 increases intracellular cAMP and typically leads to an anti-inflammatory effect. Roflumilast is a PDE4 inhibitor. It is a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with chronic obstructive pulmonary disease. Roflumilast targets the PDE4A, 4B and 4D splicing variants with similar potency in the nanomolar range. The affinity to the PDE4C splicing variants is 5 to 10-fold lower. This mechanism of action and the selectivity also apply to roflumilast N-oxide, which is the major active metabolite of roflumilast.

Roflumilast is indicated for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The recommended dosage for patients with COPD is 1 tablet (500 mcg) per day, with or without food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Initially, the clinical development of roflumilast focused on asthma, allergic rhinitis, osteoarthritis, and rheumatoid arthritis. A proof-of-concept study was conducted in patients with diabetes mellitus type II. Roflumilast in a cream formulation is being investigated for the

treatment of plaque psoriasis and atopic dermatitis. None of theafore mentioned indications are included in this submission. Instead, the maintenance treatment of COPD is the focus of the submission.

A total of 19 *in vitro* studies were conducted in human biomaterials to characterize roflumilast plasma protein binding, hepatic metabolism, and drug interaction potential. Among these 19 studies, fifteen studies were reviewed in detail. The rest studies were either exploratory or not relevant to the current submission, and therefore are not included in the current review.

Table: The list of in *vitro* studies reviewed

Index	Study	Objective
1	96/2002	*In vitro* plasma/serum protein binding
2	73/2004	*In vitro* biotransformation of roflumilast and its metabolites with human CYP isoenzymes
3	176/2002	*In vitro* metabolism by human liver microsomes
4	302/2007	*In vitro* reaction phenotyping of roflumilast N-oxide with human liver microsomes and recombinant CYP enzymes
5	283/2005	*In vitro* evaluation of roflumilast as an inhibitor of human CYP enzymes
6	90E/99	Induction of CYP expression in rat and human hepatocytes
7	102/2001	Inhibition of human CYP enzymes by roflumilast N-oxide
8	107/2002	Metabolism of roflumilast in plasma of human, rat, dog, hamster and mouse
9	212/2002	Metabolite profiling of [14C]-roflumilast in human urine from study FHP036
10	266/2002	P-glycoprotein based in vitro interaction between roflumilast and digoxin
11	48/2005	Assessment of ADCP N-oxide metabolism by CYP enzymes potentially expressed in human nasal mucosa
12	142/97	Effect on nasal mucosa of rodents
13	255/2008	Effect on nasal mucosa of rodents
14	12E/99	Metabolism by CYP isoenzymes and microsomes
15	32/2005	*In vitro* interaction

Table: The list of *in vitro* studies not reviewed.

(b) (4)

The Phase 1 & 2 program comprised of a total of 75 studies. These studies were designed to evaluate the pharmacokinetics, pharmacodynamics, intrinsic and extrinsic factors, and dose-response relationship of rolumilast. These investigations included a range of doses and assessed the influence of intrinsic and extrinsic factors. The interactions with probe drugs (i.e. inhibitors and inducers of cytochrome P450 1A2 and 3A4) were investigated to examine the phase 1 metabolism of roflumilast. Furthermore, interactions with other medications were studied, focusing on medications likely to be co-administered with roflumilast.   In addition, five dose ranging studies were also reviewed for the dose-response relationship examination, mainly

focusing on the preFEV1, rate of moderate or severe exacerbation, and discontinuation rate to provide comparative information between 250 and 500 µg once daily dosing regimen.

Table: Intrinsic and extrinsic factors investigated in clinical pharmacology studies with roflumilast.

Intrinsic factors	Extrinsic factors		
age, gender, race, liver impairment, renal impairment, genetic polymorphism	smoking, food intake, time of administration		
	drug interactions with		
	CYP inducers or inhibitors:	Other medications:	
	rifampicin, fluvoxamine, erythromycin, ketoconazole, enoxacin, cimetidine	*theophylline, digoxin, antacid (Maalox®)*	*salbutamol, budesonide, warfarin, midazolam*	*formoterol, montelukast, sildenafil, hormonal contraceptive[a]*

[a] A fixed combination of gestodene and ethinylestradiol.

Source: T-Table 2.5- 1 of page 8 of 56 in section 2.7.5 clinical-overview.pdf

Table: A list of clinical pharmacology and biopharmaceutical studies & reports reviewed.			
Index	**Study**	**Objective**	
		(b) (4)	
2	FHP015	BE of 3 tablet strengths 100, 250 and 500 µg (Form B)	
3	FHP010	Food effect study on 2 x 250 µg form B in caucasian	
4	JP704	Food effect study on 2 x 250 µg form B in Japanese	
5	FHP006	Absolute BA study 2 x 250 µg, form B	
6	FHP001	SAD study (placebo, 1.0, 2.5 and 5 mg) 1 mg is tolerated	
7	FHP002	SAD study (1 mg is tolerated)	
8	FHP005	SAD study after IV up to 0.15 mg	
9	FHP023	Dose proportionality study after multiple dose	
10	FHP039	Dose proportionality study after single and multiple dose between 250 and 500 µg	
11	FHP040	Dose proportionality study after single dose between 125, 250 and 500 µg	
12	FHP036	ADME	
13	FHP011	Distribution study	
14	FHP004	MAD 0.5 mg sid, 1.0 mg sid, 0.5 mg bid. MTD: 0.5 mg/d	
15	FHP009	MAD 0.5 mg sid	
16	CP-043	Circadian influence	
17	JP701	Japan SAD: PD in cortisol levels	
18	FHP018	Age effect elderly 500 ug SD	
19	FHP024	Age effect middle-aged 500 ug SD	
20	FHP025	Age effect elderly 250 ug MD	
21	CP-050	Age and gender	
22	CP-067	500 µg roflumilast and fluvoxamine 50 mg (1A2 strong inhibitor)	
23	FHP021	smoking (1A2 inducer)	
24	FHP027	500 µg roflumilast and digoxin 250 µg (pgp inducer)	
25	CP-044	500 µg roflumilast and Maalox 30 mL (antacid)	
26	FHP014	500 µg roflumilast and salbutamol 600 µg	
27	CP-059	500 µg and inhaled formoterol 48 µg	
28	FHP017	Rof 500 µg and budesonide 800 µg	
29	FHP026	Rof 500 µg and theophylline 750 mg	
30	CP-060	Rof 500 µg and montelukast 10 mg	
31	CP-029	Rof 500 µg and warfarin 25 mg	
32	CP-070	Rof 500 µg and sildenafil 100 mg	

Table: A list of clinical pharmacology and biopharmaceutical studies & reports reviewed.

Index	Study	Objective
		(b) (4)
33	CP-049	Rof 500 µg and repeated enoxacin 800 mg
34	CP-041	Rof 500 µg and cimetidine 800 mg
35	CP-068	500 µg roflumilast and repeated erythromycin 1.5 g (3A4 moderate inhibitor)
36	CP-066	500 µg roflumilast and repeated ketoconazole 400 mg
37	CP-061	500 µg roflumilast and single dose midazolam 2 mg (substrate)
38	CP-064	500 µg roflumilast and repeated dose refampicin 600 mg
39	CP-028	500 µg roflumilast and oral formoterol
40	CP-038	500 µg roflumilast and oral contraceptive
41	JP702	Elderly Japanese studies
42	JP703	Gender in Japanese
43	CP-048	Race (Caucasian and Japanese) (250 µg 500 µg SD on day 1 then repeated dose on days 5-15)
44	CP-069	QT study
45	CP-062	Liver impairment (250 µg QD for 14 days)
46	FHP020	Severe renal impairment 0.5 mg
47	CP-053	Determine 1A2 in (b) (6)
48	CP-054	Determine 3A4 in (b) (6)
49	114/2005	Pop PK report
50	343/2008	Pop PK report in COPD patients
51	65/2004	Pop PK report
52	66/2007	Pop PK report, validation of pop PK
53	121/2005	Pop PK report
54	19/2009	Model based prediction of using SimCyp for 500 mg for liver impairment
55	269/2003	PK and pharmacogenetic analysis of subject (b) (6)
56	M2-110	PK assessments in COPD patients
57	FHP033	250 µg 500 µg QD for male endocrine function testing with PK measurements
58	M2-117	LPS challenge study in healthy volunteers
59	FHP030	PD in COPD patients
60	JP706	Dose ranging assessment in COPD patients in Japanese
61	IN108	PK assessments and dose finding in COPD patients (250 and 500 µg) in Indian
62	FK1101	Initial dose ranging stuy (250 and 500 µg)
63	M2-107	Dose ranging study (250 and 500 µg)
64	JP708	Dose ranging study in Japanese
65	CP-065	PK in asthma children

Table: The list of clinical pharmacology and biopharmaceutical studies not reviewed.

(b) (4)

Table: The list of clinical pharmacology and biopharmaceutical studies not reviewed.
(b) (4)

A total of eighteen phase II and III studies were performed in patients with COPD to establish the therapeutic dose and to assess the efficacy and safety of roflumilast compared to placebo.

- The two pivotal, 52-week studies compared the efficacy of roflumilast 500 μg once daily (QD) versus placebo on exacerbation rate and lung function in patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations (Studies M2-124 and M2-125).
- Two 6-month studies investigated the effects of roflumilast 500 μg QD treatment in patients with moderate to severe COPD receiving long-acting bronchodilator maintenance treatment (salmeterol in Study M2-127 or tiotropium in Study M2-128).
- Seven further studies are considered supportive for this application. These include two 1-year studies (Studies M2-111 and M2-112) which assessed the effect of roflumilast 500 μg QD vs placebo on exacerbation rate and lung function and the following five 6- month placebo-controlled studies focusing on the effects of roflumilast on lung function in patients with moderate to very severe COPD. Study FK1 101 was a dose-range and proof-of-concept study with administration of placebo and two doses of roflumilast (250 μg and 500 μg QD). The dose finding was confirmed in Study M2-107 applying the same doses as in Study FK1 101. Study M2-110 confirmed the positive efficacy results related to lung function with the 500 μg dose of Study M2-107, while Study M2-121 investigated the effects of roflumilast on hyperinflation. Study FK1 103 investigated the effect of roflumilast withdrawal after 12 weeks of treatment, in addition to comparing a 24-week treatment of roflumilast with placebo.
- Seven additional studies were classified as "other studies" as they were of shorter duration (Studies IN-108, M2-119, M2-118), dissimilar in design (Studies FK1 102 and FHP 030, open-label or cross-over) or were conducted under supervision of a different sponsor in Japan (Mitsubishi-Tanabe, Studies JP-706 and JP-708).

Table: Overview phase II and III studies in COPD with roflumilast.

Study code	Roflumilast dose [µg/d]	Population FEV$_1$% pred.	Design	Duration [weeks]	Pts r and treated	Primary endpoints
Pivotal studies - severe to very severe COPD						
M2-124	500	≤50	pbo, p, r, db	52	1523[a]	exac., pre- FEV$_1$
M2-125	500	≤50	pbo, p, r, db	52	1568	exac., pre- FEV$_1$
Supportive studies						
1-year studies						
Severe to very severe COPD						
M2-111	500	≤50	pbo, p, r, db	52	1173	exac., pre-FEV$_1$
M2-112	500	≤50	pbo, p, r, db	52	1513	exac., post-FEV$_1$
6-month studies						
Moderate to severe COPD, in patients on LABD						
M2-127	500+Sal	40 to 70	pbo, p, r, db	24	933	pre-FEV$_1$
M2-128	500+Tio	40 to 70	pbo, p, r, db	24	743	pre-FEV$_1$
Moderate to severe COPD						
M2-107	250, 500	30 to 80	pbo, p, r, db	24	1411	post-FEV$_1$, SGRQ
M2-110	500	30 to 80	pbo, p, r, db	24	909	post-FEV$_1$
Moderate to very severe COPD						
M2-121	500	≤ 65	pbo, p, r, db	24	600	post-FRC, post-FEV$_1$
Early development studies, moderate to severe COPD						
FK1 101	250, 500	35 to 75	pbo, p, r, db	26	516	pre-FEV$_1$, SGRQ
FK1 103	500	35 to 75	pbo, p, r, db	24	581	post-FEV$_1$, SGRQ
Other studies, moderate to severe COPD						
IN-108	250, 500	30 to 80	pbo, p, r, db	12	118	safety
M2-119	500	30 to 80	pbo, p, r, db	12	410	post-FEV$_1$
JP-706	250, 500	30 to 80	pbo, p, r, db	24	600	post-FEV$_1$
JP-708	250, 500	pts from JP-706	pbo, p, r, db	28	152	safety
FHP 030	500	35 to 75	pbo, co, r, db	4	41	sputum neutrophils
M2-118	500	30 to 80	pbo, p, r, db	12	250	exercise endurance
FK1 102[b]	500	pts from FK1 101	open	26	397[c]	safety

[a] One patient was randomized twice (included only once). [b] FK1 102 was the open-label extension of FK1 101.
[c] These patients were randomized in FK1 101 and continued in FK1 102; all patients received roflumilast 500 µg once daily during FK1 102.
co = cross-over, COPD = chronic obstructive pulmonary disease, d = day, db = double-blind, exac. = exacerbation, FEV$_1$ = forced expiratory volume in 1 second, FRC = functional residual capacity, LABD = long-acting bronchodilators, p = parallel, pbo = placebo (controlled), post = post-bronchodilator, pre = pre-bronchodilator, pred. = predicted, pts = patients, r = randomized, Sal = salmeterol (50 µg twice daily), SGRQ = St George's Respiratory Questionnaire, Tio = tiotropium (18 µg once daily).

For detailed review of these studies, please refer to medical review.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The selection of the response endpoints were in line with the recommendations from the "Guidance for Industry: Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment".

According to the guidance, the primary and secondary efficacy endpoints should be chosen based on the drug's putative mechanism of action and the proposed indication for pivotal phase 3 studies. Roflumilast is indicated for the COPD associated with chronic bronchitis in patients at risk of exacerbations. The primary efficacy endpoint should be a clinically meaningful measure of exacerbations. Such measures can include the duration of exacerbations, severity of exacerbations, delay in the occurrence of an exacerbation, or reduction in the frequency of exacerbations. The primary and secondary efficacy/pharmacodynamic endpoints and their measurements in the pivotal clinical studies are listed in the table below.

Table. Efficacy/pharmacodynamic primary and secondary endpoints.

Study	Primary Endpoints	Secondary Endpoints
M2-124	the change from baseline to end of treatment in pre-bronchodilator FEV_1, and the number of moderate or severe exacerbations per patient-year.	post-bronchodilator FEV_1, time to mortality due to any reason, change in CRP, and TDI focal score; included a variety of additional lung function endpoints, further analyses on exacerbations (eg rates by type of exacerbation, time to first exacerbation, proportion of patients with an exacerbation, mean number of exacerbation days, duration of exacerbations), TDI (component scores), mortality due to an exacerbation, symptom score, use of rescue medication, time to study withdrawal, and the EuroQoL.
M2-125	the mean change from baseline (V2) during the treatment period in pre-bronchodilator FEV_1 [L], and the mean rate of COPD exacerbations requiring oral or parenteral corticosteroids, or requiring hospitalization, or leading to death, per patient per year	mean change in post-bronchodilator FEV_1 [L] from baseline (V2) to each post-randomization visit during the treatment period; time to mortality due to any reason; natural log-transformed CRP (C-reactive protein) [mg/L] (mean change from baseline(V2) to last scheduled study visit); mean transition dyspnea index (TDI) focal score during the treatment period.

2.2.3 What are the PK characteristics of roflumilast and roflumilast N-oxide?

a) What are the single-dose and multiple-dose PK characteristics?

Following single oral dose administration of roflumilast in healthy volunteers (FHP040), roflumilast reached maximum plasma concentrations at ~1 h. Roflumilast N-oxide, the major active metabolite, reached maximum plasma concentration at ~4 hours. The pharmacokinetic exposure of both roflumilast and roflumilast N-oxide was approximately dose proportional over

the single oral dose range of 125 µg to 500 µg (FHP040). Roflumilast was well absorbed with an absolute oral bioavailability of 79% (FHP006).

Figure: Mean concentration-time profiles of roflumilast (left) and roflumilast-N-oxide (right) in healthy subjects after a single oral dose of 125, 250 and 500 µg roflumilast (FHP040).
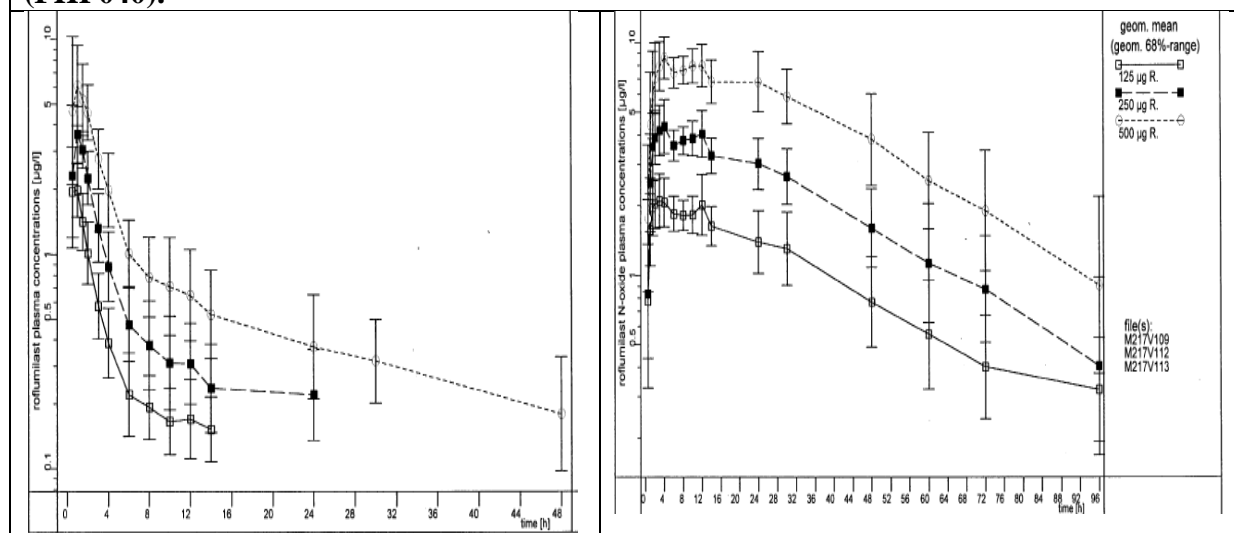
Table: Summary of PK characterististics of roflumilast (left) and roflumilast N-oxide (right) in healthy subjects following single oral dose of 125, 250, and 500 µg (geomean, 68% range; Tmax: meadian (min/max)) (FHP040).

Roflumilast				Roflumilast N-oxide		

Kinetic Characteristic	Dose of Roflumilast			Dose of Roflumilast		
Roflumilast	125 µg	250 µg	500 µg	125 µg	250 µg	500 µg
$AUC_{(0-\infty)}$ [µg/lxh]	6.6* (4.4, 10.0)	18.1** (10.4, 31.4)	40.4 (27.0, 60.3)	96.6 (69.1, 135.2)	187.4 (147.4, 238.1)	435.9 (295.6, 642.8)
C_{max} [µg/l]	2.27 (1.71, 3.02)	3.99 (3.04, 5.22)	7.34 (4.76, 11.31)	2.37 (1.86, 3.01)	4.81 (4.00, 5.78)	9.40 (7.93, 11.13)
t_{max} [h]	0.75 (0.50, 1.00)	1.00 (0.50, 1.50)	1.00 (0.50, 2.00)	6.00 (1.50, 30.00)	4.00 (3.00, 24.00)	4.00 (1.50, 24.00)
$t_{1/2}$ [h]	8.43 (3.13, 22.71)	16.44 (8.16, 33.09)	18.2 (14.43, 23.19)	24.20 (18.75, 31.23)	23.58 (15.48, 35.91)	25.30 (16.16, 39.60)
	*n = 9	**n = 10				

Following oral administration of QD doses of roflumilast 500 µg in healthy volunteers, the accumulation index (AI) based on AUC was about 1.8 for roflumilast and 2.0 for roflumilast N-oxide; the AI based on Cmax was 1.1 for roflumilast and 2.3 for roflumilast N-oxide (FHP039).

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Dose proportionality was established after multiple oral QD doses over the range of 250 µg to 1000 µg (FHP039 and FHP004).

Figure: Mean concentration-time profiles of roflumilast (left) and roflumilast-N-oxide (right) on days 1 and 12 in healthy subjects after a QD doses of 500 µg roflumilast (FHP04039).

Roflumilast	Roflumilast N-oxide

Table: Summary of PK characterististics of roflumilast (left) and roflumilast N-oxide (right) in healthy subjects following oral QD doses of 250, and 500 µg (geomean, 68% range; Tmax: meadian (min/max)) (FHP039).

Roflumilast					Roflumilast N-oxide				

Roflumilast

Pharmacokinetic Characteristic	250 µg roflumilast		500 µg roflumilast	
	Study Day 1	Study Day 12	Study Day 1	Study Day 12
AUC [µg/l x h]	18.1 (*)	17.0 (**)	35.0 (*)	33.7 (**)
(68% range)	(11.1, 29.7)	(10.5, 27.4)	(20.5, 59.8)	(19.3, 58.7)
C_{max} [µg/l]	2.92	3.06	5.27	6.01
(68% range)	(2.00, 4.25)	(2.04, 4.57)	(4.19, 6.63)	(3.75, 9.64)
t_{max} [h]	1.00	1.00	1.25	1.00
(min, max)	(0.50, 2.00)	(0.50, 1.50)	(0.50, 2.00)	(0.50, 2.00)
$t_{1/2}$ [h]	13.56	15.99	14.47	18.01
(68% range)	(7.26, 25.31)	(8.90, 28.74)	(7.86, 26.63)	(10.75, 30.19)

Roflumilast N-oxide

Pharmacokinetic Characteristic	250 µg roflumilast		500 µg roflumilast	
	Study Day 1	Study Day 12	Study Day 1	Study Day 12
$AUC_{(0-\infty)}$ [µg/l x h]	178.6	179.8	351.3	375.4
(68% range)	(115.8, 275.2)	(117.4, 275.2)	(235.5, 524.0)	(231.5, 608.7)
C_{max} [µg/l]	4.50	10.45	9.39	21.66
(68% range)	(3.50, 5.79)	(6.73, 16.23)	(7.48, 11.78)	(13.86, 33.85)
t_{max} [h]	12.00	8.00	11.00	4.00
(min, max)	(2.00, 12.00)	(2.00, 12.00)	(2.00, 12.00)	(1.00, 12.00)
$t_{1/2}$ [h]	22.13	23.13	23.16	21.16
(68% range)	(14.58, 33.58)	(15.87, 33.71)	(14.24, 37.66)	(14.08, 31.81)

*Day 1 AUC was calculated from time 0 to infinity. Day 12 AUC was calculated from 0-24 h.

b) How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The AUC for roflumilast and roflumilast N-oxide are about 60% and 30% higher in COPD patients compared to healthy subjects. The Cmax for roflumilast and roflumilast N-oxide are about 6% and 37% higher in COPD patients compared to healthy subjects.

The pharmacokinetic exposure of roflumilast and roflumilast N-oxide in COPD patients was studied in studies IN108 and M2-110 and compared to that in healthy subjects. As compared to healthy subjects, The AUC of roflumilast is 60% higher in COPD patients based on AUC_{0-10h} at steady state. The AUC of roflumilast N-oxide is about 40% higher in COPD patients based on AUC_{0-10h} at steady state. Based on population pharmacokinetic analysis, COPD patients have a 65% higher exposure ($AUC_{0-\tau}$) to roflumilast and about 8% higher exposure to roflumilast N-oxide.

Figure. Steady state (Mean±SE) roflumilast and roflumilast N-oxide concentrations in healthy subjects and COPD patients after 0.5 mg dose. Data for metabolite are shown only till 9h as there are outliers at 10 h.
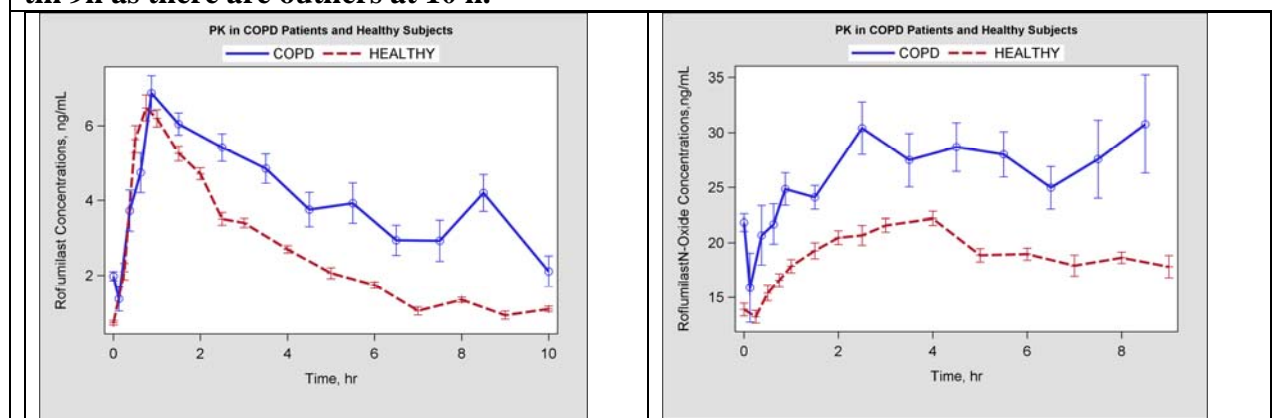
Table. Steady state Cmax (Mean±SE) of roflumilast and roflumilast N-oxide in healthy subjects and COPD patients after 0.5 mg dose.

	Analyte			
	Roflumilast		Roflumilast N-Oxide	
	Healthy	COPD	Healthy	COPD
Cmax	6.48±0.35	6.87±0.47	22.21±0.64	30.42±2.4

c) What are the characteristics of drug absorption?

Roflumilast is rapidly absorbed after oral administration. The absolute bioavailability of a 500 μg oral dose is 79%. The mean peak plasma concentrations of roflumilast and its major active metabolite roflumilast N-oxide are reached in about one and eight hours, respectively.

The absolute bioavailability of roflumilast was assessed in study FHP006. In this study, healthy subjects were given a single dose of 500 μg roflumilsat and a 150 μg i.v. dose over 15-minute infusion. Roflumilast is rapidly absorbed after oral administration. The mean peak plasma concentrations of roflumilast and its major active metabolite roflumilast N-oxide were reached in about one and eight hours, respectively. The absolute bioavailability of a 500 μg oral dose is 79%.

Table: Roflumilast and roflumilast N-oxide PK characteristics (geometric mean, 68% range) after a single dose of roflumilast 500 µg, p.o. or roflumilast 150 µg, i.v. (FHP006).

	Rof 150 µg i.v.	Rof 500 µg p.o.
Roflumilast		
AUC_{inf} [µg×h/L]	14.0 (9.71, 20.3)	37.2 (25.2, 54.9)
C_{max} [µg/L]	6.36 (5.03, 8.04)	8.32 (5.79, 11.9)
$t_{\frac{1}{2}}$ [h]	14.7 (10.0, 21.7)	15.7 (12.3, 19.9)
t_{max} [h] *	0.22 ± 0.01	0.98 ± 0.12
Cl [L/h/kg]	0.137 (0.097, 0.194)	---
$V_d$area [L/kg]	2.92 (2.38, 3.58)	---
Roflumilast -N-oxide		
AUC_{inf} [µg×h/L]	99.2 (80.0, 122)	400 (291, 550)
C_{max} [µg/L]	2.87 (2.30, 3.58)	13.1 (9.88, 17.3)
$t_{\frac{1}{2}}$ [h]	22.7 (14.8, 34.9)	20.6 (15.4, 27.5)
t_{max} [h] *	6.92 ± 0.95	8.83 ± 3.96

* t_{max}: mean±SE

d) What are the characteristics of drug distribution?

The mean volume of distribution of roflumilast was 2.9 L/kg in healthy male subjects, following a 150 µg i.v. dose. The binding of roflumilast and roflumilast N-oxide to human plasma proteins is 99% and 97%, respectively.

The *in vitro* protein binding was conducted in study 96/2002. The fraction of unboiund drug in humans was constant (1.1%) at total roflumilast plasma concentrations ranging from 1 to 10 µg/L. The unbound fraction of roflumilast N-oxide was generally higher. In humans, the free fraction of roflumilast N-oxide was 3.4% in the concentration range of 1-100 µg/l.

e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

The major route of elimination for roflumilast is through hepatic metabolism.

The profiling data suggest that [^{14}C]-roflumilast was extensively metabolized after either oral or i.v. administration. Roflumilast was not detectable in urine. Roflumilast N-oxide was only a trace metabolite in urine (less than 1%).

Table: Pharmacokinetic characteristics of [^{14}C]-radioactivity, B9302-107 and B9502-044 in plasma and balance excretion of radioactivity (geometric mean) following a single oral dose of 0.5 mg and intravenous dose of 0.3 mg [^{14}C]-B9302-107 to healthy subjects (N=6) (FHP036).

PK Charac-teristics (unit)	[^{14}C]-radioactivity		B9302-107		B9502-044	
	po	iv	po	iv	po	iv
C_{max} (µgeq. or µg/l)	18.153	12.320	8.834	8.860	8.496	5.089
AUC/0-∞ (µgeq. or µg x h/l)	592.83	425.21	28.19	26.43	314.95	215.49
t_{max}(h)*	0.50	0.50	0.50	0.50	3.67	6.00
$t_{1/2}$(h)	46.79	44.81	13.41	10.96	17.77	17.55
A^e urine$^+$ (% of dose)	70.1	70.7	-	-	-	-
A^e faeces$^+$ (% of dose)	20.2	20.6	-	-	-	-
A^e total$^+$ (% of dose)	90.3	91.2	-	-	-	-
$F_{absorption}$$^{++}$	0.84	reference	-	-	-	-
$F_{bioavailability}$$^{++}$	-	-	0.64	reference	-	-

* Mean

f) What are the characteristics of drug metabolism?

Roflumilast is extensively metabolized to roflumilast N-oxide via CYP3A4 and CYP1A2.

In human plasma, roflumilast N-oxide was identified (64.8%) in addition to the parent compound (22.7%) after oral administration of 500 mcg roflumilast (Study FHP036 and Report 107/2002). The other metabolites were not detectable. In human urine, unchanged parent compound was not detected and only a trace amount of roflumilast N-oxide (<1%) was found (Study FHP036 and report 212/2002). Four principal components, designated as M-HU01, M-HU02, M-HU04, and M-HU09, were characterized in the urine with individual metabolite concentration as percent of dose of 12, 21, 11, and 10%.

The metabolic routes in human include loss of the cyclopropylmethyl group resulting in a phenol, N-oxidation to form a quarternary N-oxide, and oxidative dechlorination to generate a phenol moiety followed by glucuronidation. Another route of roflumilast metabolism in humans

consists of cleavage of the amide bond resulting in an ADCP-related metabolite. Formation of the roflumilast N-oxide is dependent on the CYP 3A4 and 1A2 isoenzymes.

Figure: Roflumilast metabolic pathways in humans.
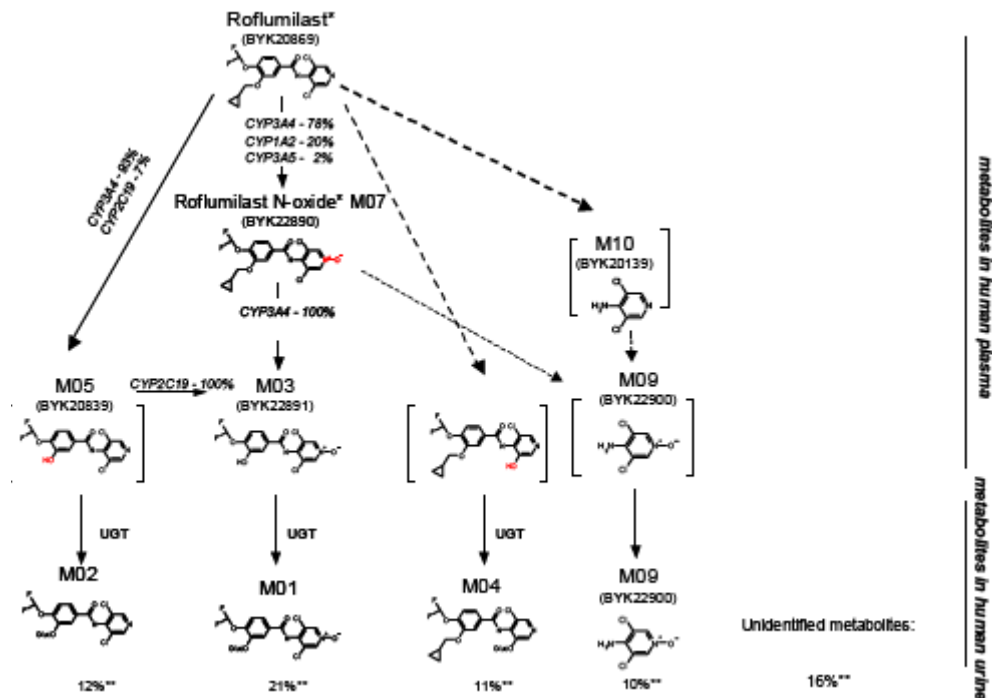
g) What are the characteristics of drug excretion?

After oral or iv administration, about 70% of the administered dose is excreted in the uine, about 20% of the dose is excreted in the feces.

The mean total clearance of roflumilast after i.v. administration of a 150 µg dose is 0.137 L/h/kg, ie 9.59 L/h in a person with a body weight of 70 kg. The mean apparent elimination half-lives of roflumilast and roflumilast N-oxide ranged between about 10 to 33 h and 20 to 44 h, respectively, after a single oral 500 µg dose. The elimination half-lives of roflumilast and its N-oxide are virtually unchanged upon multiple dosing. After oral or i.v. administration, about 70% of the dose is excreted in the urine, primarily as the glucuronides of both the hydroxy-derivatives from roflumilast and its N-oxide metabolite. About 20% of the dose is excreted in the feces (see table in section 2.2.3e).

h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Linearity was established over the once dialy oral dose range of 250 µg and 1000 µg roflumilast.

The systemic exposure (AUC and Cmax) of roflumilast and roflumilast N-oxide increased proportionally after single and repeated roflumilast QD doses of 250 µg and 500 µg (FHP039), after repeated doses of 500 µg QD, 1000 µg QD and 500 µg BID (FHP004), and after repeated QD doses of 500 µg, 750 µg and 1000 µg (FHP023).

Table: Pharmacokinetic characteristics (geometric means / 68%-range) of roflumilast (89302-107) and the metabolite 89502-044 following a gradually increasing repeated oral dose of 500 ug/d (Days 1-7), 750 ug/d (Days 8-14) and 1000 ug/d (Days 15-21) roflumilast to healthy subjects (N=12) (FHP023).

Study day	PK characteristics	Roflumilast (B9302-107)	Metabolite B9502-044
Day 7	AUC [µgxh/l]	32.61 (23.96, 44.37)	347.17 (284.71, 423.33)
	C_{max} [µg/l]	4.740 (3.714, 6.050)	20.681 (17.234, 24.818)
	$t_{\frac{1}{2}}$ [h]	14.33 (9.00, 22.82)	not ascertainable
	t_{max} [h]	2.25 ± 0.56	4.08 ± 0.40
Day 14	AUC [µgxh/l]	50.82 (36.90, 70.00)	587.34 (462.32, 746.17)
	C_{max} [µg/l]	8.153 (6.042, 11.002)	33.720 (27.281, 41.677)
	$t_{\frac{1}{2}}$ [h]	13.70 (8.67, 21.67)	not ascertainable
	t_{max} [h]	1.71 ± 0.28	5.33 ± 0.43
Day 21	AUC [µgxh/l]	65.92 (49.49, 87.81)	799.93 (638.52, 1002.15)
	C_{max} [µg/l]	11.135 (8.289, 14.958)	50.618 (43.766, 58.541)
	$t_{\frac{1}{2}}$ [h]	14.66 (10.39, 20.67)	19.64 (15.08, 25.59)
	t_{max} [h]	1.60 ± 0.39	5.17 ± 0.30

i) How do the PK parameters change with time following chronic dosing?

The PK variables of roflumilast and roflumilast N-oxide were not affected after repeated oral doses.

After repeated oral doses of roflumilast 500 µg in healthy volunteers, the accumulation index (AI) based on AUC was about 1.8 for roflumilast and 2.0 for roflumilast N-oxide; the AI based on Cmax was 1.1 for roflumilast and 2.3 for roflumilast N-oxide (FHP039). The PK variables like Tmax and T1/2 were comparable after single dosing as compared to chronic dosing for roflumilast (FHP039).
.

Table: Summary of PK characteristics of roflumilast (left) and roflumilast N-oxide (right) in healthy subjects following oral QD doses of 250, and 500 µg (geomean, 68% range; Tmax: meadian (min/max)) (FHP039).

Roflumilast	Roflumilast N-oxide

Pharmacokinetic Characteristic	250 µg roflumilast		500 µg roflumilast	
	Study Day 1	Study Day 12	Study Day 1	Study Day 12
AUC [µg/l x h]	18.1 [*]	17.0 [**]	35.0 [*]	33.7 [**]
(68% range)	(11.1, 29.7)	(10.5, 27.4)	(20.5, 59.8)	(19.3, 58.7)
C_{max} [µg/l]	2.92	3.06	5.27	6.01
(68% range)	(2.00, 4.25)	(2.04, 4.57)	(4.19, 6.63)	(3.75, 9.64)
t_{max} [h]	1.00	1.00	1.25	1.00
(min, max)	(0.50, 2.00)	(0.50, 1.50)	(0.50, 2.00)	(0.50, 2.00)
$t_{1/2}$ [h]	13.56	15.99	14.47	18.01
(68% range)	(7.26, 25.31)	(8.90, 28.74)	(7.86, 26.63)	(10.75, 30.19)

Pharmacokinetic Characteristic	250 µg roflumilast		500 µg roflumilast	
	Study Day 1	Study Day 12	Study Day 1	Study Day 12
$AUC_{(0-\infty)}$ [µg/l x h]	178.6	179.8	351.3	375.4
(68% range)	(115.8, 275.2)	(117.4, 275.2)	(235.5, 524.0)	(231.5, 608.7)
C_{max} [µg/l]	4.50	10.45	9.39	21.66
(68% range)	(3.50, 5.79)	(6.73, 16.23)	(7.48, 11.78)	(13.86, 33.85)
t_{max} [h]	12.00	8.00	11.00	4.00
(min, max)	(2.00, 12.00)	(2.00, 12.00)	(2.00, 12.00)	(1.00, 12.00)
$t_{1/2}$ [h]	22.13	23.13	23.16	21.16
(68% range)	(14.58, 33.58)	(15.87, 33.71)	(14.24, 37.66)	(14.08, 31.81)

*Day 1 AUC was calculated from time 0 to infinity. Day 12 AUC was calculated from 0-24 h.

> j) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability was less than 45% for both roflumilast and roflumilast N-oxide. The intra-subject variability was less than 20% for both roflumilast and roflumilast N-oxide.

2.2.4   Exposure-response

2.2.4.1   Is there evidence of dose and response relationship?

The pivotal studies used lung function (pre-bronchodilator FEV1) and a symptomatic benefit endpoint (rate of COPD exacerbations) as primary endpoints.   The relationship between exposure (AUC, Cmax of roflumilast, roflumilast N-oxide) and primary endpoints in the registration trials was not characterized.   The concentrations of roflumilast and roflumilast N-oxide were not measured in registration trials. Details can be found in the PM review.

The observed mean change from baseline pre-bronchodilator FEV1 in placebo, 250 and 500 mcg groups from registration trials (M2-124, M2-125), 1 year studies (M2-111, M2-112) and early dose finding studies (M2-107, FK1-101) are shown in Tablebelow.

Table. Pre-bronchodilator FEV1 [L] in placebo and treatment groups.			
Study	Dose	Mean change from baseline pre-	Mean change from baseline pre-bronchodilator FEV1 (L)-

		bronchodilator -FEV1 (L)	Placebo Corrected
M2-124 (52 wks)	Placebo	0.008	0.039[*]
	500 mcg	0.046	
M2-125 (52 wks)	Placebo	-0.025	0.058[*]
	500 mcg	0.033	
M2-111 (52 wks)	Placebo	-0.012	0.042[*]
	500 mcg	0.030	
M2-112 (52 wks)	Placebo	-0.008	0.057[*]
	500 mcg	0.049	
M2-110 (24 wks)	Placebo	-0.027	0.086[*]
	500 mcg	0.059	
M2-107 (24 wks)	Placebo	-0.039	
	250 mcg	0.024	0.064[*]
	500 mcg	0.049	0.088[*]
FK1 101 (26 wks)	Placebo	0.029	
	250 mcg	0.064	0.035
	500 mcg	0.069	0.041

*- $P < 0.05$
Source:
M2-107; FK1 101- Table 2.73.-68, Page 117 of 124 from summary-clin-efficacy-copd.pdf
M2-124; M2-125- Table 2.5-6, Page 24 of 56 from clinical-overview.pdf
M2-110- Table 2.7.3-42, Page 87 of 214 from summary-clin-efficacy-copd.pdf

For details about the effects of roflumilast on rate of COPD exacerbations please refer to the clinical review.

2.2.4.2   What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

A clear dose-response relationship was observed for diarrhoea, nausea and weight loss. Details can be found in the PM review.

The percentage of patients with safety events such as diarrhoea, nausea and weight loss in pivotal studies pool and COPD safety pool are shown in the following table.

Table. Percentage of patients with safety events such as diarrhoea, nausea and weight loss in pivotal studies pool and COPD safety pool.

Dose (µg)	% patients with		
	Diarrhoea	Nausea	Weight loss
Pivotal Studies Pool[a]			
0 (N=1545)	3.2	1.9	2.8
500 (N=1547)	8.4	4.0	10.1
COPD Safety Pool[b]			
0 (N=5491)	2.6	1.4	1.8
250 (N=797)	4.9	2.3	0.8

| 500 (N=5766) | 10.1 | 5.2 | 6.8 |

Source: Table 20 on Page 58 in Report No: iss-iss.pdf
a Includes studies M2-124, M2-125.
b Includes studies FK1 101, FK1 103, IN-108, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128.

c) Does this drug prolong the QT or QTc interval?

The result of the QT study is inconclusive because assay sensitivity cannot be established. Without a concurrent positive control, the study design cannot exclude small effects (<10 ms) on the QTc interval.

A formal QTC study was conducted in CP-069. The study report was reviewed by the IRT group and documented in Darrts on March 05, 2010. In this single center, placebo- and active-controlled, blinded (not for moxifloxacin), parallel group study, two cohorts of eighty (80) healthy subjects were enrolled. The two cohorts are dosed more than a month apart. The first forty (40) subjects (Group A) enrolled into the study received placebo on Day 1 and then twenty (20) of them received placebo and the other twenty (20) received roflumilast. The second cohort with forty (40) subjects (Group B) enrolled into the study received moxifloxacin on Day 1 and then twenty (20) of them received placebo and the other twenty (20) received roflumilast. In this design, there was no randomization between moxifloxacin and placebo. In addition, moxifloxacin was not conducted concurrently with investigational drug. This design is problematic for the following reasons: 1) moxifloxacin was not randomized with other treatment arms; 2) the time between moxifloxacin and its baseline was only one day apart while the time between study drug and its baseline was at least 16 days apart; 3) the mild moxifloxacin-induced QTcP (population corrected QT) effect was not demonstrated in this study since the largest lower 90% confidence bound for ΔΔQTcP was below 5 ms; and 4) our analysis indicated that data discrepancy for the same treatment arms existed between Group A and Group B (Table 9), which makes it 2 questionable if combining two groups together. We do not believe further analysis of existing data will be meaningful. The sponsor needs to re-evaluate the QT effect in a randomized clinical trial.

 Details of QT/IRT review can be found in QT review.

2.3   Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

    a) Elderly

The exposure of roflumilast and roflumilast N-oxide appeared to be higher in elderly subjects as compared to middle-aged or young subjects.

The potential age effect on pharmacokinetic characteristics was examined in four studies: FHP018, FHP024, FHP025, and CP-050. A summary of the pharmacokinetic findings from these studies are shown in the table below. As shown from study CP-050, the exposure between young and middle-aged population appeared to be comparable. However, the exposure in elderly were 27% higher in AUC and 16% higher in Cmax for roflumilast and 19% higher in AUC and 13% higher in Cmax for roflumilast-N-oxide than that in young volunteers. This observation is also consistent from the other three studies.

Table: Effect of age on pharmacokinetics of roflumilast and roflumilast N-oxide in studies FHP018, FHP024, FHP025, and CP-050.

Study No.	Subjects	Dose	Roflumilast		Roflumilast N-oxide	
			AUC (µg x h/L)	Cmax (µg/L)	AUC (µg x h/L)	Cmax (µg/L)
FHP018	Elderly>~65 years, n=12	0.5 mg SD	53	4.68	422	8.56
FHP024	Middle- aged (45-65 years), n=12	0.5 mg SD	40	5.43	384	8.53
FHP025	Elderly >=65 years, n=18	0.25 mg SD & MD	27 (Day 1) 39 (day 11)	2.9 (Day 1) 3.5 (Day 11)	211 (Day 1) 255 (Day 11)	3.6 (Day 1) 13.6 (Day 11)
CP-050	Young (18-45 years), n=19	0.5 mg MD	53	8.74	605	37.7
	Middle aged (45-65 years), n=22	0.5 mg MD	52	8.17	593	34.88
	Elderly (>65 year), n=22	0.5 mg MD	67	10.17	717	42.75

b) Pediatric patients

Safety and effectiveness of roflumilast in children and adolescents below 18 years of age have not been established. Roflumilast is not recommended in this population.

c) Gender

Women exhibited higher exposures of both roflumilast and roflumilast N-oxide when compared with men at all age groups.

The gender effect was evaluated in study CP-050 and population population analysis. As compared to male subjects, the AUC of roflumilast was increased by 40%, 79%, and 28%, respectively, for young, middle-aged, and elderly female subjects. The C_{max} of roflumilast was comparable between male and female subjects. As compared to male subjects, the AUC of roflumilast N-oxide was increased by 33%, 52%, and 45%, respectively, for young, middle-aged,

and elderly female subjects; the C_{max} of roflumilast N-oxide was increased by 30%, 53%, and 47%, respectively, for young, middle-aged, and elderly female subjects.

Table: Pharmacokinetic variables of roflumilast and roflumilast N-oxide in males and females in study CP-050.

Roflumilast:

	Elderly		Middle aged		Young	
	Female	Male	Female	Male	Female	Male
C_{max} [ug/l]	11.16 12.62 – 9.871	9.41 11.54 – 7.67	9.57 12.09 – 7.58	6.97 9.12 – 5.32	8.89 11.35 – 6.96	8.61 11.82 – 6.27
AUCT [h*ug/l]	76.75 107.12 – 54.99	60.15 80.20 – 45.12	70.17 85.12 – 57.84	39.25 51.61 – 29.84	63.31 94.62 – 42.36	45.32 58.39 – 35.17
CLss/FBW [l/h/kg]	0.0957 0.1375 – 0.0666	0.1068 0.1418 – 0.0804	0.1025 0.1312 – 0.0803	0.1548 0.2203 – 0.1087	0.1142 0.1739 – 0.0749	0.1385 0.1925 – 0.0996
$t_{\frac{1}{2}}$ [h]	38.5 50.0 – 29.64	25.84 31.58 – 21.14	34.32 43.94 – 26.8	24.14 32.66 – 17.84	31.47 43.03 – 23.01	29.26 49.4 – 17.32

Roflumilast N-oxide:

	Elderly		Middle aged		Young	
	Female	Male	Female	Male	Female	Male
C_{max}[ug/l]	52.81 64.75 – 43.08	35.84 44.57 – 28.82	43.09 55.4 – 33.51	28.23 35.25 – 22.6	43.31 62.09 – 30.21	33.31 44.44 – 24.97
AUCT[h*ug/l]	879.03 1127.456 – 685.34	605.76 803.99 – 456.41	731.14 931.13 – 574.1	481.136 623.25 – 371.42	703.85 1063.13 – 465.98	528.59 690.85 – 404.44
$t_{\frac{1}{2}}$[h]	43.07 60.52 – 30.65	29.28 34.04 – 25.19	39.47 49.56 – 31.42	25.36 34.19 – 18.81	35.38 51.63 - 24.24	25.4 36.69 - 17.58

d) Race

As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 25%, 47%, and 15% higher AUC, respectively, for roflumilast and 69%, 51%, and 16% higher AUC, respectively, for roflumilast N-oxide.   As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 15%, 31%, and 17% higher C_{max}, respectively, for roflumilast and 17%, 9%, and 5% higher C_{max}, respectively, for roflumilast N-oxide.

The exposure difference between Caucasians and Japanese was assessed in study CP-048. African American, Hispanic, and Caucasian healthy subjects were enrolled in several drug-drug interaction studies (CP-044, CP-066, CP-067, and CP-068). The impact of subjects being

African American and Hispanic on exposure was assessed using the combined dataset from these four studies.

As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 25%, 47%, and 15% higher AUC, respectively, for roflumilast, and 69%, 51%, and 16% higher AUC, respectively, for roflumilast N-oxide. As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 15%, 31%, and 17% higher C_{max}, respectively, for roflumilast, and 17%, 9%, and 5% higher C_{max}, respectively, for roflumilast N-oxide.

Table: Exposure of roflumilast and roflumilast N-oxide in Study CP-048 (Geomean).		
	Caucasian	Japanese
Roflumilast		
250 µg		
AUC (µg x h/L)	22.5 (Day 1)	26.0 (Day 1)
	23.3 (Day 15)	27.6 (Day 15)
Cmax (µg/L)	2.67 (Day 1)	2.99 (Day 1)
	2.87 (Day 15)	3.13 (Day 15)
500 µg		
AUC (µg x h/L)	49.4 (Day 1)	54.4 (Day 1)
	46.03 (Day 15)	52.9 (Day 15)
Cmax (µg/L)	5.2 (Day 1)	6. 1 (Day 1)
	5.9 (Day 15)	6.22 (Day 15)
Roflumilast N-oxide		
250 µg		
AUC (µg x h/L)	243 (Day 1)	278 (Day 1)
	234 (Day 15)	265 (Day 15)
Cmax (µg/L)	4.78 (Day 1)	5.61 (Day 1)
	12.2 (Day 15)	13.4 (Day 15)
500 µg		
AUC (µg x h/L)	485 (Day 1)	578 (Day 1)
	468 (Day 15)	545 (Day 15)
Cmax (µg/L)	9.98 (Day 1)	11.5 (Day 1)
	23.99 (Day 15)	28.17 (Day 15)

Table: Exposure of roflumilast and roflumilast N-oxide (mean [SD])			
	Black	Hispanic	White
Roflumilast			
500 µg			
AUC (µg x h/L)	54.4 (24)	63.4 (22.2)	42.7 (16.5)
Cmax (µg/L)	6.7 (2.0)	7.7 (1.9)	5.8 (2.5)
Roflumilast N-oxide			
500 µg			
AUC (µg x h/L)	764 (298)	682 (199)	453 (126)
Cmax (µg/L)	11.2 (3.1)	11.1 (3.0)	9.5 (1.4)

Note: data from studies CP-044, CP-066, CP-067, and CP-068.

e) renal impairment

The exposure of roflumilast in severe renal impairment patients was 21% less for AUC and 19% less for Cmax as compared to healthy subjects. The exposure of roflumilast N-oxide in severe renal impairment patients was comparable for AUC as compared to healthy subjects.

The effect of renal impairment on the exposure of roflumilast (and its principal metabolite roflumilast N-oxide) was examined after a single dose of 500 µg to patients with severe renal impairment compared to healthy volunteers (Study FHP020). As compared to healthy subjects, the roflumilast exposure in severe renal impairment patients was 21% lower for AUC and 16% lower for Cmax. The roflumilast N-oxide exposure in severe renal impairment patients was 7% lower for AUC and was 13% lower for Cmax as compared to healthy subjects.

Table: The exposure of roflumilast and roflumilast N-oxide in severe renal impairment patients and in healthy subjects (Study FHP020).

Patients with renal impairment:	B9302-107	B9502-044
$AUC_{(0-\infty)}$ (µgxh/l)	35.48 (23.73, 53.04)	428.93 (334.19, 550.54)
C_{max} (µg/l)	4.266 (2.744, 6.633)	6.840 (5.350, 8.745)
$t_{1/2}$ (h)	22.08 (14.18, 34.41)	37.40 (21.88, 63.94)
t_{max} (h)	1.38 ± 0.16	19.82 ± 4.41

Healthy control subjects:	B9302-107	B9502-044
$AUC_{(0-\infty)}$ (µgxh/l)	44.69 (33.47, 59.68)	461.18 (366.23, 580.74)
C_{max} (µg/l)	5.072 (3.625, 7.097)	7.780 (6.350, 9.534)
$t_{1/2}$ (h)	18.52 (11.43, 30.00)	28.70 (21.97, 37.49)
t_{max} (h)	1.79 ± 0.18	16.92 ± 2.88

f) hepatic impairment

When comparing patients with liver cirrhosis to healthy subjects, an increase in exposure was observed in patients with liver cirrhosis Child-Pugh stage A and B for both roflumilast and roflumilast N-oxide.

The effect of hepatic impairment on the exposure of roflumilast and roflumilast N-oxide was examined after 14 days of oral administration of roflumilast at 250 µg once daily in 16 subjects with mild to moderate hepatic impairment (Child-Pugh category A (6) and Child-Pugh category B (6)) and compared to healthy subjects (Study CP-062). As compared to healthy subjects, the AUC and C_{max} of roflumilast were 51% and 3% higher for patients with Child-Pugh A, respectively; and 92% and 26% higher for patients with Child-Pugh B, respectively. As compared to healthy subjects, the AUC and C_{max} of roflumilast N-oxide were 24% and 26% higher for patients with Child-Pugh A, respectively; and 42% and 40% higher for patients with Child-Pugh B, respectively.

Primary pharmacokinetic parameter estimates of roflumilast following a 14-day oral administration of roflumilast (250 µg once daily) in patients with liver cirrhosis Child-Pugh A and B as compared with healthy subjects; geometric mean, 68% range

Parameter	N^a	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
$AUC_{(0-24h)}$	8	30.018	45.279	57.711
(hr*µg/L)		19.907, 45.265	32.435, 63.211	29.953, 111.191
CLssFBW	8	0.119	0.075	0.066
(L/hr/kg)		0.077, 0.183	0.050, 0.113	0.031, 0.140
C_{max}	8	4.705	4.828	5.950
(µg/L)		3.822, 5.791	3.693, 6.311	4.149, 8.531

[a]There were 8 observations in each of the 3 groups

Primary pharmacokinetic parameter estimates of roflumilast N-oxide following a 14-day oral administration of roflumilast (250 µg once daily) in patients with liver cirrhosis Child-Pugh A and B as compared with healthy subjects; geometric mean, 68% range

Parameter	N^a	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
$AUC_{(0-24h)}$	8	308.69	382.66	436.13
(hr*µg/L)		210.35, 453.02	283.27, 516.94	309.55, 614.47
C_{max}	8	17.61	22.12	24.65
(µg/L)		12.71, 24.39	16.89, 28.96	17.55, 34.63

[a]There were 8 observations in each of the 3 groups

g) genetic polymorphism

CYP3A4 and CYP1A2 are the major enzymes involved in roflumilast metabolism. One subject in the Phase 1 database appeared to be a pharmacokinetic outlier; this individual carried a novel, rare CYP3A4 frameshift mutation and also had reduced CYP1A2 metabolism phenotype. The prevalence of this CYP3A4/CYP1A2 phenotype combination is expected to be low in the general population. In the absence of pharmacokinetic data according to other common reduced function alleles of CYP3A4, CYP3A5, or CYP1A2, specific dosing recommendations cannot be made.

The sponsor identified a single subject (out of 16) in study FHP027 (digoxin drug interaction study), subject   (b) (6)   who exhibited a significantly higher exposure to roflumilast and roflumilast N-oxide than other subjects enrolled in the study.   (b) (6)   roflumilast and roflumilast N-oxide AUC_{0-24} were five-fold and three-fold higher, respectively, than the total population average on both study days, and the half-life was prolonged.

	Roflumilast			Roflumilast N-Oxide		
	(b) (6) single dose	(b) (6) multiple dose	All Subjects (68% range)	(b) (6) single dose	(b) (6) multiple dose	All Subjects (68% range)
AUC0-24 (ug/l-h)	53.8	267.6	50.2 (29.8-84.6)	146.6	1396.5	504.4 (339.6-749.2)
Cmax (ug/l)	10.2	18.9	9.9 (6.9-14.2)	5.6	68.7	30.9 (22.8-42.0)
t1/2 (h)	79.0	not ascertained	14.4 (9.1-22.9)	not ascertained	not ascertained	35.5 (23.3-51.2)
Metabolic ratio	0.30	0.19	0.10 (0.09-0.10)		9.52	

Source: Sponsor's report 269/2003

Phenotyping was performed on (b) (6) for CYP1A2 (caffeine probe) and CYP3A4 (midazolam probe). (b) (6) had both reduced CYP1A2 and CYP3A4 metabolism Sequencing of *CYP1A2* revealed one silent SNP 5347 T>C in exon 7 which did not alter the amino acid sequence of the protein; (b) (6) did not carry the *CYP1A2*1K* allele. Sequencing of CYP3A4 revealed a new, previously undescribed allele in exon 13, now known as *CYP3A4*20*, which results in a frameshift that introduces a premature stop codon and truncated CYP3A4. In vitro functional studies (yeast, HEK298 cells) of this mutation revealed 1) absence of antibody binding to CYP3A4 C-terminal peptide, 2) five-fold lower expression compared the CYP3A4*1, 3) loss of heme binding, and 4) no hydroxylation of prototypic CYP3A4 substrates (testosterone, midazolam).

Pooled analysis was performed for PK data from the following multiple dose studies wherein subjects received 500 mcg of roflumilast daily (n=145), as shown in the figure below: studies FHP014, FHP017, FHP026, FHP027, FHP029, FHP039, CP050, CP060, and CP061. The exposure in subject (b) (6) from study FHP027 exceeded that of all other phase I study subjects. Thus, subject (b) (6) appears to be an outlier. The prevalence of this CYP3A4/CYP1A2 phenotype combination is expected to be low in the general population. For detailed review, please see the PG review.

Roflumilast and Roflumilast N-oxide Exposure in Multiple Dose Studies
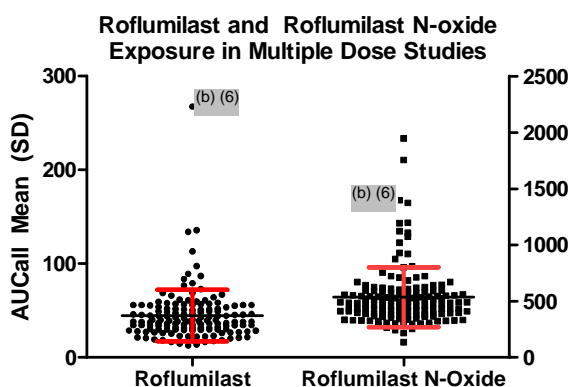
h) what pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled studies of roflumilast in pregnant women. Nonetheless, the safe use during pregnancy is not established and Roflumilast should not be used during pregnancy. There are no human studies that have investigated effects of roflumilast on preterm labor or labor at term. Roflumilast should not be used during labor and delivery.

        i)   other factors that are important to understanding the drug's efficacy and safety
None.

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The exposure of roflumilast and roflumilast N-oxide is affected by age, gender, race, and hepatic impairment. The AEs of most interest for this application are GI and weight loss. The benefit of reducing the rate of moderate or severe exacbation and increase of pre-bronchodilator FEV1 was balanced agains the risk of GI disorders and weight loss in considering the dosing recommendation.

        a)   Elderly

The exposure of roflumilast was increased in elderly patients. The clinical significance is dependent on the subgroup analysis in safety and efficacy. Please refer to medical review for further information.

        b)   Gender
The exposure of roflumilast was higher in women as compared to men. The clinical significance is dependent on the subgroup analysis in safety and efficacy. Please refer to medical review review for further information.

        c)   Race
The exposure of roflumilast was higher in Hispanic, Black and Japanese as compared to White patients. The clinical significance is dependent on the subgroup analysis in safety and efficacy. Please refer to medical review review for further information.

        d)   Renal impairment
No dose adjustment is needed for renal impairment patients.

        e)   Hepatic impairment
Roflumilast is contraindicated in hepatic moderate and severe impairment patients and use with caution in mild hepatic impairment patients.

        f)   Genetic polymorphism

Genotype data from subjects in clinical pharmacology studies were not submitted. The need for dose adjustment based on common drug metabolism gene variants cannot be determined.

g)   Pregnancy and lactation

Roflumilast should not be used during pregnancy and lactation as not adequate and well-controlled studies have been conducted.

2.4   Extrinsic Factors

2.4.1.   What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Smoking did not appear to affect the exposure of both roflumilast and roflumilast N-oxide (Study FHP021).

The effect of smoking on the PK exposure was evaluated in study FHP021. The result showed that smoking did not appear to affect the exposure of both roflumilast and roflumilast N-oxide.

Table: Effect of smoking on the roflumilast and roflumilast N-oxide exposure in study FHP021.					
Roflumilast Dose	Number of Subjects	Roflumilast (mean %change)		Roflumilast N-oxide (mean %change)	
		Cmax (90% CI)	AUC (90%CI)	Cmax (90% CI)	AUC (90%CI)
500 µg po SD	Smokers: 12 Non-smokers:12	↔	↓13% (↓35-↑19%)	↔	↑17% (↓5%-↑45%)

2.4.2.   Drug-Drug Interactions

a) is there an *in vitro* basis to suspect in vivo drug-drug interactions?

Yes. As demonstreated from in vitro experiments using recombinant cytochrome P450s, roflumilast is mainly a substrate of CYP3A4 and 1A2. Therefore, the exposure of roflumilast is expected to increase when inhibitors of CYP3A4 or CYP1A2 are coadministered and decrease when inducers of CYP3A4 or CYP1A2 are coadminitered.

In vitro metabolism of roflumilast and its pharmacodynamically active metabolite roflumilast N-oxide was evaluated in study 73/2004 using recombinant human CYP isoenzymes (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5). Taking into account the relative abundances of each CYP isoenzyme in human

liver, roflumilast was mainly oxidized to Roflumilast N-oxide by CYP3A4 and CYP1A2. A schematic diagram showing the enzymatic pathway is shown in the following figure.

Figure: contribution of cytochrome P450 isoenzymes involved in the metabolism of Roflumilast metabolites identified in human plasma were derived from *in vitro* experiments using recombinant cytochrome P450s CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5 incubated at a substrate concentration close to C$_{max}$ levels obtained *in vivo*.

b) is the drug a substrate of CYP enzymes?
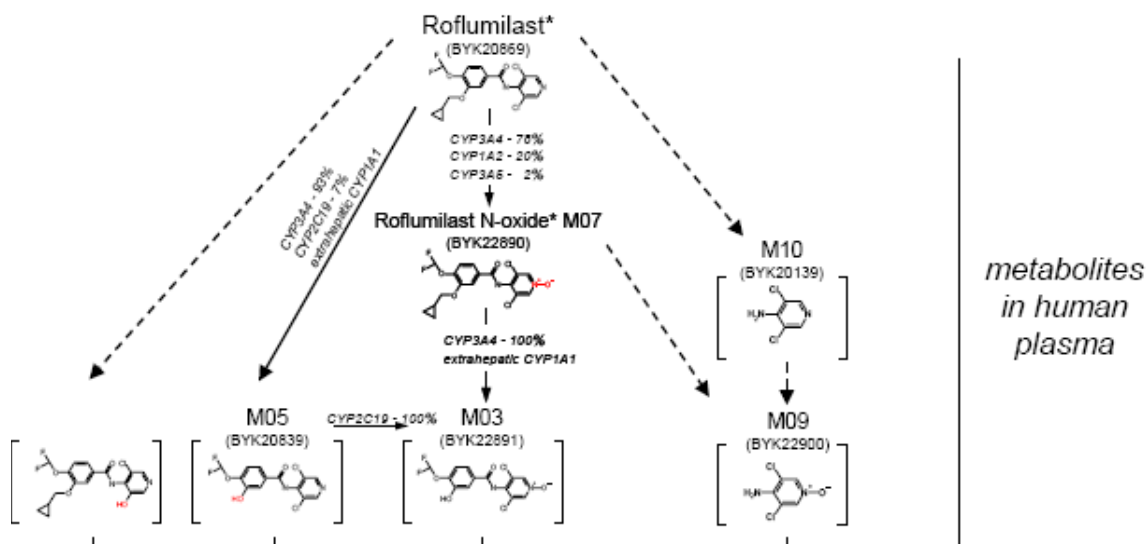
Yes. Roflumilast is the substrate of CYP1A2 and 3A4.

Roflumilast is metabolized to its major metabolite, roflumilast N-oxide, mainly by recombinant CYP1A2 and CYP3A4 (Study 73/2004). This is also confirmed in human liver microsomes, where these CYP isoforms were inhibited by the chemical inhibitors furafylline (CYP1A2) or ketoconazole (CYP3A4) (Study 176/2002).   In the presence of NADPH, roflumilast was metabolized *in vitro* to its major metabolite, roflumilast N-oxide mainly by supersomes expressing CYP1A2 or CYP3A4. Microsomes coincubated with a chemical inhibitor of Cytochrome P450-isoenzymes showed a reduction of metabolism of roflumilast to its N-oxide of $63.9\% \pm 4.5\%$ for furafylline, of $59.9\% \pm 8.0\%$ for ketokonazole and of $78.3\% \pm 1.6\%$ for the combination of furafylline and ketokonazole compared to microsomes without chemical inhibition.

In addition, the potential of roflumilast as a substrat of CYP enzymes are demonstrated from the following in vivo studies, where CYP3A4 inhibitors or inducers are coadministtered with roflumilast. The results from these studies showed that the exposure of roflumilast was

increased when coadministered with CYP3A4 inhibitor and decreased when coadministered with CYP inducer.

Coadministered Drug	Dose of Coadministered Drug	Roflumilast Dose	Number of Subjects	Roflumilast (Mean %change)		Roflumilast N-oxide (mean %change)	
				Cmax (90% CI)	AUC (90%CI)	Cmax (90% CI)	AUC (90%CI)
Erythromycin CP-068	500 mg po TID on Days 9-21	500 µg SD on days 1 and 15	16	↑40% (25-58%)	↑70% (50-92%)	↓34% (28-39%)	↔
Ketoconazole CP-066	200 mg po BID on Days 8-20	500 µg QD on days 1 and 11	16	↑23% (6-43%)	↑99% (71-131%)	↓38% (31-43%)	↔
Rifampicin CP-064	600 mg po QD on Days 5-15	500 µg SD on days 1 and 12	15	↓68% (61-73%)	↓80% (73-84%)	↑ 30% (15-48%)	↓56% (45-64%)
Fluvoxamine CP-067	50 mg po QD on Days 8-21	500 µg SD on days 1 and 15	16	12% (0-25%)	↑156% (118-201%)	↓20% (13-27%)	↑52% (32-75%)
Smoking FHP021	-	500 µg po SD	Smokers: 12 Non-smokers:12	↔	↓13% (↓35-↑19%)	↔	↑17% (↓5%-↑45%)

c) Is the drug an inhibitor and/or an inducer of CYP enzymes?

Roflumilast is not shown to be an inhibitor and/or inducer of CYP enzymes.

In vitro studies showed that roflumilast was a competitive inhibitor of CYP3A4/5 (Ki = 2.79 µM), a minor direct inhibitor of CYP2B6 (Ki = 133 µM), but was not an irreversible metabolism-dependent inhibitor of CYP2B6 or CYP3A4/5. Roflumilast did not induce CYP1A1/2, CYP2B1/2, CYP3A1/2 and CYP4A1-3 in rat hepatocyte cultures; however, it exhibited weak induction of CYP2B6 in human hepatocyte cultures at 0.1 µM, which is about 10 times the human Cmax in plasma. However, *in vivo* studies as shown in the following tabe showed that roflumilast did not alter the exposure of coadministered drugs investigated.

Table: Effect of Roflumilast on Coadministered Drug Plasma Cmax and AUC

				Coadministered Drug (mean %change)	
Coadministered Drug	dose	Roflumilast Dose	Number of Subjects	Cmax (90% CI)	AUC (90%CI)
Midazolam CP-061	1 mg iv SD 2 mg po SD	500 µg QD	18	↔	↔
Digoxin FHP027	250 µg po SD on Days 1 and 14	500 µg po QD on days 1-14	16	↔	↔
Salbutamol FHP014	200 µg TID pi for 7 days	500 µg po QD for 7 days	12	-	↔[1]

Coadministered Drug	dose	Roflumilast Dose	Number of Subjects	Coadministered Drug (mean %change)	
				Cmax (90% CI)	AUC (90%CI)
Formoterol CP028	40 µg po SD on day 10	250 µg po QD on Days 1-10	24	↔	↔
Budesonide FHP017	400 µg BID pi for 7 days	500 µg po QD for 7 days	12	↑18%[2] (↓4-↑44%)	↑16%[2] (↓9-↑48%)
Theophylline FHP026	375 mg BID po for 5 days	500 µg po QD for 5 days	24	↔	↔
Warfarin CP-029	250 mg po SD on days 14 & 8	500 µg po QD on days 1-12	21	↔	↔
Sildenafil CP-070	100 mg SD	500 µg po SD	12	↓13% (↓28-↑6%) ↓26%[3] (8-39%)	↔
Montelukast CP-060	10 mg QD on days 1 & 15-21	500 µg QD on days 3-23	24	↔	↔

[1] urinary recovery [2] monotheraoy was used as test [3] metabolite N-desmethyl sildenafil

> d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Roflumilast was not found to be an inhibitor of P-gp. No in vitro or in vivo study has been conducted to evaluate the potential of roflumilast being a substrate of P-gp.

The potential role of roflumilast as P-gp inhibitor was evaluated in an *in vitro* study 266/2002 and an *in vivo* study FHP027. Coadminister of roflumilast with digoxin did not result in the change in the digoxin exposure.

Coadministered Drug	Dose of Coadministered Drug	Roflumilast Dose	Number of Subjects	Coadministered Drug (mean %change)	
				Cmax (90% CI)	AUC (90%CI)
Digoxin FHP027	250 µg po SD on Days 1 and 14	500 µg po QD on days 1-14	16	↔	↔

> e) are there other metabolic/transporter pathways that may be important?

ADCP N-oxide is the precursor to a potentially carcinogenic metabolite that produced nasal mucosa toxicities in rodents. In rodents, the potentially carcinogenic epoxide metabolite of ADCP N-oxide is generated by CYP2G1. Humans are capable of producing ADCP N-oxide in small quantities, based on detection of ADCP N-oxide in some phase 1 study subjects. Humans have 2 CYP2G pseudogenes characterized by highly prevalent loss-of-function mutations. Whether humans have a functional CYP2G enzyme has not been definitively established, although approximately 6% and 14% of individuals may be homozygous for non-mutated CYP2G1 and CYP2G2 alleles. It is unknown if the epoxy-ADCP N-oxide is formed in humans since hydroxy-ADCP N-oxide, a stable product of the epoxide, was not assayed in humans.

Epoxy-ADCP N-oxide could also be formed by human CYP1A2, and potentially other human enzymes that are similar to rodent CYP2G1 (e.g. CYP2A or CYPF genes). A numerically higher incidence of tumor AEs was observed in the pooled COPD safety population.

In rats, olfactory mucosa toxicity following roflumilast exposure was characterized by degeneration/ necrosis and was dose-limiting, precluding long-term carcinogenicity studies. In hamsters and mice, the lower susceptibility to olfactory mucosa toxicity allowed the use of higher doses for 24-month carcinogenicity studies in these species. In mice, the number of tumor-bearing animals was comparable between control and treatment groups and neoplasia was not evident. In hamsters, roflumilast treatment was associated with epithelial cell tumors localized in the olfactory mucosa of the nasal cavity. Exposures and toxicities across the rodent species are summarized in the following table.

Table 2   Serum/plasma AUCs of ADCP and ADCP N-oxide and toxic changes in olfactory mucosa after single oral doses of ADCP

Dose of ADCP	Rat			Hamster			Mouse		
	ADCP $AUC_{0-\infty}$	N-Oxide AUC_{0-8}	Tox [a]	ADCP AUC_{0-8}	N-Oxide AUC_{0-8}	Tox [b]	ADCP AUC_{0-8}	N-Oxide AUC_{0-8}	Tox [a]
0.05 mg/kg	93		+	39		-	na		-
0.5 mg/kg	1212		+	496		(+)	76		(+)
1.5 mg/kg	3254	573 [c]	+++	1589	3694	+	180	3402	(+)
[Report no.]	[35/97, 129/96]			[188/97, 4D/98]			[14/98]		

Serum/plasma AUCs are given as µg•h/L (total concentration); geometric means   na = not ascertained

Toxicity: + = minimal degeneration, ++ = mild degeneration, +++ = moderate necrosis, ( ) in singular animals only

[a] Histopathological evaluation 48 h after drug administration

[b] Histopathological evaluation 72 h after drug administration

The sponsor asserted the following concerning the nasal toxicities observed in rodents:

> The nasal toxicity is related to the rodent-specific formation of a local SH-reactive metabolite within the nasal epithelium following the cleavage of ADCP from roflumilast. In a first step ADCP is oxidized to ADCP N-oxide. Olfactory and nasal microsomes from rodents have a high capability of converting ADCP to ADCP N-oxide. On the other hand, ADCP N-oxide results from cleavage of roflumilast N-oxide. ADCP N-oxide itself is not toxic to the olfactory mucosa. Toxicity requires a final metabolizing step, in which ADCP N-oxide is further oxidized to a SH-reactive metabolite that binds covalently to structures of the olfactory mucosa. This final step is mediated by the cytochrome P450 isoenzyme, CYP2G1, that can exclusively be found in olfactory microsomes of rodents. That metabolic activation of ADCP is necessary to induce olfactory morphological changes was confirmed by mechanistic studies in rats demonstrating that after pretreatment with phorone (GSH depletion) toxicity was increased whereas after pretreatment with metyrapone (CYP inhibitor) olfactory toxicity was inhibited.

Humans have two CYP2G pseudogenes that are characterized by highly prevalent loss-of-function polymorphisms. A functional human CYP2G gene has not been definitively characterized. In a published study (Sheng, et al. Pharmacogenetics 2000;10:667), the prevalence of the missense mutations and deletions was estimated by genotyping 200 individuals from various ancestral backgrounds (approximately 50 subjects each of white, black, Hispanic, and Asian race/ethnicity). Approximately 6% and 14% of individuals may be homozygous for potentially functional CYP2G1 and CYP2G2, respectively.

Beyond CYP2G1, CYP1A2 was capable of producing the epoxy-ADCP N-oxide metabolite in vitro, based on detection of M1, a stable downstream product. CYP2A7, 2F1 and 2C18, which share similarity with rat CYP2G1, were not tested in the sponsor's in vitro experiments. Human CYP2A6, 2A13, 1A1, 1B1, 2B6, 2C9, 2C19, 2D6, 2E1, 2J2, 3A4, and 3A5 were not able to convert ADCP N-oxide to the epoxide metabolite in vitro.

Collectively, the inability of humans to generate the potentially carcinogenic ADCP N-oxide metabolite through CYP2G1 or other CYP450 pathways has not been definitively demonstrated. See the appended Genomics Group review for more detail.

f) does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Label did not specify co-administration of another drug with roflumilast in the treatment of COPD.

g) what other co-medications are likely to be administered to the target patient population?

No clinically relevant interactions with the following drugs were observed: inhaled salbutamol, formoterol, budesonide, oral theophylline, montelukast, warfarin, sildenafil, and Maalox. Drug-drug interaction was observed when roflumilast was administered with Minulet, cimetidine, or enoxacin.

The co-medications that are likely to be administered to the COPD patients are tested to investigate their interaction potential with roflumilast. The results of the interaction studies are shown in the table below.

Table: Effect of Coadministered Drug on Roflumilast and Roflumilast N-oxidePlasma C_{max} and AUC

Coadministered Drug	Dose	Roflumilast Dose	Number of Subjects	Roflumilast (mean %change)		Roflumilast N-oxide (mean %change)	
				C_{max} (90% CI)	AUC (90%CI)	C_{max} (90% CI)	AUC (90%CI)
Cimetidine	400 mg po	500 µg po QD	16	↑46%	↑85%	↔	↑27%

Coadministered Drug	Dose	Roflumilast Dose	Number of Subjects	Roflumilast (mean %change)		Roflumilast N-oxide (mean %change)	
				Cmax (90% CI)	AUC (90%CI)	Cmax (90% CI)	AUC (90%CI)
CP-041	BID on days 6-16	on days 1 & 13		(26-70%)	(47-132%%)		(4-56%)
Maalox CP-044	30 mL po SD on day 1, 15 or 29	500 µg po SD on day 1, 15 or 29	30	↓11% (2-19%)	↔	↔	↔
Salbutamol (albuterol) FHP014	200 µg TID pi for 7 days	500 µg po QD for 7 days	12	↔	↔	↔	↔
Formoterol CP-059	24 µg pi BID on days 12-18 (A) and days 2-18 (B)	500 µg po QD on Days 2-18 (A) and on days 9-18 (B)	A: 12 B: 12	↔	↔	↔	↔
Formoterol CP028	40 µg po SD on day 10	250 µg po QD on Days 1-10	24	↔	↔	↔	↔
Budesonide FHP017	400 µg BID pi for 7 days	500 µg po QD for 7 days	12	↔	↔	↑14% (↑7-22%)	↔
Theophylline FHP026	375 mg BID po for 5 days	500 µg po QD for 5 days	24	↔	↑28% (9-51%)	↔	↔
Warfarin CP-029	250 mg po SD on days 14 & 8	500 µg po QD on days 1-12	21	↔	↔	↔	↔
Enoxacin CP049	400 mg BID on days 7-18	500 µg po QD on days 1 and 12	19	↑20% (6-37%)	↑56% (19-104%)	↓14% (3-25%)	↑23% (↓3-54%)
Sildenafil CP-070	100 mg SD	500 µg po SD	12	↓24% (12-34%)	↔	↔	↔
Minulet CP-038	75 µg estodene 30 µg ethinyles tradiol po QD on days 6-26	500 µg po SD on days 1 & 21	20	↑38% (21-58%)	↑51% (22-87%)	↓12% (5-20%)	↔
Montelukast CP-060	10 mg QD on days 1 & 15-21	500 µg QD on days 3-23	24	↔	↔	↔	↔

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.

Although no PK interaction was observed, the PD interaction was seen when roflumilast was coadministered with sildenafil (CP-70). The combination of 500 µg roflumilast & 100 mg sildenafil showed its own distinct cardiovascular HR, BP, ZCG/STI and QT/QTc response pattern, which is not explained by mere additivity of the effects of the mono-therapies (500 µg roflumilast or 100 mg sildenafil). Although there were no relevant differences in the summary measures of the time-matched changes from baseline for the uncorrected QT of the combination treatment relative to placebo, the maximum and average change from baseline of the HR-corrected QT-intervals tended to be larger for the combination treatment, also relative to the mono-therapies roflumilast and sildenafil.

      h) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

No in vitro or in vivo study has been conducted to evaluate the potential of roflumilast being a substrate of P-gp.

> *k) What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?*

None.

2.4.3. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

> *a) Smoking*

No dose adjustment is needed.

> *b) Drug-drug interaction*

The maximum tolerated dose was found to be 500 µg QD based on the safety and tolerability data from study FHP004. In this study, dosing regimens of 500 µg QD, 500 µg BID, and 1 mg QD were evaluated in 11 subjects (all are white, male, and young subjects) for the safety and tolerability of roflumilast. Adverse events reported most frequently under treatment with 0.5 mg/d roflumilast were: diarrhea, increased frequency of defaecation, loose stool (5/11 subjects), headache (5/11 subjects), sleep disturbances (2/11 subjects), lumboischialgia, lumbalgia (2/11 subjects). Adverse events were more frequent and pronounced under treatment with 1.0 mg/d roflumilast. The adverse events reported most frequently were: nausea, anorexia (1.0 mg s.i.d.: 5/9 subjects: 0.5 mg b.i.d.: 8/8 subjects), headache (1.0 mg s.i.d.: 5/9 subjects: 0.5 mg b.i.d.: 6/8 subjects), gastrointestinal complaints such as diarrhea and abominal pain (1.0 mg s.i.d.: 5/9 subjects; 0.5 mg b.i.d.: 2/8 subjects), lumboischialgia, lumbalgia (1.0 mg s.i.d.: 4/9 subjects: 0.5 mg b.i.d.: 3/8 subjects). There were four discontinuations following 500 µg BID treatment and one discontinuation following 1000 µg QD treatment related with drug treatment. One discontinuation following 500 mg QD treatment due to infection was considered not associated with drug treatment. The mean PK variables roflumilast and roflumilast N-oxide are shown in the table below:

Parameter	Roflumilast			Roflumilast N-Oxide		
	500 µg QD	500 µg BID	1000 µg QD	500 µg QD	500 µg BID*	1000 µg QD*
AUC (µgxh/L)	33	54	61	432	862	865
Cmax (µg/L)	5.5	7.4	11	21	39	44
Cmin (µg/L)	0.5	0.87	0.76	14	32	29

*the values of the PK variable were predicted based on population PK base model.
N=4, 8, and 7 for 500 µg QD, 500 µg BID, and 1000 µg QD, respectively.

Among the three dosing regimens, 500 µg BID appeared to have more AEs then 1000 µg QD, which had more AEs than 500 µg QD. Therefore, safety of roflumilast is shown to be correlated with dose and dosing regimen, although the number of subjects in the study is small.

Coadministration with the following compounds does not need dose adjustment: midazolam (or other CYP3A4 substrates), digoxin (or other P-gp substrates), maalox, salbutamol, formoterol, budesonide, warfarin, and montelukast.

Roflumilast should use with caution when coadministered with Minulet, enoxacin, theophylline, cimetidine, fluvoxamine, ketoconazole, erythromycin, smoking, and sildernafil.

Roflumilast should not be taken with rifampicin (or strong CYP inducers).

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Roflumilast is likely a BCS class II compound. Roflumilast is practically insoluble in water (Cs: 0.52-0.56 mg/L) and hexane (Cs: 10.4-12.0 mg/L), sparingly soluble in ethanol (Cs: 17.2-18 g/L) and freely soluble in acetone (Cs: >100 g/L).
Partition coefficient between 1-octanol and aqueous phosphate buffer ate pH 7.4 is logP=3.99.

(b) (4)
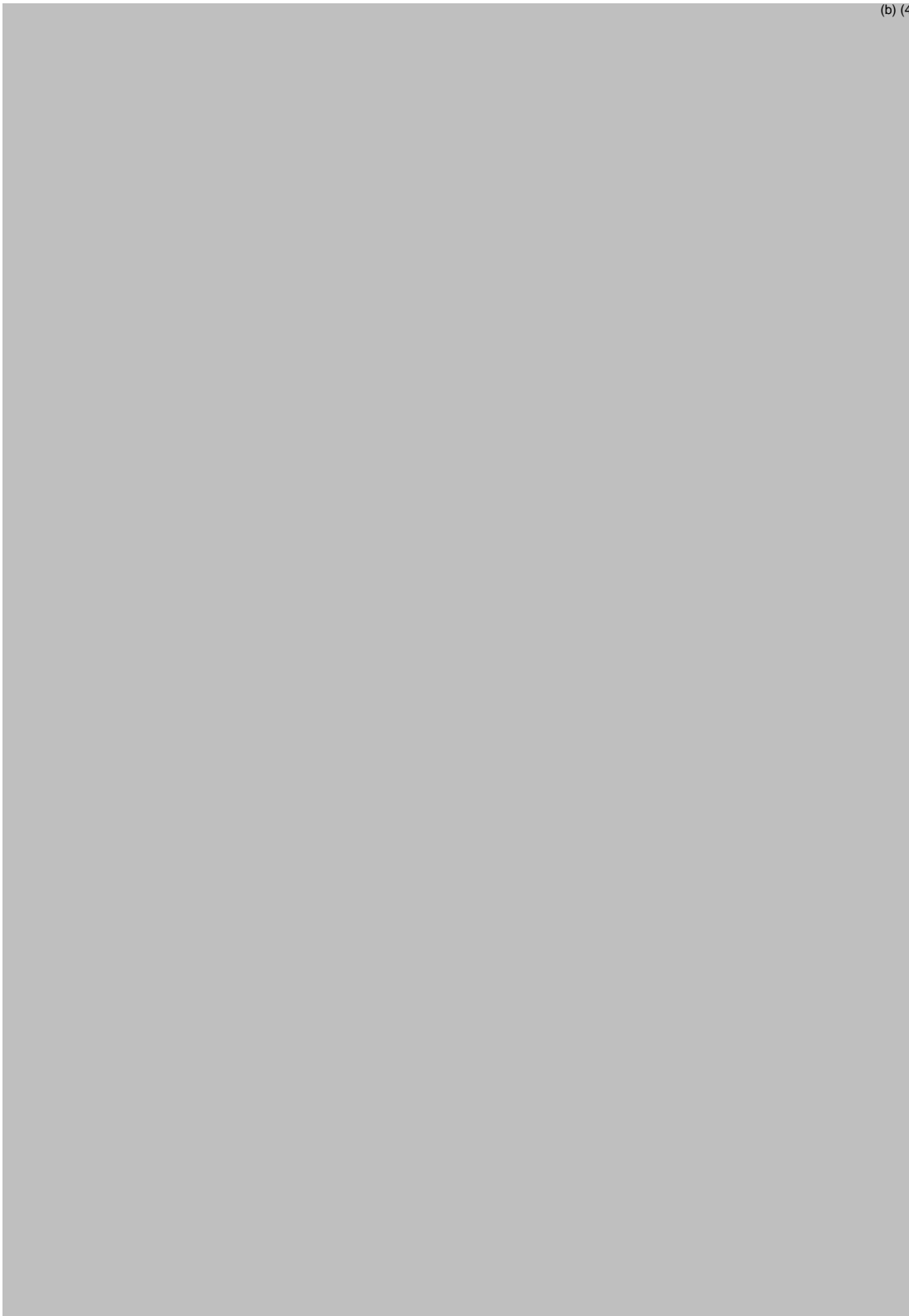
2.5.4. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food caused 12% increased in AUC and 41% incrase in Cmax for roflumilast. Food did not appear to affect the exposure of roflumilast N-oxide.

The effect of food on roflumilat PK was investigated in study FHP010. A food effect was seen for roflumilast with respect to systemic exposure (12% increase under fed conditions) and peak exposure (41% decrease under fed conditions). For roflumilast N-oxide, a food effect was seen with respect to systemic exposure (9% decrease under fed conditions) but not with respect to peak exposure.

T-Table 2.7.1 - 6   Roflumilast, roflumilast N-oxide and ADCP PK characteristics (geometric mean, 68% range) after a single dose of roflumilast 500 μg, p.o. either under fed or fasted conditions [FHP010 (11/98K)]

	Fed	Fasted
Roflumilast		
AUC_{inf} [μg×h/L]	34.8 (29.6, 41.0)	31.2 (24.6, 39.5)
C_{max} [μg/L]	3.84 (3.01, 4.90)	6.51 (4.97, 8.53)
$t_{1/2}$ [h]	11.1 (7.3, 17.0)	10.3 (6.4, 16.4)
t_{max} [h] *	1.96 ± 0.35	0.96 ± 0.19
Roflumilast N-oxide		
AUC_{inf} [μg×h/L]	304 (255, 362)	350 (283, 434)
C_{max} [μg/L]	8.40 (7.02, 10.0)	8.81 (7.07, 10.9)
$t_{1/2}$ [h]	20.6 (13.5, 31.5)	19.6 (13.7, 28.1)
t_{max} [h] *	12.0 ± 0.82	12.2 ± 0.76
ADCP		
AUC_{inf} [μg×h/L]	n.a.	n.a.
C_{max} [μg/L]	0.065 (0.045, 0.093)	0.075 (0.066, 0.084)
$t_{1/2}$ [h]	n.a.	n.a.
t_{max} [h] *	19.1 ± 5.72	26.6 ± 10.6

* t_{max}: mean±SE

T-Table 2.7.1 - 7   Roflumilast and roflumilast N-oxide test/reference ratios (point estimate [% of reference], 90% confidence interval) of AUC_{inf} and C_{max} after a single dose of roflumilast 500 μg either under fed (test) or fasted conditions (reference) [FHP010 (11/98K)]

	Roflumilast	Roflumilast N-oxide
AUC_{inf}	112 (100, 125)	91 (79, 104)
C_{max}	59 (49, 70)	95 (90, 101)

T-Table 2.7.1 - 8   AUC test/reference ratios (point estimate [% of reference], 90% confidence interval) of roflumilast N-oxide (test) and roflumilast (reference) after a single dose of roflumilast 500 μg either under fed or fasted conditions [FHP010 (11/98K)]

	Fed	Fasted
AUC ratio roflumilast N-oxide/roflumilast	911 (802, 1034)	1111 (1024, 1206)

Applying a bioequivalence range of 80 to 125%, a food effect was seen for roflumilast with respect to systemic exposure (12% increase under fed conditions) and peak exposure (41% decrease under fed conditions). For roflumilast N-oxide, a food effect was seen with respect to systemic exposure (9% decrease under fed conditions) but not with respect to peak exposure.

45

Under fed and fasted conditions, the formation of roflumilast N-oxide was similar (about 9-fold higher under fed and 11-fold higher under fasted conditions when compared with roflumilast).

2.6   Analytical Section

2.6.1   How are the active moieties identified and measured in the plasma in the clinical pharmacology studies?

Roflumilast and roflumilat N-oxide were identified via high performance liquide chromatography (HPLC) with fluorescence detection (FLD) or HPLC coupled with tandem mass spectrometry (HPLC-MS/MS) method.

Analytical measurements of roflumilast and roflumilast N-oxide were initially performed using HPLC with FLD after post-column photochemical derivatization (Studies 70/96 and 143/98). The measurement was switched to a fast and sensitive HPLC-MS/MS method [Studies 73/2001 and 188/2007]. The minor roflumilast metabolites ADCP and ADCP N-oxide were analyzed using a reversed-phase chromatography using HPLC-MS/MS (Study 124/2002).

2.6.2 Which metabolites have been selected for analysis and why?

Roflumilast N-oxide was selected as it is an active metabolite and its systemic exposure is about 10-fold higher than roflumilast. ADCP and ADCP N-oxide were also analyzed in selected studies as they are linked to the side effects (nasal lesion) in animal studies.

2.6.3 Howe was the assay performed for roflumilast and roflumilat N-oxide?
The analytical methods performed for roflumilast and roflumilat N-oxide were validated.

Characteristics of relevant HPLC-MS/MS (-FLD) methods used in clinical studies for the determination of roflumilast and roflumilast N-oxide concentrations are summarized in the following table:

Table: Characteristics of most important analytical HPLC-MS/MS (-FLD) methods used in clinical studies for the determination of roflumilast and roflumilast N-oxide concentrations in plasma

Report	Sample volume [μL]	LLOQ [μg/L]	Calibration range [μg/L]	Quality control samples			
				Intra-day		*Inter*-day	
				Precision [%CV]	Accuracy [%]	Precision [%CV]	Accuracy [%]
Roflumilast							
143/98 [a]	1000	0.1	0.1 to 10	0.8 to 3.3	91 to 102	1.9 to 2.1	93 to 101
73/2001	400	0.1	0.1 to 20	2.7 to18	85 to 105	4.1 to 12	86 to 101
10/2003 [b]	500	0.1	0.1 to109	2.2 to 9.2	89 to 110	7.6 to 12	99 to 109
188/2007	200	0.1	0.1 to 50	1.9 to 11	95 to 119	3.5 to 10	98 to109
268/2008 [c]	500	0.04	0.04 to 59.9	2.5 to 10	88 to 111	4.5 to 10	100 to 107
Roflumilast N-oxide							
143/98 [a]	1000	0.5	0.5 to 100	0.1 to 11	96 to 114	1.9 to 8.1	100 to112
73/2001	400	0.1	0.1 to 40	2.3 to 6.8	81 to 91	2.4 to 5.5	83 to 90
10/2003 [b]	500	0.1	0.1 to109	1.8 to 13	80 to 115	4.8 to 8.0	94 to 102
188/2007	200	0.1	0.1 to 50	0.7 to 9.5	93 to 101	1.9 to 7.6	97 to 98
268/2008 [c]	500	0.04	0.04 to 59.9	0.8 to 10	100 to 114	3.3 to 5.9	103 to 111

LLOQ=lower limit of quantification
[a] HPLC-FLD

(b) (4)

2.6.4 What was the variability in the PK parameter estimates in this application?

Single dose pharmacokinetic variables of roflumilast and roflumilast N-oxide in human plasma across various studies are summarized in the following table.

Table: Plasma PK characteristics of roflumilast and roflumilast N-oxide after a single dose of roflumilast 500 μg, p.o. in healthy (fasted) subjects

Study	Roflumilast				Roflumilast N-oxide			
	AUC_{inf} [µg×h/L]	C_{max} [µg/L]	$t_{1/2}$ [h]	t_{max} [h]	AUC_{inf} [µg×h/L]	C_{max} [µg/L]	$t_{1/2}$ [h]	t_{max} [h]
FHP006	37.2	8.32	15.7	0.88	400	13.1	20.6	4.00
FHP010	31.2	6.51	10.3	0.75	350	8.81	19.6	13.0
FHP015	33.8	7.75	9.70	0.50	382	9.79	22.3	12.0
FHP021, S	37.3	7.82	12.9	0.90	459	10.2	26.1	8.38
FHP021, NS	42.5	7.46	14.4	0.94	391	8.95	24.8	12.5
FHP039	35.0	5.27	14.4	1.25	351	9.39	23.1	11.0
FHP040	40.4	7.34	18.2	1.00	435	9.40	25.3	4.00
CP-042	26.6	5.96	18.7	1.50	154	7.95	36.8	4.00
CP-043, MO	40.6	3.79	20.0	1.50	377	6.61	26.9	12.0
CP-043, EV	38.9	3.06	20.0	2.00	386	6.79	28.0	12.0
CP-049	50.6	7.69	22.8	1.00	529	10.9	24.7	4.00
EM-056, FB	56.9	8.21	26.8	0.75	574	9.53	32.6	4.00
EM-056, FE	56.6	9.59	26.6	0.75	568	9.79	31.2	4.00
CP-064	38.4	6.86	15.6	1.00	414	9.45	23.9	5.00
CP-066	44.3	5.63	23.7	1.69	595	10.7	31.5	9.56
CP-067	55.2	7.12	33.1	1.28	780	10.5	44.0	10.4
CP-068	61.0	6.97	28.0	1.59	646	10.4	32.4	8.69
CP-070	42.3	6.08	17.4	1.03	417	9.39	24.9	8.03
Median	40.5	7.04	18.4	1.00	415	9.49	25.7	8.53
Range (min, max)	(26.6, 61.0)	(3.06, 9.59)	(9.7, 33.1)	(0.50, 2.00)	(154, 780)	(6.61, 13.1)	(19.6, 44.0)	(4.0, 13.0)

Geometric means; medians for t_{max} (except for FHP021: arithmetic means), AUC was calculated from time 0 to infinity; S=smoker, NS=non-smoker, MO=morning, EV=evening, FB=Formula B, FE=Formula E

Source: T-Table 2.7.2 – 110 on page 123 out of 187 in section 2.7.2 summary-clin-pharm.pdf

After a single dose of roflumilast 500 µg, p.o., the median systemic exposure (AUC) of roflumilast across studies was 40.5 µg*h/L, ranging from 26.6 to 61.0 µg*h/L. The median peak concentration (C_{max}) was 7.04 µg/L, ranging from 3.1 to 9.60 µg/L. The median terminal plasma half life ($t_{1/2}$) was 18.4 h, ranging from 9.7 to 33.1 h. The median time to peak concentration (t_{max}) was 1 h, ranging from 0.5 to 2 h. The median AUC of roflumilast N-oxide across studies was 415 µg*h/L, ranging from 154 to 780 µg*h/L. The median C_{max} of roflumilast N-oxide was 9.49 µg/L, ranging from 6.6 to 13.1 µg/L, the median $t_{1/2}$ was 25.7 h, ranging from 19.6 to 44.0 h, and the median time t_{max} was 8.53 h, ranging from 4 to 13 h.

Repeated dose pharmacokinetic variables of roflumilast and roflumilast N-oxide in human plasma are summarized in the following table.

Table: Plasma PK characteristics of roflumilast and roflumilast N-oxide after
repeated doses of roflumilast 500 µg, QD, p.o. in healthy (fasted) subjects

Study	Roflumilast					Roflumilast N-oxide				
	AUC_{0-24h} [μg×h/L]	C_{max} [μg/L]	C_{trough}^{b} [μg/L]	$t_{1/2}$ [h]	t_{max} [h]	AUC_{0-24h} [μg×h/L]	C_{max} [μg/L]	C_{trough}^{b} [μg/L]	$t_{1/2}$ [h]	t_{max} [h]
FHP004[a]	32.8	5.46	n.a.	8.20	2.60	351	21.5	n.a.	10.6	5.90
FHP014	30.8	7.23	0.529	16.6	0.75	400	24.4	14.6	20.5	3.00
FHP017	32.4	7.39	0.470	14.7	0.50	389	23.7	11.8	19.8	3.50
FHP026	33.7	7.00	0.67	17.6	0.75	401	24.0	13.1	26.0	2.25
FHP027[c]	50.2	9.93	1.00	14.4	1.00	504	30.9	19.4	34.5	2.25
CP-029	42.9	6.86	0.690	13.0	2.00	449	24.3	14.1	29.4	4.00
FHP039	33.7	6.01	0.54	18.0	1.00	375	21.6	11.6	21.1	4.00
CP-050, E	67.2	10.1	1.86	30.9	1.00	717	42.7	29.3	34.9	2.00
CP-050, MA	52.4	8.17	1.30	28.7	1.00	593	34.8	23.6	31.6	3.00
CP-050, Y	53.0	8.74	1.00	30.2	1.00	605	37.7	22.5	29.7	3.00
CP-060	35.2	7.29	0.486	15.9	1.00	417	23.7	13.9	33.4	4.00
CP-061	41.2	7.94	0.75	16.9	1.00	436	24.5	14.4	46.5	4.00
CP-065, A	35.9	5.19	0.804	16.0	2.00	469	25.3	16.6	42.1	2.00
Median	35.9	7.29	0.72	16.6	1.00	436	24.4	14.5	29.7	3.00
Range (min, max)	(30.8, 67.2)	(5.19, 10.1)	(0.47, 1.86)	(8.20, 30.9)	(0.50, 2.60)	(351, 717)	(21.5, 42.7)	(11.6, 29.3)	(10.6, 46.5)	(2.00, 5.90)

Geometric means; for t_{max}, medians or arithmetic means; n.a.=not ascertained; E=elderly; MA=middle aged; Y=young; A=adult
[a] Pharmacokinetics under fed conditions
[b] C_{trough}: geometric means of concentrations at pre-dose (0h)
[c]   (b) (6)

Source: T-Table 2.7.2 – 111 on page 124 out of 187 in section 2.7.2 summary-clin-pharm.pdf

After repeated doses of roflumilast 500 μg, QD, p.o. the median systemic exposure (AUC) of roflumilast across studies was 35.9 μg*h/L, ranging from 30.8 to 67.2 μg*h/L. The median peak concentration (C_{max}) was 7.29 μg/L, ranging from 5.19 to 10.1 μg/L. The median trough concentrations (C_{trough}) was 0.72 μg/L, ranging from 0.47 to 1.86 μg/L. Compared with single dose results, a similar order of magnitude in the across-study variability was found for plasma half life and time to peak concentration: The median effective plasma half life ($t_{1/2}$) was 16.6 h, ranging from 8.2 to 30.9 h, and the median time to peak concentration (t_{max}) was 1 h, ranging from 0.5 to 2.6 h.

The across-study variability of roflumilast N-oxide was generally consistent with findings seen for the parent drug roflumilast, i.e., higher or lower pharmacokinetic results of roflumilast in particular studies were mirrored by the results of roflumilast N-oxide. The median systemic exposure (AUC) of roflumilast N-oxide across studies was 436 μg*h/L, ranging from 351 to 717 μg*h/L. The median peak concentration (C_{max}) of roflumilast N-oxide was 24.4 μg/L ranging from 21.5 to 42.7 μg/L. The median trough concentration (C_{trough}) was 14.5 μg/L, ranging from 11.6 to 29.3 μg/L. Compared with single dose results, a similar order of magnitude in the across-study variability was found for plasma half life and time to peak concentration: The median effective plasma half life ($t_{1/2}$) was 29.7, ranging from 10.6 to 46.5 h), and the median time to peak concentration (t_{max}) was 3 h, ranging from 2 to 5.9 h.

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4.   Appendixes

4.1 Pharmacometrics Review

Office of Clinical Pharmacology:
Pharmacometrics review

1 Summary of Findings

1.1 **Key Review Questions**

The purpose of this review is to address the following key questions.

1.1.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for effectiveness?

The pivotal studies used lung function (pre-bronchodilator FEV1) and a symptomatic benefit endpoint (rate of COPD exacerbations) as primary endpoints.
The relationship between exposure (AUC, Cmax of roflumilast, roflumilast N-oxide) and primary endpoints in the registration trials was not characterized. The concentrations of roflumilast and roflumilast N-oxide were not measured in registration trials.

The observed mean change from baseline pre-bronchodilator FEV1 in placebo, 250 and 500 mcg groups from registration trials (M2-124, M2-125), 1 year studies (M2-111, M2-112) and early dose finding studies (M2-107, FK1-101) are shown in Table below.

Table 2. Pre-bronchodilator FEV1 [L] in placebo and treatment groups.

Study	Dose	Mean change from baseline pre-bronchodilator -FEV1 (L)	Mean change from baseline pre-bronchodilator FEV1 (L)- Placebo Corrected
M2-124 (52 wks)	Placebo	0.008	0.039*
	500 mcg	0.046	
M2-125 (52 wks)	Placebo	-0.025	0.058*
	500 mcg	0.033	
M2-111 (52 wks)	Placebo	-0.012	0.042*
	500 mcg	0.030	
M2-112 (52 wks)	Placebo	-0.008	0.057*
	500 mcg	0.049	
M2-110 (24 wks)	Placebo	-0.027	0.086*
	500 mcg	0.059	
M2-107 (24 wks)	Placebo	-0.039	
	250 mcg	0.024	0.064*
	500 mcg	0.049	0.088*
FK1 101 (26 wks)	Placebo	0.029	
	250 mcg	0.064	0.035
	500 mcg	0.069	0.041

*- P<0.05
Source:
M2-107; FK1 101- Table 2.73.-68, Page 117 of 124 from summary-clin-efficacy-copd.pdf
M2-124; M2-125- Table 2.5-6, Page 24 of 56 from clinical-overview.pdf
M2-110- Table 2.7.3-42, Page 87 of 214 from summary-clin-efficacy-copd.pdf

For details about the effects of roflumilast on rate of COPD exacerbations please refer to the clinical review.

1.1.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Table shows the percentage of patients with safety events such as diarrhoea, nausea and weight loss in pivotal studies pool and COPD safety pool. A clear dose-response relationship was observed for diarrhoea, nausea and weight loss.

Table 3. Percentage of patients with safety events such as diarrhoea, nausea and weight loss in pivotal studies pool and COPD safety pool.

Dose (µg)	% patients with		
	Diarrhoea	Nausea	Weight loss
Pivotal Studies Pool[a]			

0 (N=1545)	3.2	1.9	2.8
500 (N=1547)	8.4	4.0	10.1
COPD Safety Pool[b]			
0 (N=5491)	2.6	1.4	1.8
250 (N=797)	4.9	2.3	0.8
500 (N=5766)	10.1	5.2	6.8

Source: Table 20 on Page 58 in Report No: iss-iss.pdf
a Includes studies M2-124, M2-125.
b Includes studies FK1 101, FK1 103, IN-108, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128.

1.1.3 Are pharmacokinetics of roflumilast and roflumilast N-oxide similar between healthy subjects and COPD patients?

No. The pharmacokinetics of roflumilast and roflumilast N-oxide are different between healthy subjects and COPD patients (based on data from Study M2-110, IN-108). The clearance of roflumilast and roflumilast N-oxide is slower in COPD patients in comparison to healthy subjects.

Figure 1 shows the time course of steady state roflumilast and roflumilast N-oxide concentrations in healthy subjects and COPD patients after 500 μg dose. The AUC of roflumilast is 60% higher in COPD patients based on AUC_{0-10h} at steady state. The AUC of roflumilast N-oxide is about 40% higher in COPD patients based on AUC_{0-10h} at steady state. Based on population pharmacokinetic analysis, COPD patients have a 65% higher exposure ($AUC_{0-\tau}$) to roflumilast and about 8% higher exposure to roflumilast N-oxide.

Figure 1. Roflumilast and roflumilast N-oxide concentrations at steady state (mean±standard error) in COPD patients and healthy subjects after 500 μg dose.
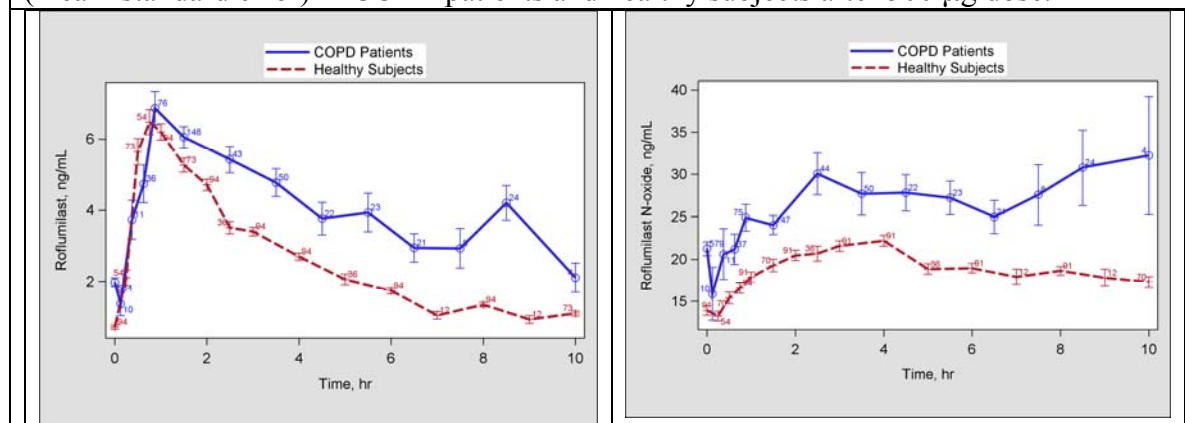
1.1.4 Are the proposed labeling statements for special populations, drug-drug interactions acceptable?

The sponsor's proposed labeling language for Special Populations/Race needs to be modified. Refer to Section 1.3 below.

1.2 Recommendations

The sponsor's proposed labeling language for Special Populations/Race needs to be modified. Refer to Section 1.3 below.

1.3 Label Statements

Labeling statements to be removed are shown in red strikethrough font and suggested labeling to be included is shown in underline blue font.

In Label Section 12.3: Pharmacokinetics (Special Populations/Race)

(b) (4)

Please refer to Dr Ping Ji's review for the proposed language which incorporates estimates of AUC and Cmax derived using non-compartmental analysis from several studies.

2 Pertinent regulatory background

The submission dated on 15 July 2009 is the original submission for roflumilast. The sponsor is seeking the marketing approval for the indication of maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbation. The sponsor conducted two registration trials evaluating the effects of 500 µg dose administered as a tablet once daily. Sponsor did not characterize pharmacokinetics of roflumilast in the registration trials. The sponsor also evaluated the effects of 250 and 500 µg dose in dose finding studies.

3 Results of Sponsor's Analysis

3.1 Population Pharmacokinetic Analysis

The current submission includes five population PK study reports (
Table 4).

Table 4 Summary of Population Pharmacokinetic Study Reports

Type	Report	Subjects	Objectives of the study
Pop-PK	114/2005	Healthy Subjects	Summary Report: Population pharmacokinetics of roflumilast and roflumilast N-oxide in healthy subjects
Pop-PK	343/2008	COPD Patients	Summary Report: Population pharmacokinetics of roflumilast and roflumilast N-oxide in COPD patients

		COPD	
Pop-PK	65/2004	Patients	Population pharmacokinetic analysis of study IN-108
Pop-PK	121/2005	Asthma Patients	Population pharmacokinetic analysis of study FK1021
Pop-PK	66/2007	COPD Patients	Population pharmacokinetic analysis of study M2-110

Population pharmacokinetic analysis of data from healthy subjects
The demographics of the healthy subjects included in the analysis is shown in Table 5.

Table 5. **Demographics of the dataset used for model building**

Gender	N	%
Female	87	25.7
Male	251	74.3
Smoking Use	**N**	**%**
Nonsmokers	229	67.8
Smokers	109	32.2
Alcohol Use	**N**	**%**
Non-Users	104	30.8
Users	234	69.2
Race	**N**	**%**
Non-Black, Non-Hispanic	296	87.6
Black	27	7.99
Hispanic	15	4.44
Age (Years)	**Mean**	**SD**
	38.2	14.7
Weight (kg)	**Mean**	**SD**
	75.4	11.2

Figure 2 shows the steady state roflumilast parent and metabolite concentration-time profile with box-plots of the observed concentrations (dose-normalized to a 500 μg dose) overlaid with the typical individual (population) predictions obtained from the base model (a 2-compartment model with first-order absorption and a lag time on the absorption) in healthy subjects.

Figure 2. (A) Roflumilast Parent, Steady State: Mean Concentration-Time Profile From the Base Model, Dose Normalized to 500 μg (B) Roflumilast Metabolite, Steady State: Mean Concentration-Time Profile From the Base Model, Dose Normalized to 500 μg in healthy subjects.
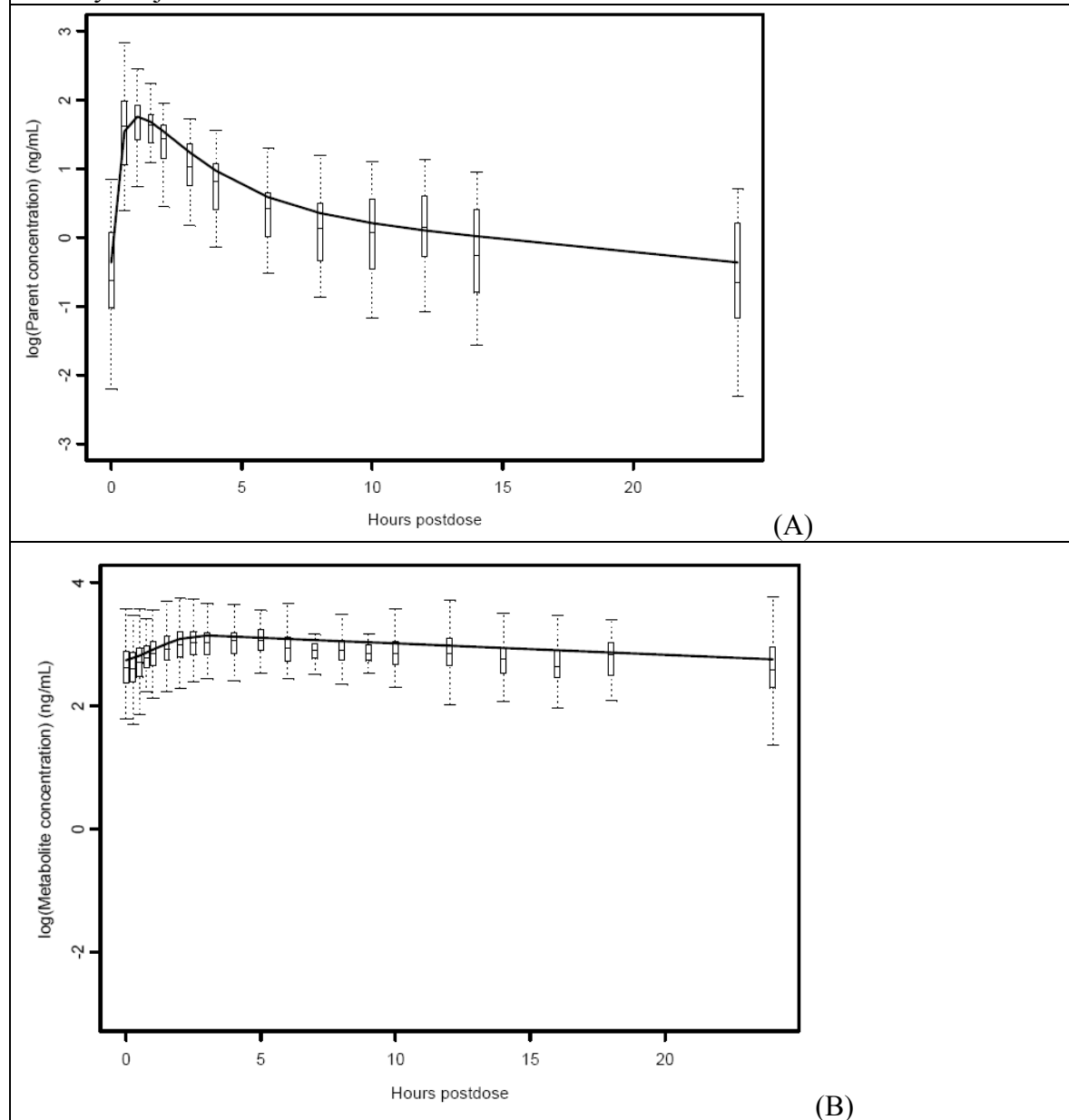

(A)

(B)

Figure 3 shows the observed vs predicted (population predicted) and observed vs individual predicted roflumilast concentrations for all doses and also for the individual dose groups. The predicted concentrations are distributed randomly around the identity line (solid black line) indicating that the model describes the data adequately. Table 6 shows the parameter estimates

for the roflumilast base (no covariates), full (all covariates) and final (covariates identified by WAM) model.

Table 6. Parameter Estimates (SE) for the Roflumilast Base, Full, and Final Models.

Parameter (SE)	Base		Full		Initial Final		Final With race	
OFV	-9023.112		-9391.524		-9383.408		-9397.811	
Drop From Base	--		368.412		360.296		374.699	
Nearness to Full	-368.412		--		8.116		--	
Tlag (hr) (θ_1)	0.152	(0.0159)	0.158	(0.0149)	0.159	(0.0148)	0.158	(0.0150)
Food (θ_9)	--		-0.307	(0.294)	-0.308	(0.294)	-0.308	(0.296)
Ka (hr^{-1}) (θ_2)	0.493	(0.0223)	0.533	(0.0293)	0.532	(0.0285)	0.533	(0.0290)
Food (θ_{11})	--		-0.701	(0.155)	-0.699	(0.152)	-0.699	(0.153)
CL (L/hr) (θ_3)	12.7	(0.294)	9.92	(0.446)	9.93	(0.433)	10.5	(0.490)
Age (θ_{12})	--		-0.140	(0.0550)	--		--	
Sex (θ_{13})	--		0.203	(0.0603)	0.221	(0.0602)	0.191	(0.0588)
Smoking (θ_{15})	--		0.344	(0.0588)	0.356	(0.0594)	0.307	(0.0584)
Black (θ_{20})	--		--		--		-0.140	(0.0713)
Hispanic (θ_{21})	--		--		--		-0.297	(0.0581)
V$_C$ (L) (θ_4)	13.1	(1.07)	13.9	(1.38)	14.3	(1.33)	14.3	(1.37)
Weight (θ_{17})	--		0.497	(0.161)	--		--	
Q (L/hr) (θ_5)	20.1	(0.487)	20.3	(0.517)	20.3	(0.507)	20.3	(0.514)
V$_P$ (L) (θ_6)	204	(5.08)	201	(5.17)	201	(5.14)	201	(5.15)
F$_{Rel}$	1		1		1		1	
Food (θ_{19})	--		0.0214	(0.0720)	--		--	
CV (θ_7) (σ) (%)	25.9	(0.956)	25.1	(0.756)	25.1	(0.755)	25.1	(0.756)
$\omega^2(\eta[Tlag])$	2.29	(1.79)	1.73	(1.35)	1.72	(1.34)	1.73	(1.36)
$\omega^2(\eta[Ka])$	0.114	(0.0285)	0.155	(0.0761)	0.154	(0.0713)	0.154	(0.0730)
$\omega^2(\eta[CL])$	0.172	(0.0136)	0.140	(0.0109)	0.142	(0.0113)	0.136	(0.0111)
$\omega^2(\eta[V_C])$	0.713	(0.0804)	0.729	(0.0765)	0.734	(0.0758)	0.734	(0.0776)
$\omega^2(\eta[Q])$	0.0740	(0.0115)	0.0726	(0.0107)	0.0727	(0.0106)	0.0726	(0.0106)
$\omega^2(\eta[V_P])$	0.115	(0.0131)	0.117	(0.0127)	0.118	(0.0126)	0.117	(0.0124)
$\omega(\eta[Q, V_P])$	0.0737	(0.0111)	0.0701	(0.0101)	0.0705	(0.0103)	0.0703	(0.0100)

Table 9, Page 33 from 114-2205-study-report.pdf

These parameter estimates yield the following implications:
- The presence of the covariates sex, smoking, and race reduced the intersubject variability in the clearance from a coefficient of variation (CV) of 41.5% for the base model to 36.9% for the final model.
- Clearance (CL): The population estimate $\pm$ SE of the clearance (θ_3) is 10.5 $\pm$ 0.490 L/hr for nonsmoking, non-black, non-Hispanic females.
- Sex on CL: For males, the estimated covariate effect (θ_{13}) is 0.191 $\pm$ 0.0588, meaning that their clearance is 19.1% greater than that of females. Increased clearance in males implies that the AUC$_{(0-24)}$ in males is less than that in females.

- Smoking on CL: For smokers, the estimated covariate effect (θ_{15}) is 0.307 ± 0.0584, meaning that their clearance is 30.7% greater than that for nonsmokers. Increased clearance in smokers implies that the $AUC_{(0-24)}$ in smokers is less than that in nonsmokers.
- Race on CL: For blacks, the estimated covariate effect (θ_{20}) is -0.140 ± 0.0713, meaning that their clearance is 14.0% less than that for non-black, non-Hispanics. For Hispanics, the estimated covariate effect (θ_{21}) is -0.297 ± 0.0581, meaning that their clearance is 29.7% less than that for non-black, non-Hispanics. Consequently, areas under the curve (AUC) in blacks and Hispanics is greater than those in non-black, non-Hispanics.
- Food on lag time (Tlag): For all data except from that resulting from the fed arm of Study FHP-010, the population estimate $\pm$ standard error (SE) of Tlag (θ_1) is 0.158 ± 0.0150 hr. For data resulting from the fed arm of Study FHP-010, the estimated covariate effect (θ_9) is -0.308 ± 0.296, meaning that a high-fat meal reduces the Tlag by 30.8%, to 0.109 hr.
- Food on absorption rate constant (Ka): For all data except from that resulting from the fed arm of Study FHP-010, the population estimate $\pm$ SE of Ka (θ_2) is 0.533 ± 0.0290 hr^{-1}. For data resulting from the fed arm of Study FHP-010, the estimated covariate effect (θ_{11}) is -0.699 ± 0.153, meaning that a high-fat meal reduces the absorption rate constant by 69.9%, to 0.160 hr^{-1}.

Figure 4 shows the observed vs predicted (population predicted) and observed vs individual predicted roflumilast N-oxide concentrations for all doses and also for the individual dose groups. The predicted concentrations are distributed randomly around the identity line (solid black line) indicating that the model describes the data adequately.

Table 7 shows the parameter estimates for the roflumilast N-oxide base (no covariates), full (all covariates) and final (covariates identified by WAM) model.

Table 7. Parameter Estimates (SE) for the Roflumilast N-oxide Base, Full, and Final Models.

Parameter (SE)	Base		Full		Initial Final		Final With Race	
OFV	-10,310.430		-10,982.441		-10,974.671		-11,064.271	
Drop From Base	--		672.011		664.241		753.841	
Nearness to Full	-672.011		--		7.770		--	
Tlag (hr) (θ_1)	0.149	(0.0219)	0.157	(0.0194)	0.157	(0.0195)	0.156	(0.0194)
D1 (hr) (θ_2)	2.28	(0.0754)	2.22	(0.0696)	2.22	(0.0697)	2.21	(0.0700)
Food (θ_6)	--		2.41	(0.416)	2.37	(0.354)	2.36	(0.352)
CL (L/hr) (θ_3)	1.05	(0.0283)	0.773	(0.0468)	0.814	(0.0445)	0.883	(0.0472)
Age (θ_7)	--		-0.480	(0.0981)	-0.486	(0.179)	-0.471	(0.106)
Sex (θ_8)	--		0.567	(0.126)	0.418	(0.107)	0.467	(0.108)
Weight (θ_9)	--		-0.497	(0.185)	--		--	
Smoking (θ_{10})	--		0.308	(0.0758)	0.314	(0.0646)	0.235	(0.0590)
Alcohol (θ_{11})	--		0.00354	(0.0626)	--		--	
Black (θ_{19})	--		--		--		--	
Hispanic (θ_{20})	--		--		--		--	
V (L) (θ_4)	56.5	(1.03)	60.3	(2.33)	60.8	(2.14)	65.8	(1.94)
Weight (θ_{12})	--		0.824	(0.142)	0.818	(0.144)	1.00	(0.117)
F_{Rel}	1		1		1		1	
Age (θ_{13})	--		-0.315	(0.0395)	-0.316	(0.0682)	-0.269	(0.0404)
Sex (θ_{14})	--		0.162	(0.0562)	0.154	(0.0517)	0.231	(0.0465)
Smoking (θ_{16})	--		0.0129	(0.0335)	--		--	
Alcohol (θ_{17})	--		-0.0239	(0.0338)	--		--	
Food (θ_{18})	--		0.0133	(0.0347)	--		--	
Black (θ_{21})	--		--		--		0.431	(0.0525)
Hispanic (θ_{22})	--		--		--		0.267	(0.0751)
CV (θ_5) (σ) (%)	25.1	(0.830)	24.0	(0.728)	24.0	(0.729)	24.1	(0.727)
$\omega^2(\eta[D1])$	0.254	(0.0240)	0.262	(0.0245)	0.262	(0.0247)	0.268	(0.0245)
$\omega^2(\eta[CL])$	0.194	(0.0247)	0.159	(0.0209)	0.164	(0.0212)	0.150	(0.0206)
$\omega^2(\eta[V])$	0.0814	(0.00748)	0.0523	(0.00524)	0.0526	(0.00511)	0.0449	(0.00495)
$\omega(\eta[D1, CL])$	-0.00800	(0.0128)	0.00843	(0.00421)	0.0113	(0.00563)	0.0221	(0.00688)
$\omega(\eta[D1, V])$	0.0505	(0.00930)	0.0377	(0.0103)	0.0385	(0.00811)	0.0536	(0.00885)
$\omega(\eta[CL, V])$	-0.0200	(0.00831)	-0.000532	(0.00766)	-0.000475	(0.00394)	-0.0110	(0.00502)

Table 12, Page 43 from 114-2205-study-report.pdf

These parameter estimates yield the following implications:
- The presence of the covariates age, sex, and smoking reduced the intersubject variability in the clearance from a CV of 44.0% in the base model to 38.7% in the final model. Similarly, the presence of the covariate weight reduced the intersubject variability in the volume of distribution from 28.5% to 21.2%.
- CL: The population estimate $\pm$ SE of the metabolite CL (θ_3) is 0.883 $\pm$ 0.0472 L/hr for a 40-year-old, 70 kg, nonsmoking female.

- Age on CL: The estimated covariate effect of age (θ_7) is -0.471 $\pm$ 0.106, indicating that clearance is reduced with increasing age. For example, for a 75-year-old subject, the typical CL would be 0.657 L/hr.
- Sex on CL: For males, the estimated covariate effect (θ_8) is 0.467 $\pm$ 0.108, meaning that their CL is 46.7% greater than that of females.
- Smoking on CL: For smokers, the estimated covariate effect (θ_{10}) is 0.235 $\pm$ 0.0590, meaning that their CL is 23.5% greater than that of nonsmokers. Increased clearance in smokers implies that the AUC(0-24) in smokers is less than that in nonsmokers.
- Weight on volume of distribution (V): For a 70 kg subject, the population estimate $\pm$ SE of the apparent volume of distribution (θ_4) is 65.8 $\pm$ 1.94 L. The estimated covariate effect of weight (θ_{12}) is 1.00 $\pm$ 0.117, indicating that the apparent volume increases proportionally with body weight. For example, for a 100 kg subject, the typical apparent volume would be 94.0 L.
- Food on duration of formation (D1): For all data except from that resulting from the fed arm of Study FHP-010, the population estimate $\pm$ SE of the duration of formation (θ_2) is 2.21 $\pm$0.0700 hr. For data resulting from the fed arm of Study FHP-010, the estimated covariate effect (θ_6) is 2.36 $\pm$ 0.352, meaning that a high-fat meal increases the duration of formation by 236%, to 7.43 hr.
- F$_{Rel}$: The bioavailability (F$_{Rel}$) for roflumilast metabolite relative to parent was fixed to 1 for a 40-year-old non-black, non-Hispanic female.
- Age on F$_{Rel}$: The estimated covariate effect of age (θ_{13}) is -0.269 $\pm$ 0.0404, indicating that the relative bioavailability decreases with age. For example, for a 75-year-old subject, the typical bioavailability of the metabolite relative to that of a 40-year old would be 0.844.
- Sex on F$_{Rel}$: For males, the estimated covariate effect (θ_{14}) is 0.231 $\pm$ 0.0465, meaning that their bioavailability of the metabolite relative to that of females of the same age is increased by 23.1% to 1.231.
- Race on F$_{Rel}$: For blacks, the estimated covariate effect (θ_{21}) is 0.431 $\pm$ 0.0525, meaning that their bioavailability of the metabolite relative to that of non-blacks and non-Hispanics is increased by 43.1% to 1.431. For Hispanics, the estimated covariate effect (θ_{22}) is 0.267 $\pm$ 0.0751, meaning that their bioavailability of the metabolite relative to that of nonblacks and non-Hispanics is increased by 26.7% to 1.267. Consequently, AUCs in blacks and Hispanics are greater than those in non-black, non-Hispanics.
- When the effects of age on the clearance and F$_{Rel}$ are taken into account simultaneously, the AUC increases with increasing age. Similarly, with regard to gender, males have lower AUCs than females.

Figure 3. Diagnostic Plots for roflumilast pharmacokinetic analysis in healthy subjects (The solid line is the concordance line – the 45° line through the origin. The dashed line is the regression line)

Parent Full Model: Observed vs Predicted — Dose: 0.5-mg

Parent Full Model: Observed vs Individual Predicted — Dose: 0.5-mg

Parent Full Model: Observed vs Predicted — Dose: 0.75-mg

Parent Full Model: Observed vs Individual Predicted — Dose: 0.75-mg

Parent Full Model: Observed vs Predicted — Dose: 1.0-mg

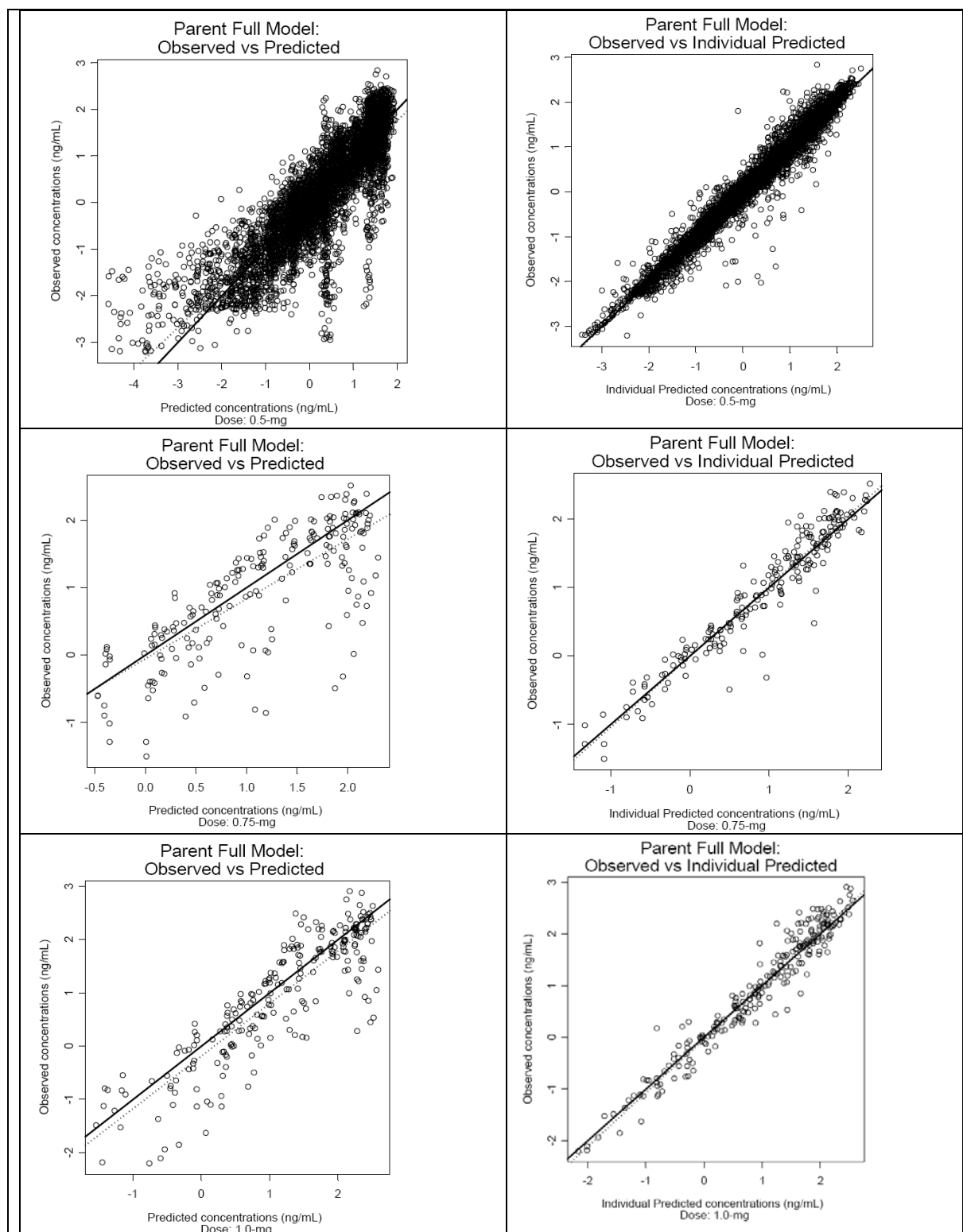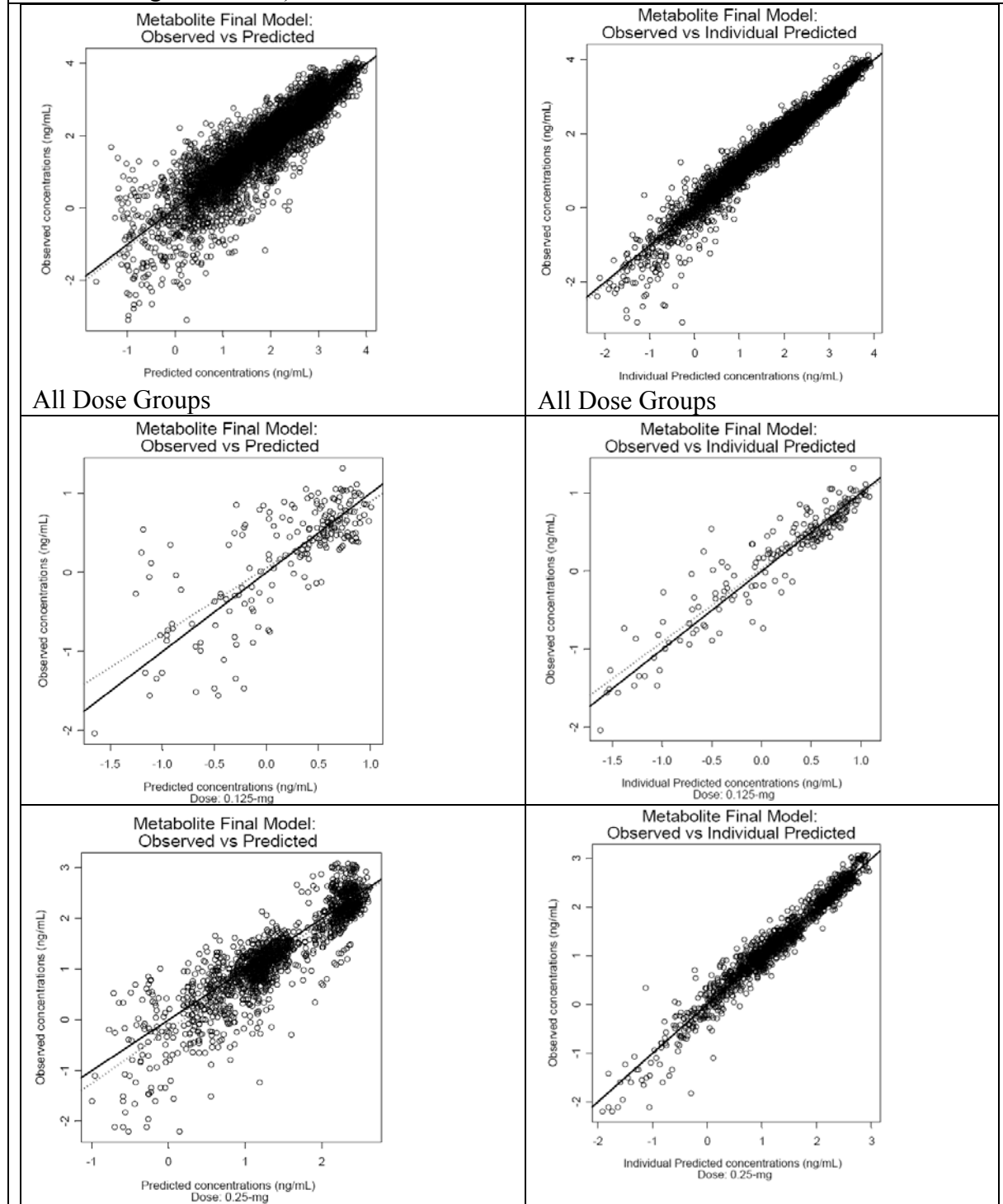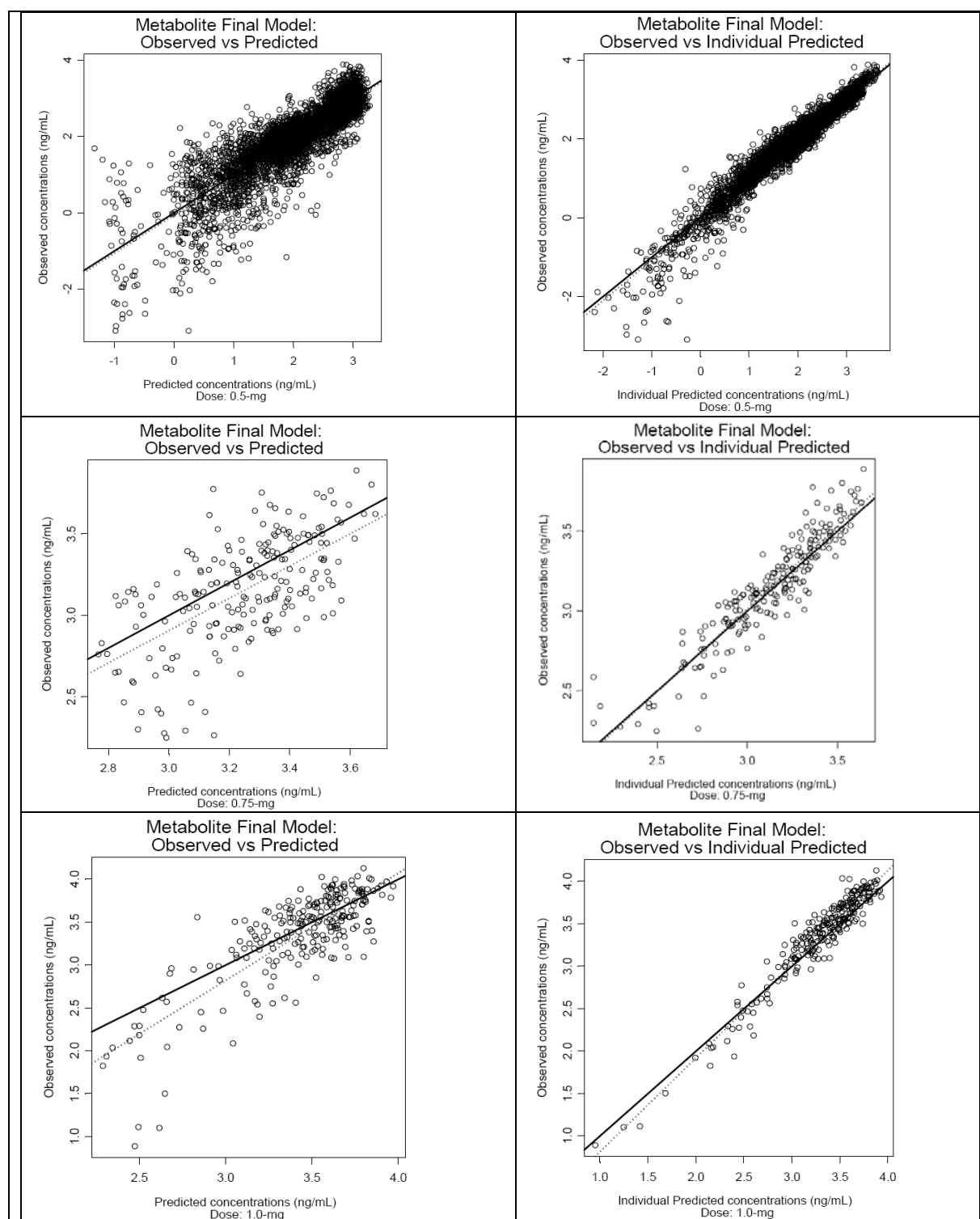Parent Full Model: Observed vs Individual Predicted — Dose: 1.0-mg
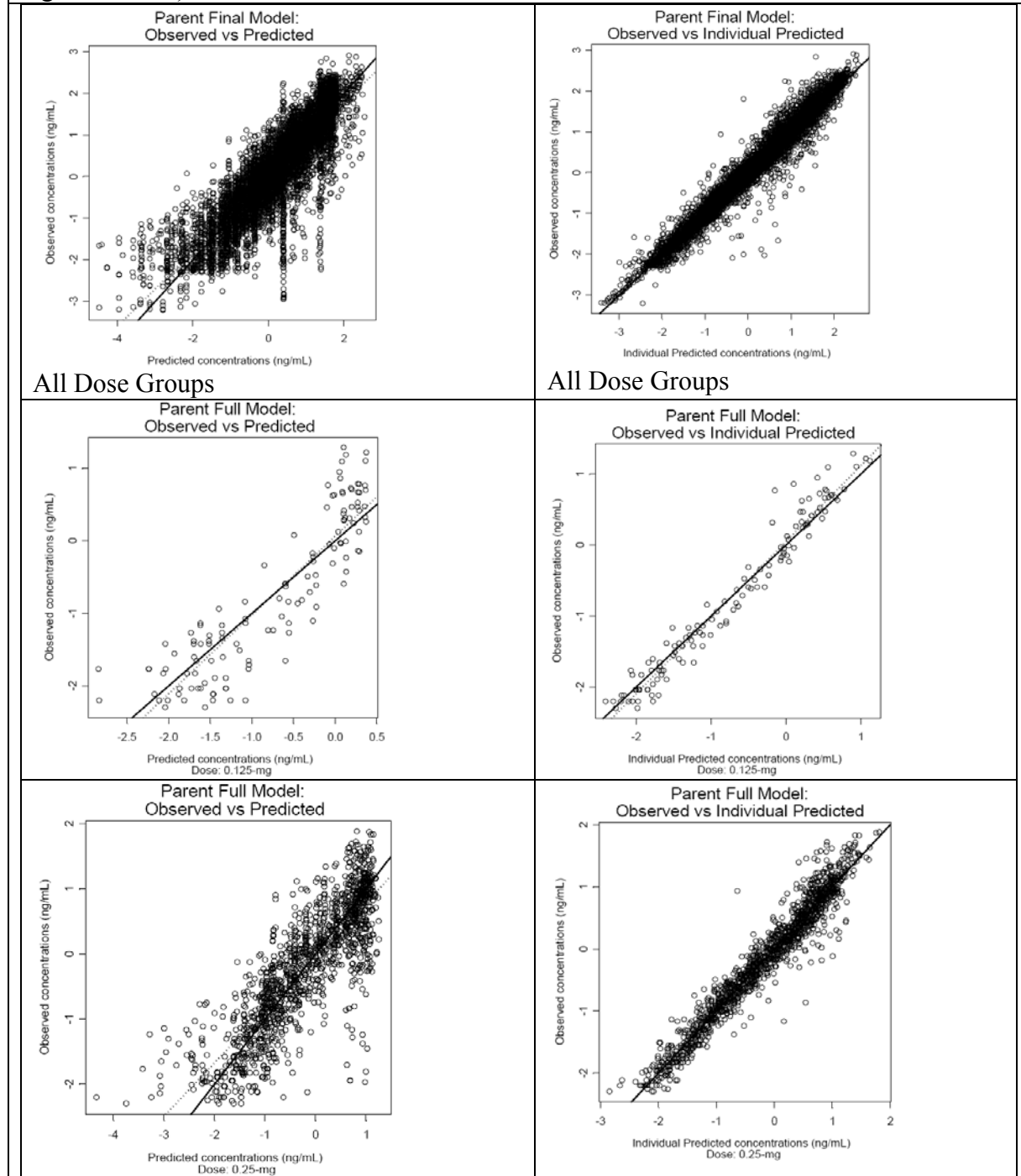
Figure 4. Diagnostic Plots for roflumilast N-oxide pharmacokinetic analysis in healthy subjects (The solid line is the concordance line – the 45° line through the origin. The dashed line is the regression line)


All Dose Groups

All Dose Groups

Metabolite Final Model: Observed vs Predicted (Dose: 0.5-mg)

Metabolite Final Model: Observed vs Individual Predicted (Dose: 0.5-mg)

Metabolite Final Model: Observed vs Predicted (Dose: 0.75-mg)

Metabolite Final Model: Observed vs Individual Predicted (Dose: 0.75-mg)

Metabolite Final Model: Observed vs Predicted (Dose: 1.0-mg)

Metabolite Final Model: Observed vs Individual Predicted (Dose: 1.0-mg)

Population pharmacokinetic analysis of data from subjects with COPD
To estimate the effect of the disease (COPD) on the pharmacokinetics of roflumilast and roflumilast N-oxide (metabolite), the model structure for roflumilast and roflumilast N-oxide and the covariate effects found in the healthy subjects models were not changed. No attempt to build a new model only based on the sparse PK data was attempted.

Figure 5. Goodness of fit plots for roflumilast and roflumilast N-oxide pharmacokinetic analysis in COPD patients (Final model): DV vs. IPRED and DV vs. PRED (Plots includes the diagonal line and two curves (linear regression of (log) data and a line based on polynomial regression(LOWESS)))
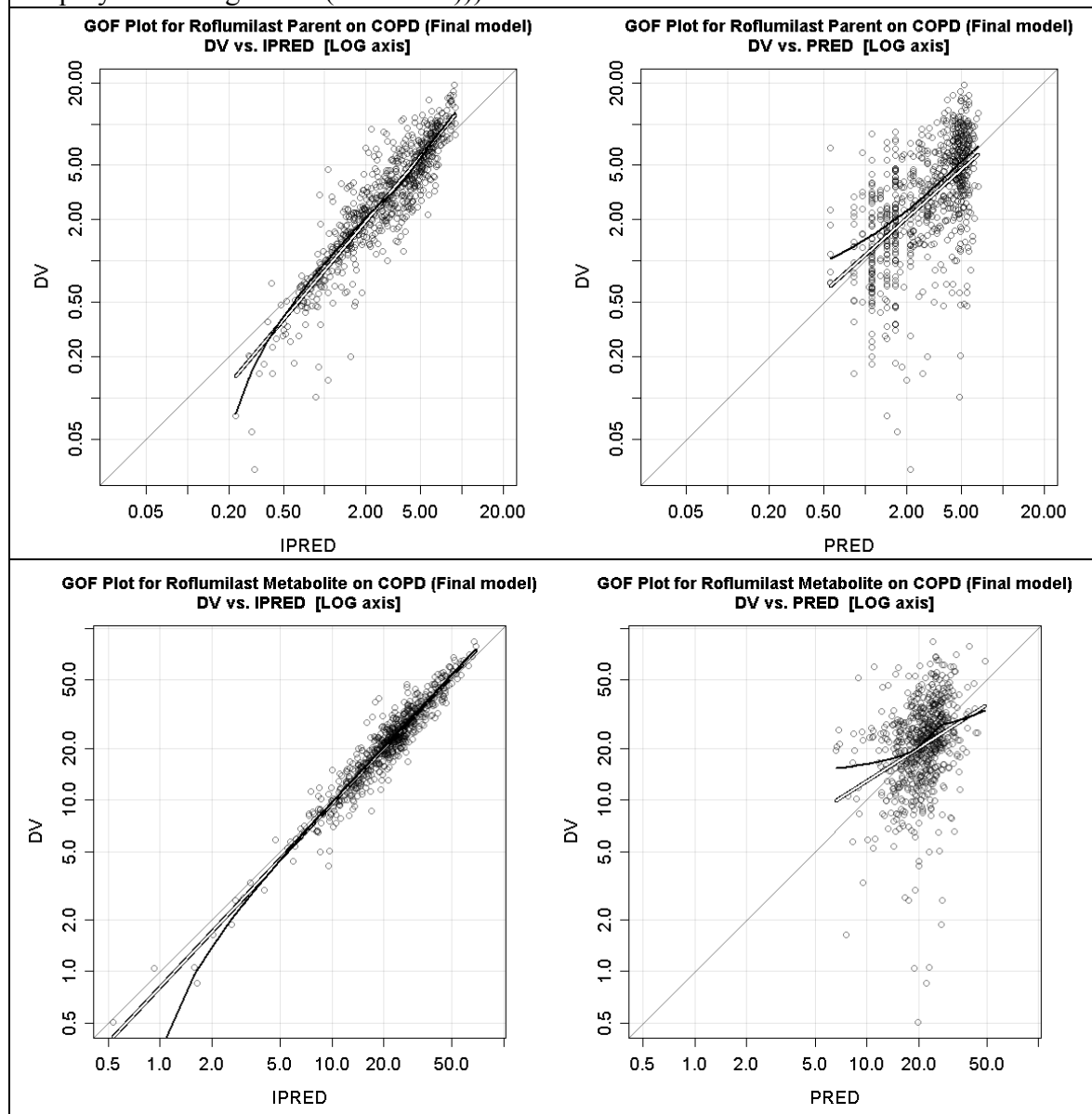
The parameter estimates yield the following implications:

- Significant effect of COPD were found on roflumilast and roflumilast N-oxide clearance (CL) and the central volume of distribution (VC).
- Clearance of roflumilast parent in COPD patients was reduced by 39.4%, while the central volume was increased by nearly two-fold when compared with the healthy subjects.
- COPD effects were found also on clearance (CL) and the volume of distribution (V) of roflumilast N-oxide (metabolite). The volume of distribution and clearance of roflumilast N-oxide in COPD patients was decreased by 21% and 8% respectively.
- The final models for both roflumilast and roflumilast N-oxide were used to estimate the exposure of roflumilast and roflumilast N-oxide in the COPD patient population. COPD patients have a 65% higher exposure (AUC) to roflumilast parent and a only about 8% higher exposure to roflumilast N-oxide.

The differences between healthy subjects and subjects with COPD was attributed to the role of inflammatory cytokines in differential up and down regulation of cytochrome P450s.

Reviewer's Comments: The population pharmacokinetic analysis conducted by the sponsor was reviewed. No labeling statements are derived based on population pharmacokinetic analysis. However, the model does underpredict the higher concentrations in patients for rofumilast (Figure 6). The model does provide reasonable fit of roflumilast N-oxide concentration data (Figure 7).

Figure 6. Goodness of fit plots for roflumilast pharmacokinetic analysis in COPD patients. The solid black line is the concordance line – the 45° line through the origin line.
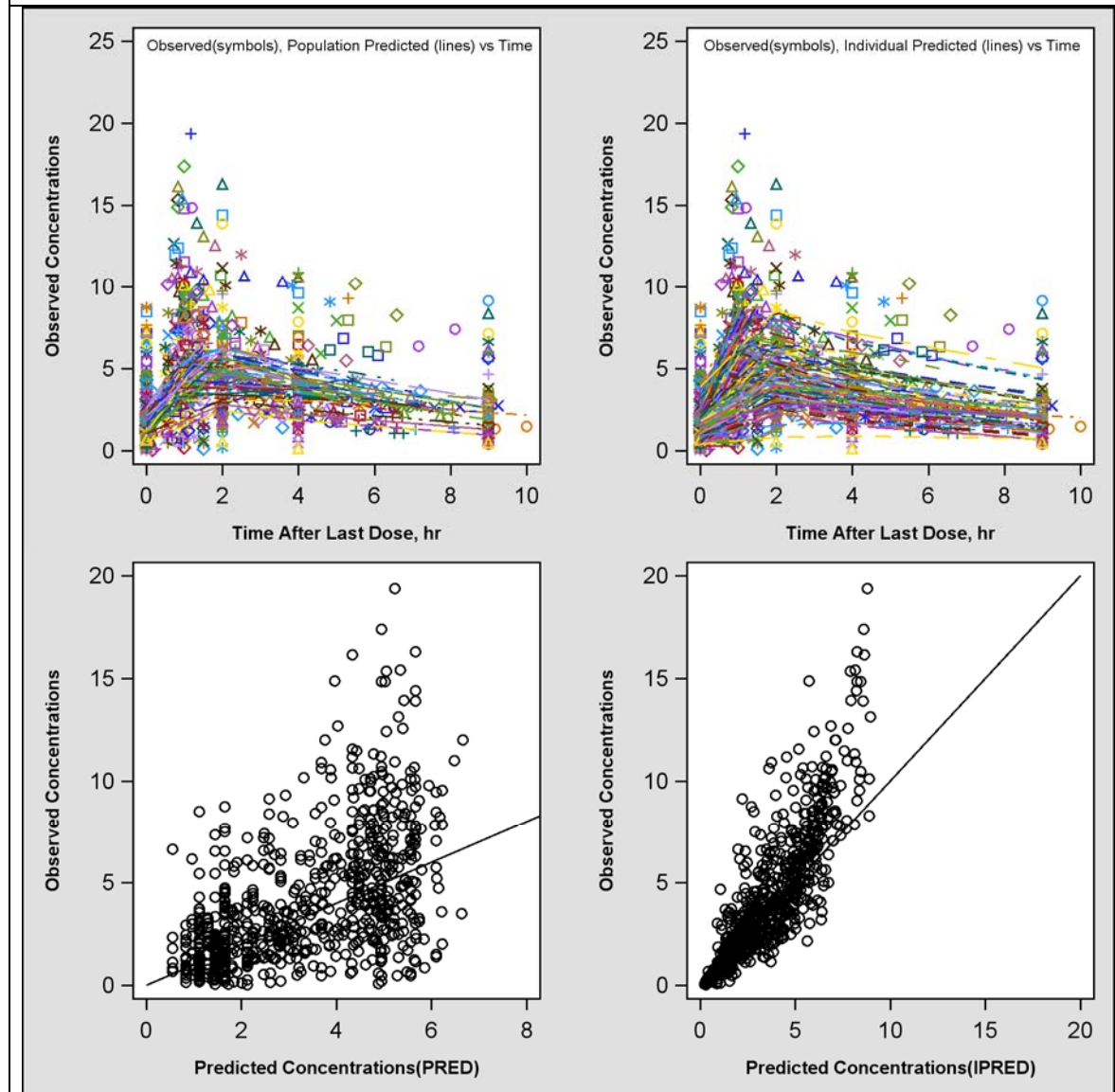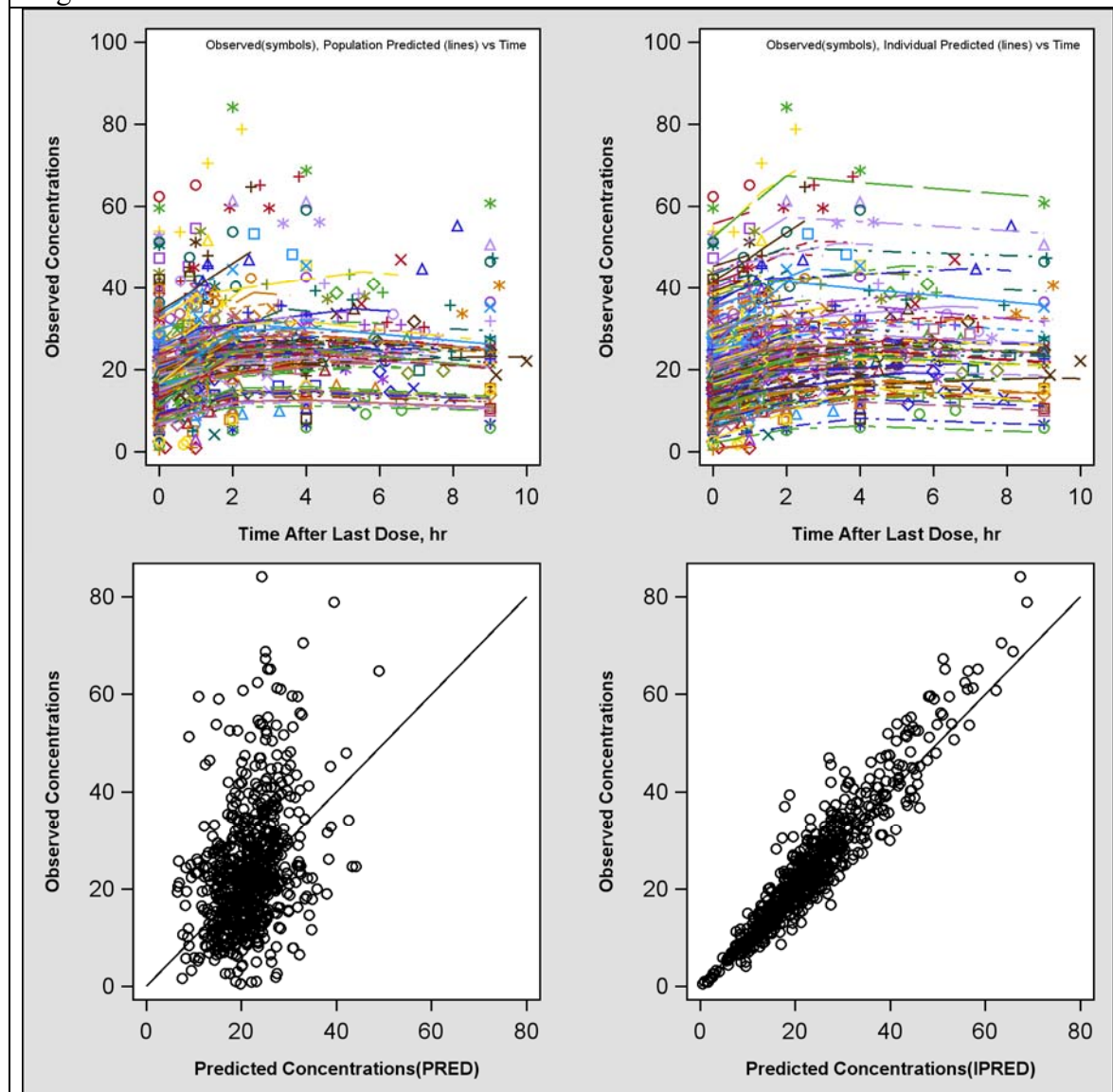
Figure 7. Goodness of fit plots for roflumilast N-oxide pharmacokinetic analysis in COPD patients. The solid black line is the concordance line – the 45° line through the origin line.

3.2 Prediction of changes in pharmacokinetics in subjects with hepatic impairment at 500 μg dose using SimCYP®.

The effects of various degrees of hepatic impairment on the pharmacokinetics of roflumilast were studied with 250 μg dose. Simulations using SimCYP® were conducted to predict the changes in pharmacokinetics of roflumilast in patients with hepatic impairment after administration of 500 μg dose.

Table 1 shows the physiological parameters (including liver volume and blood flows, enzyme abundances) used for simulations in SimCYP® for the healthy and patients with liver cirrhosis (Child-Pugh A; CP-A and Child-Pugh B; CP-B) groups.

Table 8. Summary of physiological and biochemical parameters associated with healthy volunteers (HV) and patients with liver cirrhosis (CP-A and CP-B).

|	HV	CP-A	CP-B
Liver volume fraction	1	0.81	0.65
CYP1A2 (ρmol/mg)	52	32.9	13.6
CYP2C9 (ρmol/mg)	73	50.4	38.0
CYP2C19 (ρmol/mg)	14	4.5	3.6
CYP2D6 (ρmol/mg)	8	6.1	2.6
CYP3A4 (ρmol/mg)	137	80.8	53.2
Gut CYP3A4 (nmol per total gut)	70	70	70
Albumin (g/L)	44.7	41.1	33.9
α1-acid glycoprotein (g/L)	0.8	0.57	0.52
Haematocrit (%)	40.94	36.6	32.9
Cardiac output (L/h)	306	355	403
Portal blood flow (males)(L/h)	58.2	52.9	36.9
Portal blood flow (females)(L/h)	65.8	59.9	41.7
Hepatic arterial blood flow (L/h)	19.9	28	32.3
Villous blood flow (L/h)	18.4	23.7	28
GFR (ml/min)	120	83.7	69.9

The simulated plasma concentration-time profiles of roflumilast on the last day of dosing given as daily doses of 250 μg for 14 days in HV, CP-A and CP-B subjects are shown in Figure 8. The simulated concentration-time profiles were compared with the observed data to verify the assumptions used in SimCYP® software. Figure 8 shows that the simulations overpredict the observed data in patients with liver cirrhosis.

Figure 8. Simulated plasma concentration-time profiles of roflumilast 250 μg in healthy volunteers and patients with livers cirrhosis Child Pugh-A and Child Pugh-B on the final day after oral daily dosing for 14 days. Grey lines represent 20 individual trials (n = 8 subjects), the solid black line is the mean of the population (20 x 8) and the solid circles represent mean in vivo data.
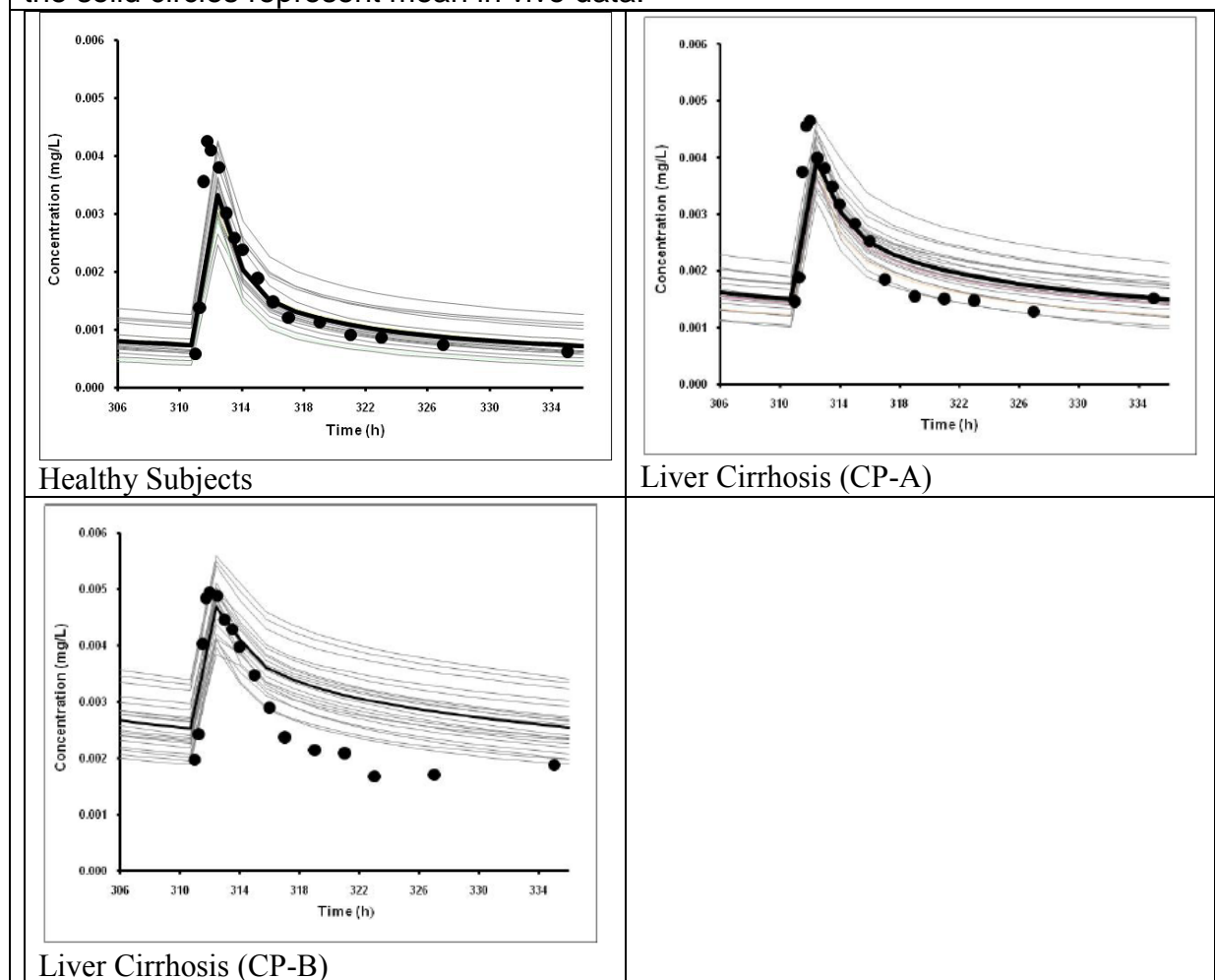
Healthy Subjects

Liver Cirrhosis (CP-A)

Liver Cirrhosis (CP-B)

The simulated plasma concentration-time profiles of roflumilast on the last day of dosing given as daily doses of 500 μg for 14 days in HV, CP-A and CP-B subjects are shown in Figure 9.

Figure 9.   Simulated plasma concentration-time profiles of roflumilast 500 µg in healthy volunteers and patients with livers cirrhosis Child Pugh-A and Child Pugh-B on the final day after oral daily dosing for 14 days. Grey lines represent 20 individual trials (n = 8 subjects), the solid black line is the mean of the population (20 x 8) and the solid circles represent *in vivo* data.

Healthy Subjects

Liver Cirrhosis (CP-A)

Liver Cirrhosis (CP-B)
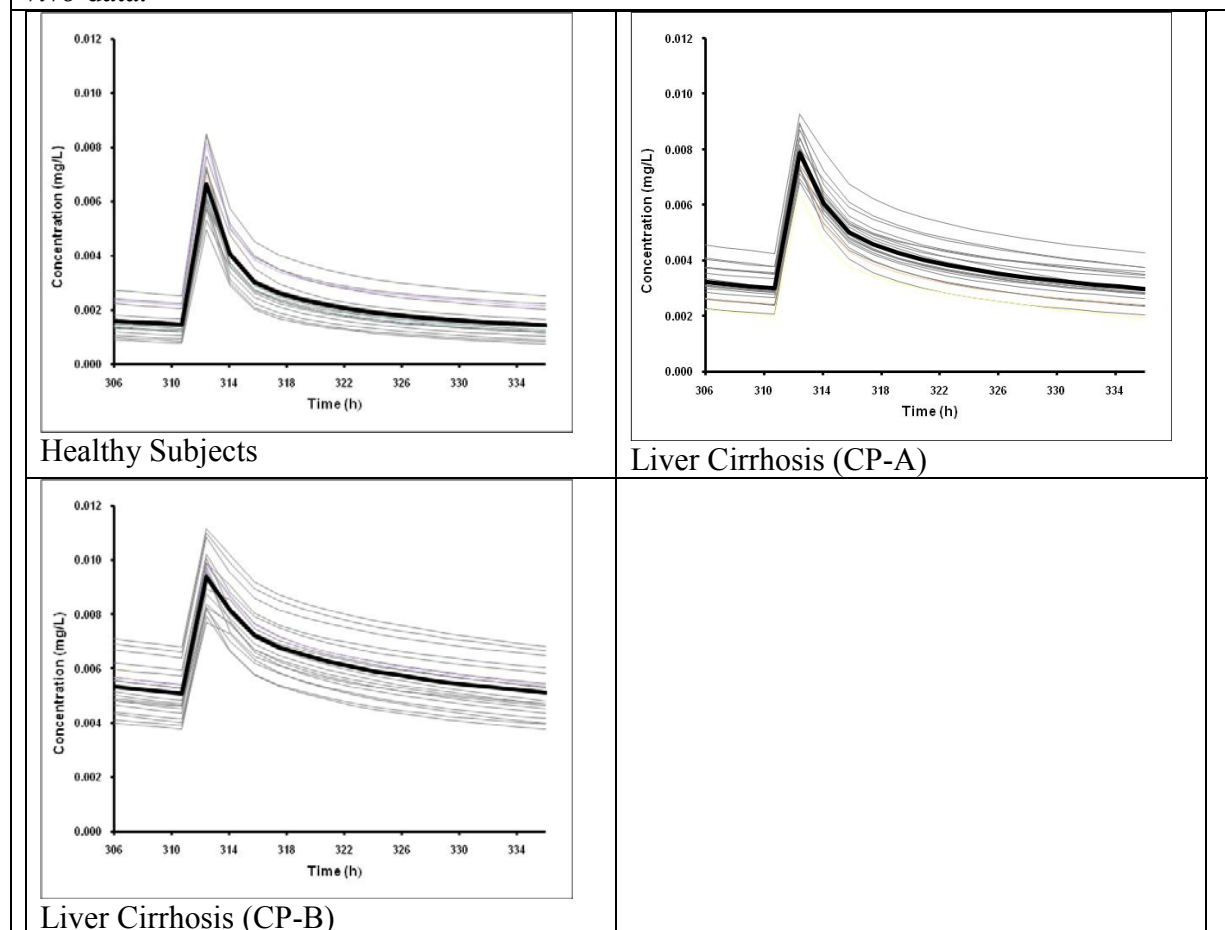
The sponsor concluded that the liver cirrhosis induced changes in pharmacokinetics of roflumilast and roflumilast N-oxide after 500 µg dose will be similar to those observed after 250 µg dose. In addition, the in vitro metabolism data suggests that

- Formation rates of roflumilast N-oxide and descyclopropyl roflumilast by CYP1A2, CYP3A4, CYP2C9 and CYP2C19 are not saturable at, and are linear up to a concentration of approximately 201 µg/L roflumilast.   When this concentration is compared with the roflumilast C_{max} of 5.95 µg/L in patients with moderate (Child-Pugh B) liver impairment following repeated oral doses of roflumilast 250 µg, the concentration in the *in vitro* system is approximately 33-folds higher than that in the *in vivo* setting. Even if the dose is increased to roflumilast 500 µg, the SimCYP® predicted C_{max} of roflumilast in patients with moderate (Child-Pugh B) liver impairment would be

8.76 μg/L. The difference between this concentration and the highest 'linear' concentration tested *in vitro* is still approximately 22- fold.

- Formation rates of descyclopropyl roflumilast N-oxide, the main metabolite of roflumilast Noxide by CYP1A1, CYP3A4 and CYP2C19, are also not saturable at, and are linear up to a concentration of approximately 1467 μg/L roflumilast N-oxide. When this concentration is compared with the roflumilast N-oxide C_{max} of 24.6 μg/L in patients with moderate (Child-Pugh B) liver impairment following repeated oral doses of roflumilast 250 μg, the concentration in the *in vitro* system is approximately 59-fold higher than that in the *in vivo* setting. As shown for the metabolism of roflumilast, the metabolism of roflumilast N-oxide is not likely to be saturated in patients with mild and moderate liver impairment following repeated oral doses of up to roflumilast 500 μg.

Reviewer's Comments: Figure 8 shows that the simulations overpredict the observed data indicating that some of the physiological parameters might not be reliable. However, based on the in vitro metabolism data (please refer to Dr Ping Ji's review for more details), it appears that the changes in pharmacokinetics of roflumilast and roflumilast N-oxide after 500 μg dose would be similar to those observed after 250 μg dose.

4 Reviewer's Analysis
NA
4.1 Introduction
NA
4.2 Objectives
NA
4.3 Methods

4.3.1 Data Sets
Data sets used are summarized in Table 9.
Table 9. Analysis Data Sets

Study Number	Name	Link to EDR

4.3.2 Software
NA
4.3.3 Models
NA
4.4 Results
NA

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Metwithrace.csv	Dataset used to develop PK model for roflumilast N-oxide in healthy subjects	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Roflumilast_NDA22522_HZ\PPK Analyses\Reviewer\Final Model\Healthy\Metabolite\Final
Parentwithrace2.csv	Dataset used to develop PK model for roflumilast in healthy subjects	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Roflumilast_NDA22522_HZ\PPK Analyses\Reviewer\Final Model\Healthy\Parent\FinalModel
meangraph_nooutliers.sas	SAS file for analyzing differences in pharmacokinetics of roflumilast and roflumilast N-oxide between healthy subjects and COPD patients	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Roflumilast_NDA22522_HZ\PPK Analyses\Reviewer\Other Model Name\MeanGraphs
COMBINEDPATIENTPARENT_NM_ENH.CSV"	Roflumilast PK data from COPD patients for analyzing differences in pharmacokinetics of roflumilast	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Roflumilast_NDA22

	and roflumilast N-oxide between healthy subjects and COPD patients	522_HZ\PPK Analyses\Reviewer\Final Model\Patient\Parent\FinalMo del\FinalModel
COMBINEDPATIENTMETA BOLITE_NM_ENH.CSV"	Roflumilast N-oxide PK data from COPD patients for analyzing differences in pharmacokinetics of roflumilast and roflumilast N-oxide between healthy subjects and COPD patients	\\cdsnas\PHARMACOMETRI CS\Reviews\Ongoing PM Reviews\Roflumilast_NDA22 522_HZ\PPK Analyses\Reviewer\Final Model\Patient\Metabolite\Met abolite\Final

4.2 Genomics Group Review

NDA Number	22,522
Submission Type; Code	Standard
Applicant Name	NycoMed
Submission Date	5/13/2009
Generic Name	Roflumilast
Proposed Indication	Maintenance of chronic obstructive pulmonary disease
Primary Reviewer	Mike Pacanowski, Pharm.D., M.P.H.
Secondary Reviewer	Issam Zineh, Pharm.D., M.P.H.

1   Background

The current submission is a New Drug Application for the new molecular entity roflumilast. The proposed indication is maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

Roflumilast inhibits phosphodiesterase 4 (PDE4; specifically, PDE4A, 4B and 4D splicing variants), which leads to elevated intracellular cAMP levels and mitigates COPD-related malfunctions of leukocytes, airway and pulmonary vascular smooth muscle cells, endothelial and airway epithelial cells and fibroblasts. The major metabolite, roflumilast N-oxide, inhibits PDE4 with similar specificity.

Roflumilast is metabolized to ADCP and ADCP N-oxide, which are structurally similar to monocyclic aromatic amines; these moieties may form epoxides and are potentially carcinogenic. Nasal toxicities/tumors were observed in rodent carcinogenicity studies. In rodents, CYP2G1 mediates conversion of ADCP N-oxide to the epoxide. Humans are not known to have a functional CYP2G1 ortholog.

During the development program, the sponsor discovered one subject in a multiple-dose pharmacokinetics study who had an exposure that was substantially higher than others enrolled in the same study. The sponsor performed extensive DNA sequence analysis and phenotyping of

this subject.

The purpose of this review is to evaluate the 1) pharmacogenetic basis for pharmacokinetic outliers and 2) genomic basis for species-specific carcinogenicity and human cancer risk.

2   NDA Content Related to Genomics
The sponsor has not identified any biomarkers to guide dose, select patients, or predict efficacy or safety. Pharmacokinetic and pharmacogenetic analysis was performed on a single subject in FHP027 who exhibited increased systemic exposure to roflumilast. This subject underwent phenotyping for CYP3A4 and CYP1A2 (reports 21/2003 [CP-053] and 22/2003 [CP-054]). Genomic analyses were otherwise not performed or submitted.

3   Key Questions and Summary of Findings
3.1   What genetic factors contribute to variable roflumilast exposures or responses?
CYP3A4 and CYP1A2 are the major enzymes involved in roflumilast metabolism. One subject appeared to be a pharmacokinetic outlier in study FHP027 (and compared to all other subjects receiving multiple doses of 500 mcg roflumilast); this individual carried a novel, rare CYP3A4 frameshift mutation, and had a reduced CYP1A2 metabolism phenotype. The prevalence of this CYP3A4/CYP1A2 phenotype combination is expected to be low in the general population. In the absence of pharmacokinetic data according to other common reduced function alleles of CYP3A4, CYP3A5, or CYP1A2, specific dosing recommendations cannot be made.

3.1.1 Roflumilast metabolism
Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. Formation of the pharmacologically active metabolite, roflumilast N-oxide, is dependent on the CYP3A4 (major) and 1A2 (minor) isoenzymes.

3.1.2 Pharmacogenetic analysis of a pharmacokinetic outlier
The sponsor identified a single subject (out of 16) in study FHP027, subject (b) (6), who exhibited a significantly higher exposure to roflumilast and roflumilast N-oxide than other subjects enrolled in the study. FHP027 evaluated the drug interaction between 500 mcg digoxin and 250 mcg digoxin in an open, randomized, two-period crossover design. The subject was a nonsmoking 41 year-old Caucasian (Brazilian) female (height 162 cm, weight 62 kg) with no significant past medical history. The pharmacokinetic observations are summarized in the following table. (b) (6) roflumilast and roflumilast N-oxide AUC_{0-24} were five-fold and three-fold higher, respectively, than the total population average on both study days, and the half-life was prolonged.

	Roflumilast			Roflumilast N-Oxide		
	(b) (6) single dose	(b) (6) multiple dose	All Subjects (68% range)	(b) (6) single dose	(b) (6) multiple dose	All Subjects (68% range)
AUC0-24 (ug/l-h)	53.8	267.6	50.2 (29.8-84.6)	146.6	1396.5	504.4 (339.6-749.2)
Cmax (ug/l)	10.2	18.9	9.9 (6.9-14.2)	5.6	68.7	30.9 (22.8-42.0)
t1/2 (h)	79.0	not ascertained	14.4 (9.1-22.9)	not ascertained	not ascertained	35.5 (23.3-51.2)
Metabolic ratio	0.30	0.19	0.10 (0.09-0.10)		9.52	

Source: Sponsor's report 269/2003

Phenotyping was performed on (b) (6) for CYP1A2 (caffeine probe; control n=6 [healthy female]) and CYP3A4 (midazolam probe; control comparison to literature values, n=144). (b) (6) had reduced CYP1A2 metabolism with an activity index 1.48, as compared to the median of 3.84 (minimum of 2.31) for control subjects. (b) (6) weight normalized clearance for midazolam was 2.99 ml/min-kg) compared to the lower 25^n percentile of the control subjects 2.61-3.88 ml/min-kg.(Reports 21/2003, 22/2003)

Sequencing of *CYP1A2* exons, intron/exon boundaries, and 5'UTR revealed one silent SNP 5347 T>C in exon 7 which did not alter the amino acid sequence of the protein. This SNP has not been shown to affect CYP1A2 activity *in vivo*. (b) (6) did not carry the CYP1A2*1K allele. Sequencing of CYP3A4 exons, intron/exon boundaries, and 5'UTR revealed a new, previously undescribed allele in exon 13 (based on literature review of sequencing data obtained from 413 Caucasians, 195 African Americans, and 230 Chinese). (b) (6) was heterozygous for an adenine insertion at position 1529/1530, now known as CYP3A4*20, which results in a frameshift that introduces a premature stop codon and truncated CYP3A4 (loss of 10 C-terminal amino acids). In vitro functional studies (yeast, HEK298 cells) of this mutation revealed 1) absence of antibody binding to CYP3A4 C-terminal peptide, 2) five-fold lower expression compared the CYP3A4*1, 3) loss of heme binding, and 4) no hydroxylation of prototypic CYP3A4 substrates (testosterone, midazolam). The study report(s) for these experiments were not reviewed.

The sequencing and functional study results were published in 2006. For additional information on the results and methods, please see the following manuscript: Westlind-Johnsson, et al. Clin Pharmacol Ther 2006;79:339.

Taken together, the results suggest that (b) (6) had reduced CYP3A4 function due to a newly discovered mutation. The functional consequences of the CYP3A4 variant were evident in a phenotyping probe study, and were further supported by in vitro studies. The subject also had a reduced activity phenotype for CYP1A2, although the subject did not carry the common reduced function *1K variant. The prevalence of this CYP3A4/CYP1A2 phenotype combination is expected to be low in the general population.

3.1.3 Variability in roflumilast exposure
The between-subject variability for AUC and Cmax ranged from 19-44% for roflumilast and 23-31% for roflumilast N-oxide. Pooled analysis was performed for PK data from the following

multiple dose studies wherein subjects received 500 mcg of roflumilast daily (n=145): studies FHP014, FHP017, FHP026, FHP027, FHP029, FHP039, CP050, CP060, and CP061. The exposure in subject (b) (6) from study FHP027 exceeded that of all other phase I study subjects.

Roflumilast and Roflumilast N-oxide Exposure in Multiple Dose Studies
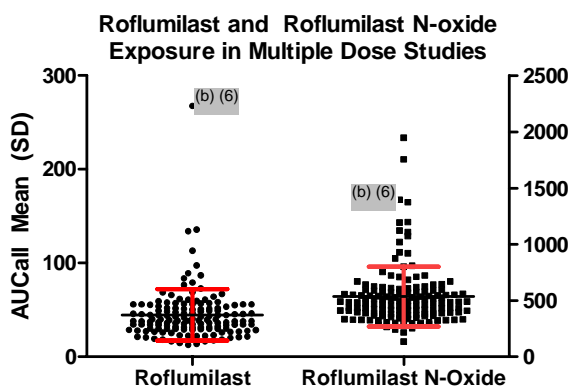
3.1.3.1 CYP450 mediated drug interactions

Summary results of clinical drug-drug interaction studies are summarized in the following table (from Clinical Pharmacology reviewer, Ping Ji). No dose modifications are recommended by the sponsor based on these pharmacokinetic changes.

Drug	Drug Properties	Roflumilast		Roflumilast N-oxide	
		Cmax	AUC	Cmax	AUC
midazolam	CYP3A4 Substrate	↔	↔	↔	↔
erythromycin	CYP3A4 moderate inhibitor	↑40%	↑70%	↓34%	↔
ketoconazole	CYP3A4 strong inhibitor	↑23%	↑99%	↓38%	↔
rifampicin	CYP3A4 inducer	↓68%	↓80%	↑ 30%	↓56%
fluvoxamine	CYP1A2 strong inhibitor	↔	↑156%	↓20%	↑52%
smoking	CYP1A2 inducer	↔	↓13%	↔	↑17%
digoxin	P-gp substrate	↔	↔	↔	↔
Maalox	Anti-acid	↔	↔	↔	↔

Source: Clinical Pharmacology reviewer, Ping Ji

3.1.3.2 Race effects on roflumilast pharmacokinetics

Racial differences in roflumilast may point to an underlying genetic mechanism to roflumilast pharmacokinetics. The exposure of roflumilast and roflumilast N-oxide in Japanese appeared to be higher than in Caucasian subjects, as shown from study CP-048. As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 25%, 47%, and 15% higher AUC, respectively, for roflumilast and 69%, 51%, and 16% higher AUC, respectively, for roflumilast N-oxide. As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 15%, 31%, and 17% higher C_{max}, respectively, for roflumilast and 17%, 9%, and 5% higher C_{max}, respectively, for roflumilast N-oxide (see primary Clinical Pharmacolgy review). The population pharmacokinetic model predicted a 42% and 28% higher total PDE4 inhibitory activity of roflumilast in Blacks and Hispanics, respectively, as compared with whites. No relevant differences in safety or tolerability between race groups were observed in the pooled

data of COPD phase II and III studies.

3.2 Are ADCP-related nasal toxicities mediated by CYP2G1 specific to rodent species?

The potentially carcinogenic epoxide metabolite of ADCP N-oxide is generated by rodent CYP2G1. Humans are capable of producing ADCP N-oxide in small quantities, although the true prevalence of ADCP N-oxide exposure following roflumilast treatment is not known. It is unknown if the epoxy-ADCP N-oxide is formed since M1, a stable product of the epoxide, was not assayed in humans. Humans have two CYP2G pseudogenes; a functional human CYP2G gene has not been definitively characterized. Based on published literature, 6% and 14% of individuals may be homozygous for potentially functional CYP2G1 and CYP2G2, respectively. CYP1A2 was capable of producing the epoxy-ADCP N-oxide metabolite in vitro, based on detection of hydroxy-ADCP N-oxide. CYP2A7, 2F1 and 2C18, which share similarity with rat CYP2G1, were not tested in the sponsor's in vitro experiments. Human CYP2A6, 2A13, 1A1, 1B1, 2B6, 2C9, 2C19, 2D6, 2E1, 2J2, 3A4, and 3A5 were not able to convert ADCP N-oxide to the epoxide metabolite in vitro. Collectively, the inability of humans to generate the potentially carcinogenic ADCP N-oxide metabolite through CYP2G1 or other CYP450 pathways has not been definitively demonstrated. A numerically higher incidence of tumor AEs was observed in the pooled COPD safety population.

3.2.1 Olfactory toxicities observed in rodents and proposed mechanism

The concentration and olfactory toxicity profiles for rats, hamsters, mice are summarized in the following table. In rats, olfactory mucosa toxicity was characterized by degeneration/ necrosis and was dose-limiting, precluding long-term carcinogenicity studies. In hamsters and mice, the lower susceptibility to olfactory mucosa toxicity allowed the use of higher doses for 24-month carcinogenicity studies in these species (reports 22/98, 133/97). In mice, the number of tumor-bearing animals was comparable between control and treatment groups and neoplasia was not evident. In hamsters, roflumilast treatment was associated with epithelial cell tumors localized in the olfactory mucosa of the nasal cavity. Overall, the olfactory mucosa toxicity/carcinogenicity studies produced heterogeneous results across rodent species.

Table 2   Serum/plasma AUCs of ADCP and ADCP N-oxide and toxic changes in olfactory mucosa after single oral doses of ADCP

Dose of ADCP	Rat			Hamster			Mouse		
	ADCP $AUC_{0-\infty}$	N-Oxide AUC_{0-8}	Tox [a]	ADCP AUC_{0-8}	N-Oxide AUC_{0-8}	Tox [b]	ADCP AUC_{0-8}	N-Oxide AUC_{0-8}	Tox [a]
0.05 mg/kg	93		+	39		-	na		-
0.5 mg/kg	1212		+	496		(+)	76		(+)
1.5 mg/kg	3254	573 [c]	+++	1589	3694	+	180	3402	(+)
[Report no.]	[35/97, 129/96]			[188/97, 4D/98]			[14/98]		

Serum/plasma AUCs are given as µg•h/L (total concentration); geometric means   na = not ascertained

Toxicity: + = minimal degeneration, ++ = mild degeneration, +++ = moderate necrosis, ( ) in singular animals only

[a] Histopathological evaluation 48 h after drug administration

[b] Histopathological evaluation 72 h after drug administration

The sponsor summarized the carcinogenicity profile of roflumilast as follows:

The nasal toxicity is related to the rodent-specific formation of a local SH-reactive metabolite within the nasal epithelium following the cleavage of ADCP from roflumilast. In a first step ADCP is oxidized to ADCP N-oxide. Olfactory and nasal microsomes from rodents have a high capability of converting ADCP to ADCP N-oxide. On the other hand, ADCP N-oxide results from cleavage of roflumilast N-oxide. ADCP N-oxide itself is not toxic to the olfactory mucosa. ***Toxicity requires a final metabolizing step, in which ADCP N-oxide is further oxidized to a SH-reactive metabolite that binds covalently to structures of the olfactory mucosa. This final step is mediated by the cytochrome P450 isoenzyme, CYP2G1, that can exclusively be found in olfactory microsomes of rodents.*** *That metabolic activation of ADCP is necessary to induce olfactory morphological changes was confirmed by mechanistic studies in rats demonstrating that after pretreatment with phorone (GSH depletion) toxicity was increased whereas after pretreatment with metyrapone (CYP inhibitor) olfactory toxicity was inhibited.*

Further, the sponsor asserts that "due to rodent-specific metabolism, [the] nongenotoxic, secondary tumors are considered to have no clinical relevance to humans."

3.2.2 ADCP N-oxide generation in humans

The human metabolic pathway for roflumilast is depicted in section 3.1; M09 is ADCP N-oxide. ADCP N-oxide is purported to be the precursor to the epoxide moiety (structure shown in figure below), which could lead to cytotoxicity, increased cell proliferation and neoplasia, as has been demonstrated for chloracetanilides (Jeffrey, et al. Toxicol Pathol 2006;34:827).

from Jeffrey, et al. *Toxicol Pathol* 2006; 34; 827.
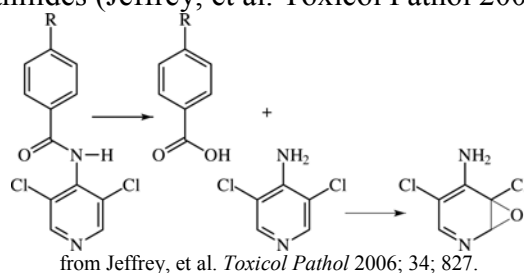
In the human urine metabolite profiling study (study FHP036; n=6), ADCP N-oxide in urine accounted for approximately 10% of the dose following orally administered roflumilast. ADCP N-oxide was measured in the following clinical studies: CP064, CP066, CP067, FHP004, and FHP039. ADCP N-oxide was detectable in two subjects (11 and 15) enrolled in study FHP039. The maximum ADCP N-oxide concentrations in these subjects were 1.31 ng/ml and 1.28 ng/ml, which were slightly above than the lower limit of quantitation of 0.5 ng/ml. Human AUCs were 13.9 mcg-h/l and 24.2 mcg-h/l, which is substantially lower than that observed in rodent species (as shown in table above).

Taken together, humans are capable of producing ADCP N-oxide in small quantities, although the true prevalence of ADCP N-oxide exposure following roflumilast treatment is not known. It is unknown if the epoxy-ADCP N-oxide is formed since hydroxy-ADCP N-oxide, a stable

product of the epoxide, was not assayed in humans.

The exposures to ADCP N-oxide in rodent, dogs and monkeys are significantly higher than that seen in humans, as shown in the following table.

Table 2.4 ‑ 21: Plasma/serum AUC at NOAEL for drug-related organ toxicity in chronic oral toxicity studies and calculation of exposure ratios

Species	Mouse	Mouse	Rat	Hamster	Dog	Dog	Monkey	Humans
NOAEL (mg/kg/day)	4 Rof	4 Rof-NO	0.8 Rof	4 Rof	0.6 Rof	1.2 Rof-NO	0.25 Rof	500 µg Rof
Duration (weeks)	26	26	26	13	52	52	43 [e]	1
AUC_{0-24h} (µg·h/L) total drug								
Roflumilast	153.1	14.4 [a]	30.9	44.4 [d]	510.1	41.3	251.3	32.8
Roflumilast N-oxide	512.5	1419.4	755.0	981.5 [d]	65.9	482.6	857.7	351.4
ADCP	12.7 [a, b]	n.d.	279.9 [c]	93.3 [d]	28.7	n.d.	33.4	4.1
ADCP N-oxide	196.2	n.d.	310.3 [c]	293.1 [d]	<LLOQ	n.d.	<LLOQ	<LLOQ

Source: Nonclinical Overview

3.2.3 Prevalence of functional human CYP2G1

CYP2G1 is expressed in mammalian olfactory tissues. Two CYP2G-related pseudogenes, CYP2G1P and CYP2G1P, have been identified in the human genome. These genes reside in the CYP2A, CYP2B, CYP2F gene cluster on chromosome 19q. CYP2G1/2P share approximately 80% identity with rat CYP2G1. Neither of the CYP2G pseudogenes are purported to be functional due to penetrant loss-of-function mutations. *CYP2G1P* contains a single nucleotide deletion in exon 2 that shifts the reading frame and a 2.4-kbp deletion that results in loss of exons 4 through 6. *CYP2G2P* contains two nonsense mutations in exons 1 and 3 that result in in-frame stop codons. The coding sequence of CYP2G1P and CYP2G2P (excluding exons 4-6) differ by 3%.(Sheng, et al. Pharmacogenetics 2000;10:667)

Copyright Material Withheld

Source: Sheng, et al. Pharmacogenetics 2000;10:667

In a published study (Sheng, et al. Pharmacogenetics 2000;10:667), the prevalence of the missense mutations and deletions was estimated by genotyping 200 individuals from various ancestral backgrounds (approximately 50 subjects each of white, black, Hispanic, and Asian race/ethnicity). The assay could not distinguish homozygous from heterozygous deletions in

CYP2G1P. Also, the assays for variants of the two pseudogenes are notably complex given the sequence homology.

The CYP2G1P exon 4-6 deletion was detectable in 98% of whites, 82% of blacks, 92% of Hispanics, and 100% of Asians. Overall, 6% of the population may have two copies of CYP2G1P lacking the deletion, which could potentially encode a functional CYP2G gene. All subjects who had exons 1 and 2 sequenced (n~10) possessed the CYP2G1P exon 2 deletion. Due to the homology with CYP2G2P, it could not be determined whether this coincided with the exon 4-6 deletion. Consequently, the true prevalence of a (potentially) functional CYP2G1P remains undefined.

The CYP2G2P exon 3 C>T dysfunctional allele (T) frequencies were as follows (homozygous frequency in parentheses): white 86% (79%), black 54% (44%), Hispanic 69% (46%), and Asian 78% (65%). Across all racial/ethnic groups, 29 of the 207 subjects were homozyogous for the wild-type allele, 18 of whom were black. The CYP2G2P exon 1 mutation was detected in all individuals (n>50) who had exons 1 and 2 sequenced, but again, it could not be reliably determined given the homology with CYP2G1P.

3.2.4 Involvement of other CYP450 enzymes in ADCP N-oxide metabolism
To identify enzymes that have sequence homology with rat CYP2G1, rat CYP2G1 (NP_036919.1) and the human protein reference sequence (refseq_protein) were aligned using BLASTp. The following proteins were identified in rank order as the most homologous (first ten): CYP2A6, 2A13, 2A7, 2C9, 2F1, 2C19, 2C9, 2B6, 2C18, and 2E1. Sequence identities were 47% to 58%. The CYP2A, 2G (pseudogenes), and 2F genes all cluster on chromosome 19q13.2.

In vitro studies (report 48/2005) demonstrated that human CYP2A6, 2A13, 1A1, 1B1, 2B6, 2C9, 2C19, 2D6, 2E1, 2J2, 3A4, and 3A5 do not metabolize ADCP N-oxide to hydroxy-ADCP N-oxide. CYP2S1, CYP2F1, CYP4B1, and CYP2C18 are expressed in nasal mucosa and/or lung, but were not tested (due to assay availability/quality). CYP1A2 supersome incubations did yield M1, but this was not the case using pooled microsome or purified CYP1A2 preparations. Of the human proteins sharing rat CYP2G1 sequence similarity, CYP2A7, 2F1 and 2C18 were not fully tested in vitro.

3.2.5 Cancer incidence in COPD clinical trials
Exposure time-adjusted tumors AEs for the pooled COPD safety population, as provided by the applicant, are noted in the following table. The incidence of all tumor types was numerically higher in the roflumilast exposed subjects as compared to placebo. Specifically, roflumilast was associated with a higher incidence of lung cancer (hazard ratio 2.10, 95% confidence interval 1.15-3.82; analysis stratified for age, gender, race, smoking status, COPD severity, region and history of cancer).

T-Table 11: Exposure time-adjusted summary of tumor AEs in the COPD safety pool by tumor type

Tumor type	Rtotal (N=6563) (ET=3585.7)			Placebo (N=5491) (ET=3405.4)			Total (N=12054) (ET=6991.1)		
	n	inc.	n'	n	inc.	n'	n	inc.	n'
All Tumor AEs	**98**	**27.3**	**105**	**72**	**21.1**	**80**	**170**	**24.3**	**185**
Lung cancer	33	9.2	33	17	5.0	17	50	7.2	50
Skin neoplasms	14	3.9	14	12	3.5	12	26	3.7	26
Other and not further specified neoplasms[b]	9 (8)[a]	2.5 (2.2)[a]	9 (8)[a]	16 (13)[a]	4.7 (3.8)[a]	17 (14)[a]	25 (21)[a]	3.6 (3.0)[a]	26 (22)[a]
Prostate cancer	14	3.9	14	7	2.1	7	21	3.0	21
Other gastro-intestinal neoplasms	5	1.4	6	13	3.8	13	18	2.6	19
Neoplasms of the urinary tract	9	2.5	11	5	1.5	5	14	2.0	16
Colon and rectal cancer	9	2.5	9	2	0.6	2	11	1.6	11
Gynecologic neoplasms	3	0.8	3	4	1.2	5	7	1.0	8
Hematologic neoplasms	5 (6)[a]	1.4 (1.7)[a]	5 (6)[a]	1 (4)[a]	0.3 (1.2)[a]	1 (4)[a]	6 (10)[a]	0.9 (1.4)[a]	6 (10)[a]
Neoplasms of the upper respiratory tract	1	0.3	1	1	0.3	1	2	0.3	2

[a] After the safety analyses were completed, it was detected that 4 patients were categorized erroneously into the tumor type 'other and not further specified neoplasms' although they should have been categorized into 'hematologic neoplasms'. The affected patients in the roflumilast group were: 1 patient (M2-121, CRF ID 90070) with paraproteinemia; in the placebo group: 1 patient (M2-125, CRF ID 90215) with paraproteinemia and 2 patients (M2-125, CRF IDs 91041 and 97653) with plasmacytoma [Table 1.4.12]. The adjusted numbers of patients in these tumor type categories are indicated in brackets.
[b] The category 'other and not further specified neoplasms' includes tumors which either occurred in very few patients (bone neoplasm, neuroendocrine carcinoma), or were not-further specified (eg metastasis).
Note: Number of patients with AEs per 1000 patient years of exposure = (n / total exposure time [years] of patients in treatment group) × 1000.
AE = adverse event; ET = Total exposure time (years); N = number of patients in treatment group, n = number of patients with at least one event in the category, inc = number of patients with at least one event in the category per 1000 patient years of exposure, n' = number of events in the category, Rtotal = both treatment groups combined (Roflumilast 250 µg once daily and Roflumilast 500 µg once daily po), PBO = Placebo once daily po; po = per os.
Source data: [Table 1.4.7].

Source: 351-2008 study report

4   Comments

4.1   Nasal toxicities/tumors were observed in rodent carcinogenicity studies. ADCP N-oxide, the precursor to the epoxide metabolite, was quantifiable in 2 subjects enrolled in phase 1/2 studies. The concentrations were at or near the lower limit of the assay's sensitivity, thus the

actual number of individuals that produce ADCP N-oxide and its metabolite may be greater. The ADCP N-oxide exposures were lower than what was observed in the animal carcinogenicity studies. A higher incidence of tumor AEs was observed in the pooled COPD safety population (safety anlaysis pending clinical review).

4.2   The potentially carcinogenic epoxide metabolite of ADCP N-oxide is generated by rodent CYP2G1. The presence or absence of a functional human CYP2G gene has not been definitively characterized. The CYP2G1P exon 4-6 deletion and CYP2G2P exon 3 mutation are highly prevalent null alleles in human populations. The exon 2 deletion of CYP2G1P and the exon 1 mutation of CYP2G2P cannot be reliably assayed due to the similarity of the gene sequences. Thus, based on published literature, 6% and 14% of individuals may be homozygous for a potentially functional CYP2G1 and CYP2G2, respectively. The potentially functional alleles were more commonly observed in blacks.

4.3   CYP1A2 was capable of producing the epoxy-ADCP N-oxide metabolite in vitro, based on assay of a stable downstream product. CYP1A2 induction, as might occur with smoking and certain CYP1A2 genotypes (e.g., CYP1A2*1F), may increase production of the epoxide metabolite in vivo. Human CYP2A6, 2A13, 1A1, 1B1, 2B6, 2C9, 2C19, 2D6, 2E1, 2J2, 3A4, and 3A5 were not able to convert ADCP N-oxide to this metabolite in vitro (based on assay of downstream product).

4.4   The sponsor should quantify the potentially carcinogenic epoxide metabolite of ADCP N-oxide in humans following multiple doses of roflumilast (ideally, in the presence of a CYP1A2 inducer and/or CYP1A2*1F genotype).

4.5   The sponsor should assess whether human CYP2A7, 2F1 and 2C18 are capable of converting ADCP N-oxide to the epoxide moiety in vitro. These enzymes share similarity with rat CYP2G1, and were not tested in the sponsor's in vitro experiments (report 48/2005).

4.6   The sponsor should consider collecting DNA in future studies evaluating the safety and efficacy of roflumilast.

4.7   CYP3A4 and CYP1A2 are the major enzymes involved in roflumilast metabolism. One subject appeared to be a pharmacokinetic outlier in study FHP027 (and compared to all other subjects receiving multiple doses of 500 mcg roflumilast); this individual carried a novel, rare CYP3A4 frameshift mutation, and had a reduced CYP1A2 metabolism phenotype. The prevalence of this CYP3A4/CYP1A2 phenotype combination is expected to be low in the general population. In the absence of pharmacokinetic data according to other common reduced function alleles of CYP3A4, CYP3A5, or CYP1A2, specific dosing recommendations cannot be made.

5   Recommendations
The Office of Clinical Pharmacology Genomics Group has reviewed the current NDA submission for roflumilast in the treatment of chronic obstructive pulmonary disease. The

sponsor should conduct studies to address items 4.4 and 4.5. Comment 4.6 should be conveyed to the applicant.

6   Label Recommendations
None.

4.3 Individual Study Review

96/2002 **Study Protocol No.:**   (b) (4)

Study Title:	*In vitro* plasma/serum protein binding of [^{3}H]-roflumilast and [^{3}H]-roflumilast N-oxide in different species, including human
Principal Investigator:	(b) (4)
Study Period:	12/1999 to 10/2002
Report No.:	96/2002

Objectives: To determine the plasma/serum protein binding in mouse, rat, hamster, dog, monkey and human of [^{3}H]-roflumilast and [^{3}H]-roflumilast N-oxide: determination of the free (unbound) fraction

Results:

Mean unbound fraction in plasma/serum							
	Species	Mouse	Rat	Hamster	Dog	Monkey	Human
Roflumilast	Conc. range (µg/l)	1 – 200	1 – 50	1 – 50	1 - 500	1 - 250	1 - 10
	unbound fraction (%)	3.7	2.0	2.9	1.6	2.1	1.1
Roflumilast N-oxide	Conc. range (µg/l)	1 – 500	1 – 500	1 – 1250	1 – 1250	1 – 500	1 – 100
	unbound fraction (%)	12.7	9.5	11.0	10.9	12.9	3.4

Conclusions:

The fraction of unbound drug in humans was constant (1.1%) at total roflumilast plasma concentrations ranging from 1 to 10 µg/l. The free (unbound) fraction was higher by 45% to 90% in the dog, rat and monkey (1.6 to 2.1%), while the free fraction in the mouse and hamster serum were about three times higher than that observed in humans.

The unbound fraction of roflumilast N-oxide was generally higher. In humans, the free fraction of roflumilast N-oxide was 3.4% in the concentration range 1 - 100 µg/l. In animals, the fraction of the unbound drug ranged from 9.5% to 12.9%, the highest fraction of unbound drug being observed in mouse and monkey.

73/2004

Study Protocol No.:	(b) (4)
Study Title:	*In vitro* biotransformation of BYK20869 and its metabolites with human cytochrome P450 isoenzymes
Principal Investigator:	(b) (4)
Study Period:	12/2003 to 3/2005
Report No.:	73/2004

Objective: This study was designed to elucidate the in vitro metabolism of Roflumilast (BYK20869/B9302-107) and its pharmacodynamically active metabolite Roflumilast N-oxide (BYK22890/B9502-044) in order to quantify the relative contributions of human CYP isoenzymes to oxidative metabolism and to clarify the metabolic pathways of both compounds.

Results: Roflumilast was oxidized to Roflumilast N-oxide by CYP3A4 and by CYP1A2. Taking into account the relative abundances of each CYP isoenzyme in human liver, CYP3A4 contributed 78.2% to Roflumilast N-oxidation whereas CYP1A2 accounted for 20.2% of Roflumilast N-oxide formation. Roflumilast desalkylation to Descyclopropyl Roflumilast was mainly carried out by CYP3A4 (93.1%) with a minor contribution of CYP2C19 (6.9%) and extrahepatic CYP1A1. In parallel, desalkylation of Roflumilast N-oxide was completely catalyzed by CYP3A4 with a contribution of extrahepatic CYP1A1. Descyclopropyl Roflumilast N-oxide was exclusively formed by CYP2C19 from Descyclopropyl Roflumilast.

Conclusion: The data show that hepatic metabolism of Roflumilast and Roflumilast N-oxide is carried out by CYP3A4 and CYP1A2. In case of concomitant administration of Roflumilast together with CYP3A4 inhibitors, clinically relevant drug-drug interactions seem unlikely or may occur with a moderate effect since the contribution of CYP1A2 to Roflumilast oxidation and CYP1A1 to desalkylation of Roflumilast N-oxide represents alternative metabolic routes for these two compounds.

176/2002 **Study Protocol No.:**   (b) (4)

Study Title:	Metabolism of roflumilast (BYK20869, B9302-107) by human liver microsomes *in vitro*
Principal Investigator:	Dr. Dirk Rocker
Study Period:	12/2001 to 9/2003
Report No.:	176/2002

Objectives:

This study was designed to identify the P450-isoenzymes, which mediate metabolism of roflumilsat (BYK20869, B9302-107) to its N-oxide *in vito* by human liver microsomes.

Results:

In the presence of NADPH, roflumilast was metabolized in vitro to its major metabolite, BYK22890 (B9502-044, N-oxide) mainly by supersomes expressing CYP1A2 or CYP3A4. Microsomes coincubated with an chemical inhibitor of Cytochrome P450-isoenzymes showed a reduction of metabolism of roflumilast to its N-oxide of $63.9\% \pm 4.5\%$ for furafylline, of $59.9\% \pm 8.0\%$ for ketokonazole and of $78.3\% \pm 1.6\%$ for the combination of furafylline and ketokonazole compared to microsomes without chemical inhibition.

Conclusion:

Roflumilast was metabolized to its N-oxide (BYK22890) by human liver microsomes. The Km was ~1.8 μM whereas Vmax was ~11.1 pmol*mg-1*min-1. Roflumilsat N-oxidation could also be shown for supersomes expressing CYP1A2 or CYP3A4. This was confirmed by human liver microsomes, where these cytochrom P450-isoforms were inhibited by the chemical inhibitors furafylline (CYP1A2) or ketoconazole (CYP3A4).

302/2007

Study Protocol No.:	(b) (4)
Study Title:	*In vitro* reaction phenotyping of BYK22890 with human liver microsomes and recombinant CYP enzymes

Principal Investigator:
Study Period: 11/2006 to 5/2007
Report No.: 302/2007

Objective

The aim of this study was to examine the *in vitro* metabolism of BYK22890 in order to determine the role of human flavin-containing monooxygenases (FMO) and cytochrome P450 (CYP) enzymes in the *O*-dealkylation of BYK22890 to BYK22891.

Results and Discussion

The role of CYP3A4 in the formation of BYK22891 was again confirmed in human liver microsomal incubations of BYK22890 (5 μM) in the presence of chemical inhibitors. The strongest inhibition of BYK22891 formation (74%) was observed by the direct-acting CYP3A4/5 inhibitor, ketoconazole, at 10 μM. Similarly, the metabolism-dependent CYP3A4 inhibitor azamulin (at 5 μM) inhibited BYK22891 formation by approximately 73%. However, the strong inhibition observed by the CYP3A4 inhibitors ketoconazole and azamulin was incomplete, suggesting that CYP3A4 may not be entirely responsible for the formation of BYK22891 in human liver microsomes.

In conclusion, the results of this study suggest that cytochrome P450 enzymes, not FMO enzymes, contribute to the *O*-dealkylation of BYK22890 to BYK22891 by human liver microsomes. Of the CYP enzymes evaluated, CYP3A4 appears to be a major contributor to the formation of BYK22891. Several other CYP enzymes may also have a minor contribution to the formation of BYK22891 (*e.g.*, CYP2B6 and CYP2C8). In addition, CYP1A1 may contribute to the *O*-dealkylation of BYK22890 to BYK22891 in extrahepatic tissue.

283/2005   **Study Protocol No.:**

Study Title:	*In vitro* evaluation of roflumilast as an inhibitor of human cytochrome P450 enzymes
Principal Investigator:	(b) (4)
Study Period:	4/2005 to 8/2005
Report No.:	283/2005

Objective

This study was designed to evaluate the ability of roflumilast to inhibit CYP2B6 and CYP3A4/5 in human liver microsomes, with the aim of ascertaining the potential of roflumilast to inhibit the metabolism of concomitantly administered drugs.

Results and Discussion

Roflumilast was determined to be a competitive inhibitor of CYP3A4/5 with a Ki value of 2.79 μM. Under the experimental conditions examined, roflumilast caused little direct inhibition of CYP2B6, with an estimated Ki value of 133 μM.

Roflumilast did not appear to be an irreversible metabolism-dependent inhibitor of CYP2B6 or CYP3A4/5.

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90E/99 **Study Protocol No.:**

Study Title:	*In vitro* evaluation of B9302-107 as an inducer of microsomal cytochrome P450 expression in rat and human hepatocytes
Principal Investigator:	(b) (4)
Study Period:	6/1998 to 4/1999
Report No.:	90E/99

Objective: To evaluate the effects of B9302-107 on the expression of liver microsomal cytochrome P450 enzymes in primary cultures of rat and human hepatocytes, with the aim of predicting the potential of B9302-107 to cause clinically relevant drug interactions.

Study Design: Rat Hepatocytes: Cultures of rat hepatocytes were treated with 0.1, 0.01, 0.001 µM B9302-107, or various positive controls daily for three days. Twenty-four hours after the final treatment, microsomes were prepared, and the expression of CYP1A1/2, CYP2B1/2, CYP3A1/2 and CYP4A1-3 was estimated by determining 7-ethoxyresorufin *O*-dealkylase, 7-pentoxyresorufin *O*-dealkylase, testosterone 16ß-hydroxylase, testosterone 6ß-hydroxylase, and lauric acid 12-hydroxylase activity, respectively.

Human Hepatocytes: Cultures of human hepatocytes were treated with 0.1, 0.01, 0.001 µM B9302-107, or various positive controls daily for three days. Twenty-four hours after the final treatment, microsomes were prepared, and the expression of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 was estimated by determining 7-ethoxyresorufin *O*-dealkylase, coumarin 7-hydroxylase, 7-ethoxy-4-trifluoromethylcoumarin *O*-dealkylase, diclofenac 4'-hydroxylase, *S*-mephenytoin 4'-hydroxylase and testosterone 6ß-hydroxylase activity, respectively.

Conclusions: 1. Treatment of cultures of rat hepatocytes with B9302-107 resulted in no induction of CYP1A1/2, CYP2B1/2, CYP3A1/2 and CYP4A1-3. Under similar experimental conditions, the positive control inducers, ß-naphthoflavone, phenobarbital, dexamethasone, and clofibric acid caused a marked induction of CYP1A1/2, CYP2B1/2, CYP3A1/2 and CYP4A1-3, respectively.

2. Treatment of cultures of human hepatocytes with B9302-107 resulted in a weak induction of CYP2B6 (at the highest concentration studied, 0.1 µM, which is about 10 times the human C_{max} in plasma).

3. Treatment of cultures of human hepatocytes with B9302-107 showed no induction of CYP1A2, CYP2A6, CYP2C9, CYP2C19 and CYP3A4/5. Under similar experimental conditions, the positive control inducers, ß-naphthoflavone (inducer of CYP1A2), phenobarbital (inducer of CYP2A6, 2B6, 2C9, 2C19, and 3A4/5), and rifampin (modest inducer of CYP2A6, 2B6, 2C9, 2C19 and a strong inducer of CYP3A4/5) caused a marked induction of the appropriate P450 enzyme.

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102/2001 **Study Protocol No.:**

Study Title:	Evaluation of B9502-044 as an inhibitor of human cytochrome P450 enzymes
Principal Investigator:	
Study Period:	3/2000 to 6/2001
Report No.:	102/2001

Objective: This study was designed to evaluate the ability of B9502-044 to inhibit the major P450 enzymes in human liver microsomes, with the aim of ascertaining the potential for B9502-044 to inhibit the metabolism of other drugs.

Results/
Conclusions: The results of this study show that, as a direct acting (metabolism-"independent") reversible inhibitor, 1) B9502-044 appears to be a competitive inhibitor of CYP1A2, and CYP2A6 with K_i values of 160 and 420 µM, respectively; 2) B9502-044 appears to be an uncompetitive inhibitor of CYP4A9/11 with a K_i value of 450 µM; 3) B9502-044 appears to be a non-competitive inhibitor of CYP2B6 with a K_i value of 280 µM; 4) B9502-044 appears to be a mixed inhibitor of CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 with K_i values (for the primary mechanism of inhibition) of 60, 77, 210 and 59 µM, respectively; 5) B9502-044 has little or no capacity to inhibit CYP2D6 and CYP2E1. The rank order of K_i values for the inhibition of the enzymes listed above is as follows: CYP3A4/5 ≈ CYP2C8 < CYP2C9 < CYP1A2 < CYP2C19 < CYP2B6 < CYP2A6 < CYP4A9/11 << CYP2D6 ≈ CYP2E1. B9502-044 has little or no capacity to function as a reversible metabolism-dependent inhibitor of any of the other P450 enzymes examined, with the exception of CYP1A2 and CYP3A4/5.

B9502-044 caused moderate reversible metabolism-dependent inhibition of CYP1A2 and weak reversible metabolism-dependent inhibition of CYP3A4/5. Finally, B9502-044 has little or no capacity to function as an "irreversible" metabolism-dependent inhibitor of any of the other P450 enzymes examined.

Based on the information on the *in vitro* inhibitory potential of B9502-044, coupled with its plasma C_{ss} of 0.1 µM (free + bound concentration), up to 0.169% inhibition of CYP3A4-mediated metabolic processes *in vivo* (fractional inhibition) may be expected. Thus, clinically significant pharmacokinetic interactions between B9502-044 and drugs metabolized primarily by CYP3A4 would not be expected provided that the free plasma C_{ss} of B9502-044 is comparable to its concentration at the active sites of CYP3A4/5. Because the inhibition of CYP3A4/5 by B9502-044 was the most potent inhibition observed in this study, the compound would not be expected to inhibit the clearance of drugs that are metabolized by the other enzymes examined.

107/2002 **Study Protocol No.:** **107/2002**

Study Title:	Metabolism of roflumilast in plasma of the species man, dog, hamster and mouse
Principal Investigator:	
Study Period:	1/2001 to 7/2003
Report No.:	107/2002

Objective:

The objective was to study the metabolism of roflumilast in plasma of the species man, rat, dog, hamster and mouse after oral administration of roflumilast.

The human plasma samples were from ADME study FHP036.

Results and Discussion:

In mouse plasma, the major metabolite roflumilast N-oxide (B9502-044) as well as the minor metabolite ADCP N-oxide were found. One minor metabolite isobaric to roflumilast N-oxide was identified as the same mono oxygenized metabolite as found in dog plasma. Most probably this metabolite carries a hydroxy function at the amide nitrogen atom, as described above. Further, the corresponding glucuronidated compound was identified. One dechlorinated minor metabolite was identified which was most probably oxidized in the

DCP part at one of the aromatic carbon atoms. Two corresponding N-oxides were also found to a minor extent. The parent compound roflumilast together with the metabolites roflumilast N-oxide and ADCP N-oxide covered 55.8 % of the total radioactivity in mouse plasma. All metabolites together with the parent compound covered 71.7 % of the total radioactivity in hamster plasma.

212/2002 **Study Protocol No.:**	**BY217/FHP036/U**
Study Title:	Metabolite profiling of $[^{14}C]$-B9302-107 (roflumilast) in human urine
Principal Investigator:	Zhe-ming Gu, Ph.D.
Study Period:	4/2002 to 10/2002
Report No.:	212/2002

Objectives:

To investigate metabolic pathways of roflumilast in human urine and to elucidate the structure of the major metabolites. The urine samples were from the human ADME study FHP036.

Results:

The profiling data suggests that [^{14}C]-B9302-107 was extensively metabolized by male subjects through either oral (PO) or IV administration. Eighteen significant radioactive regions were integrated. Similar radioactivity distribution patterns were observed for both oral and IV dose groups. Unchanged parent compound was not detectable in urine and the major human plasma metabolite, roflumilast N-oxide (M-HU07), is only a trace metabolite. M-HU04, and M-HU09, were characterized or identified by LC/ESI-MS in either positive or negative ionization mode. The major metabolic routes in human include loss of the cyclopropylmethyl group resulting in a phenol, N-oxidation to form a quarterny N-oxide, and oxidative dechlorination to generate a phenol moiety followed by glucuronidation. Another route of B9302-107 metabolism in human proceeds via cleavage of the amide bond resulting in an ADCP-related metabolite. The proposed metabolic pathways of [^{14}C]-B9302-107 in human are illustrated in the following chart:
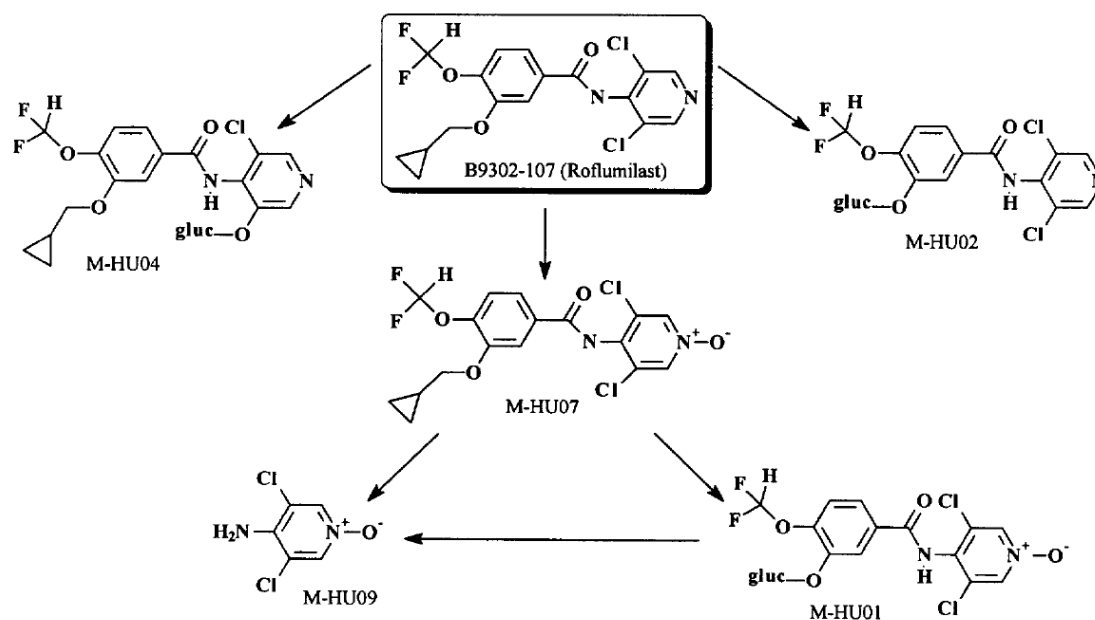
Proposed Metabolic Pathways of B9302-107 (Roflumilast) in Human

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Summary on Percent Distribution of Radioactivity (%Dose) in Pooled 0-168 Hour Human Urine Samples from Oral and IV Doses

Metabolite Region	Metabolite Code	PO	IV
1	N/A	1.33	1.21
2	N/A	0.76	1.02
3	M-HU09	10.03	8.03
4	N/A	0.66	0.44
5	N/A	0.30	0.32
6	M-HU01	20.95	18.28
7	N/A	0.54	0.81
8	M-HU02	12.32	12.35
9	N/A	1.44	1.64
10	N/A	0.91	1.06
11	N/A	0.95	1.37
12	N/A	0.74	0.88
13	N/A	1.60	2.32
14	N/A	0.52	0.77
15	M-HU04	11.09	13.32
16	N/A	0.93	1.42
17	N/A	1.47	1.96
18	M-HU07	0.89	1.05

266/2002 **Study Protocol No.:**   (b) (4) @

Study Title:	BYK20869 does not significantly inhibit P-glycoprotein transporter in Caco-2 cells
Principal Investigator:	Richard Kim, MD
Study Period:	11/2000 to 4/2003
Report No.:	266/2002

Objectives:

This study was carried out in order to investigate a possible drug-drug interaction between roflumilast and digoxin based on the drug transporter P-glycoprotein (P-gp).

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Results:

A potential role of BYK20869 as an inhibitor of P-gp was assessed using Caco-2 cells, a human colon adenocarcinoma cell line which constitutively expresses P-gp. It has previously been shown that [^{3}H]- digoxin transport in Caco-2 cells is mediated by P-gp. When BYK20869 (100 μM) was studied in this format, a lack of a significant inhibition of [^{3}H]- digoxin transport was observed (Figure 1). A known P-gp inhibitor, verapamil, at 20 μM was able to fully inhibit the directional movement of digoxin, consistent with complete inhibition of P-gp.

Conclusion:

In essence, these findings strongly suggest that BYK20869 is not a P-gp inhibitor, and that BYK20869 is unlikely to cause P-gp related drug-drug interactions in humans.

xxxxx **Study Protocol No.:**	(b) (4)
Study Title:	Assessment of ADCP N-oxide (B9502-054) metabolism by cytochrome P450 enzymes potentially expressed in human nasal mucosa
Principal Investigator:	(b) (4)
Study Period:	8/2004 to 2/2005
Report No.:	48/2005

Objective:

The aim of the present study was to determine whether 11 CYP enzymes, including CYP1A1, 1A2, 1B1, 2B6, 2C8, 2C18, 2D6, 2E1, 2J2, 3A4, and 3A5, which are potentially expressed in human nasal mucosa or lung, are active in the formation of M1 (hydroxy-ADCP N-oxide) from ADCP N-oxide. M1 is the stable rearrangement product of the putative, labile epoxy-ADCP N-oxide.

Results and Discussion:

M1 was the only metabolite detected by HPLC in reaction mixtures of mouse CYP2G1 with ADCP N-oxide. The rate of M1 formation by mouse 2G1 was about 5 nmol/hr/nmol P450 and served as reference. A degradation product of ADCP N-oxide (D1) increased in abundance over time in the substrate stock. This product had similar retention time to that of M1 under the HPLC conditions used, and it interfered with the detection of M1. Formation of M1/D1 by mouse CYP2G1 was inhibited by GSH and by an anti-2A5/2G1 antibody, findings that confirm CYP2G1-dependent production of the reactive intermediate that leads to M1 formation.

CYP2C18 failed quality control; two different preparations were tested, both were found to have little activity toward known CYP2C18 substrates. Therefore, CYP2C18 could not be tested for ADCP N-oxide metabolism.

CYP1A2 supersomes produced M1/D1 in an NADPH-dependent manner, suggesting possible activity of CYP1A2 in M1 formation. Nevertheless, CYP1A2 supersome-mediated formation of M1/D1 was not quenched by the addition of saturating GSH, or by an inhibitory anti-CYP1A2 antibody. Furthermore, NADPH-dependent formation of M1/D1 was not seen with purified CYP1A2 in a reconstituted system or with pooled human liver microsomes, which contained functional CYP1A2. Therefore, it was concluded that CYP1A2 was not active in forming M1.

No formation of M1 was detected with any of the other tested P450 supersomes (CYP1A1, 1B1, 2B6, 2C8, 2D6, 2E1, 2J2, 3A4, and 3A5), with a detection limit of ~0.5 nmol/hr/nmol P450.

Results of additional studies confirmed that preparations of the 10 human CYPs and the pooled human liver microsomes used in this study were active with the respective known substrates.

Thus, it was concluded that none of the 10 human CYPs tested are capable of producing M1 from ADCP N-oxide.

xxxxx	**Summary Report**
Study Title:	Levels of ADCP and ADCP N-oxide metabolites of roflumilast in human drug-drug interaction studies with potent CYP3A4 and 1A2 inhibitors
Principal Investigator:	Dr. Gezim Lahu

Introduction:
Based on *in vitro* data, CYP3A4 and CYP1A2 are the predominant enzymes involved in the Phase I metabolism of roflumilast with a minor contribution of CYP2C19 [Ref. 1]. Various studies have been conducted to investigate the extent of interaction of well-known and established inducers and inhibitors of CYP3A4 on the metabolism of roflumilast. The effect of ketoconazole (a potent inhibitor of CYP3A4) and fluvoxamine (a potent inhibitor of CYP3A4 and CYP1A2) [Ref. 2] on roflumilast pharmacokinetics is documented in clinical study report (CSR) 398/2004 (Pfizer Study A582-1012) and CSR 400/2004 (Pfizer Study A582-1013), respectively. Additionally, the effect of rifampicin (a potent inducer of CYP3A4 and other CYPs) on roflumilast pharmacokinetics has been investigated in study CP-064, which is documented in CSR 8/2005. All these studies have been conducted during the second half of the year 2004.

The main objectives of these studies were to investigate the effect of the inducers and inhibitors on roflumilast and roflumilast N-oxide pharmacokinetics. The study designs are briefly described in sections 2.1, 2.2, and 2.3 for studies A582-1012, A582-1013, and CP-064, respectively. However, until now no detailed investigation of the above-mentioned inducers and inhibitors on other roflumilast metabolites, namely ADCP and ADCP N-oxide, has been reported. This report describes the levels of ADCP and ADCP N-oxide based on the analysis of plasma samples from studies A582-1012 and A582-1013, and also discusses the data of the metabolite levels determined in study CP-064 and reported in CSR 8/2005.

Discussion:
Data from all the above-mentioned studies show that plasma levels of ADCP and ADCP N-oxide were below limit of quantitation. These findings based on the data analyzed indicate that neither induction nor inhibition of CYP3A4 and CYP1A2 has any effect on the levels of ADCP and ADCP N-oxide. It is assumed that ADCP and ADCP N-oxide are derived from roflumilast and roflumilast N-oxide by amide cleavage. This cleavage is so low that neither with increased roflumilast levels nor with increased N-oxide levels (as seen in A582-1012 and A582-1013) any measurable quantities of ADCP or ADCP N-oxide appear in plasma.

Conclusion:
The results of plasma samples analyses from drug-drug interaction studies suggest that neither inhibition nor induction of CYP3A4 and 1A2 increase the ADCP and ADCP N-oxide plasma levels. All plasma values of ADCP and ADCP N-oxide were below the LLOQ.

255/2008   **Summary Report**

Study Title:	Roflumilast: Casual relationship between olfactory metabolism and olfactory toxicity in rodents
Principal Investigator:	Michael David
Report Date:	1/2009
Report No.:	255/2008

Introduction:

The non-clinical safety of roflumilast has been tested in routine studies, and toxicity to the olfactory epithelium was observed especially in rats but also to a lesser degree in hamsters and mice. Non-rodents such as dogs and monkeys did not show any derangements in the olfactory mucosa despite of higher drug exposure. Several investigative studies were performed focusing on this rodent-specific toxicity of roflumilast to olfactory mucosa in order to assess any human risk. Drug metabolism and distribution studies provided evidence that the toxic damage to the rodent olfactory mucosa was due to the formation of a reactive metabolite from ADCP (amino-dichloro-pyridine), the cleavage product of roflumilast. The reactive metabolite is formed by a rodent-specific cytochrome P450 isozyme (CYP2G1) and damages the rodent olfactory mucosa.

Because of the toxicity of roflumilast to the nasal mucosa of rodents, it was not unexpected that a few tumors appeared in the nasal region during long-term treatment of hamsters in the course of the 24-month carcinogenicity assays. This tumorigenic effect of roflumilast is related to the olfactory toxicity that leads to regenerative proliferation of mucosa cells. Cell proliferation contributes to carcinogenesis by providing opportunities for somatic mutations to occur since DNA does not replicate with complete fidelity. Chemicals that induce cytotoxicity and sustained increases in cell proliferation, therefore, enhance the likelihood of nasal carcinogenesis. The non-genotoxic nature of the tumorigenic effect is supported by the lack of genotoxic potential of roflumilast and metabolites.

The present discussion summarizes the results of the various investigations and concludes with a safety assessment with regard to the use of roflumilast in humans.

Executive Summary:

At the end of the 24-month treatment period in the carcinogenicity assays of roflumilast, an increased incidence of tumors was noted in the nasal cavity of hamsters in the high-dose groups. This tumorigenic effect of roflumilast observed in hamsters is related to a rodent-specific olfactory toxicity, which leads to regenerative proliferation of cells in the olfactory mucosa. No olfactory toxicity has been seen in dogs and monkeys. The non-genotoxic nature of the tumorigenic effect in hamster is supported by the lack of genotoxic potential of roflumilast and its metabolite, amino-dichloro-pyridine (ADCP), especially as no DNA-adducts are formed.

Nasal mucosa toxicity seen after roflumilast administration to rodents (rat is the most sensitive species) is not caused by the parent compound: There is no correlation between nasal mucosa toxicity and roflumilast levels across various animal species. Moreover, when using radiolabels in different parts of the molecule and after manipulation of drug metabolism in rats it is evident that (i) binding of radioactivity to nasal tissue parallels nasal mucosa toxicity and (ii) metabolic activation has to take place prior to binding as the parent compound itself does not bind to nasal tissue.

The nasal mucosa toxicity is attributed to the rodent-specific formation of a SH-reactive metabolite. The prerequisite for the formation of this metabolite is, firstly, breakdown of roflumilast and roflumilast N-oxide to form ADCP metabolites in an amidase cleavage reaction. This is supported by the finding that only radioactivity from the labeled ADCP-moiety of roflumilast was found covalently bound in rat nasal mucosa, while radiolabel from the benzyl-moiety was not fixed to the tissue.

ADCP N-oxide is a major metabolite of roflumilast in rodents, but mostly below the limit of quantitation in human plasma. Human nasal and hepatic microsomes, as well as a post-mitochondrial S9 fraction of human liver, produced no detectable levels of ADCP or ADCP N-oxide upon incubation with roflumilast. The likely route of ADCP N-oxide formation in humans is amide cleavage of roflumilast N-oxide that may occur in the kidney, explaining the urinary excretion.

An outline of the metabolic scheme appears below.

Dechlorination
Dealkylation   ⟵   Roflumilast   ⟹   Roflumilast N-oxide   ⟶   Dealkylation
Conjugation   Conjugation

ADCP   ⤏   ADPC N-oxide   ─X─⟶   Epoxy-ADCP N-oxide
                                CYP2G1
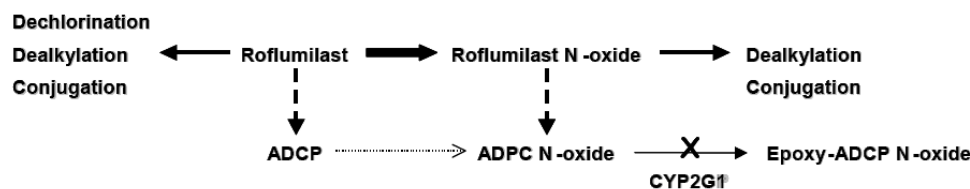
The presence of ADCP or even the presence of ADCP N-oxide as such in the systemic circulation does not confer nasal toxicity as demonstrated by appreciable exposure of the dog and monkey to ADCP leading to no nasal toxicity, or by high systemic exposure of mouse and

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hamster to ADCP N-oxide leading to only minor nasal toxicity as compared to the rat. Obviously it is essential for nasal mucosa toxicity that ADCP N-oxide as a precursor for its reactive epoxy-derivative is formed locally in the olfactory mucosa. This metabolite is then able to react with the SH-groups of glutathione or proteins at the site of its formation. The metabolic activation and olfactory fixation with subsequent toxicity can be reduced by cytochrome P450 (CYP) inhibition or, on the other hand, increased by glutathione depletion. The conversion of ADCP N-oxide to the proximal olfactory toxicant, epoxy-ADCP N-oxide is catalysed only by the olfactory tissue-specific CYP2G1 isoenzyme in rodents.

Humans do not possess a functional CYP2G gene, since the orthologous genes contain loss-of-function mutations. Studies with the two major human olfactory CYPs, CYP2A6 and 2A13, revealed no epoxide formation. Additional in-vitro studies were conducted to further evaluate the possibility of oxidation of ADCP N-oxide by other human CYP isoenzymes and revealed also no epoxy-ADCP N-oxide formation. Test isoenzymes included CYP1A1, 1A2, 1B1, 2B6, 2C8, 2C18, 2D6, 2E1, 2J2, 3A4, and 3A5, which are potentially expressed in human nasal mucosa and/or lung. Collectively, the data show that none of the CYP isoenzymes, which may occur in human nasal mucosa and lungs, are capable of generating the toxic epoxy-ADCP N-oxide from ADCP N-oxide.

As expected, human nasal mucosa has been shown not to retain roflumilast when the drug ^{18}F-labeled in the side chain of the benzyl-moiety was used in a PET study. Five clinical trials using olfactometry gave no hints for roflumilast disturbing olfactory function. The profile of adverse effects is of no concern specifically with respect to olfactory function in all clinical trials. Therefore, it is concluded that the nasal mucosa toxicity observed in rodents as well as the nasal cavity tumors seen in the high-dose groups of the hamster carcinogenicity study are of no relevance to humans.

Study Title:	Roflumilast (B9302-107) and dichloroaminepyridine (B9202-045). Comparative *in vitro* metabolism using microsomes prepared from nasal olfactory and respiratory epithelium and liver of rat, mouse, hamster, dog, monkey and human.
Principal Investigator:	
Study Period:	5/1998 to 5/1999
Report No.:	122E/99

Objective:

To compare in vitro metabolism of carbon-14 labelled Roflumilast (B9302-107) and aminodichloropyridine (ADCP; B9202-045; a potential metabolite) using hepatic, olfactory and respiratory microsomes prepared from tissues obtained from the rat, mouse, hamster, dog, cynomolgus monkey and a pool of human donors.

Results:

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- Extent of metabolism of ADCP by nasal microsomes of rat, mouse, hamster and dog was almost complete.
- In contrast to mouse and hamster, rat and dog liver microsomes have only little capacity to metabolise ADCP.
- Ability of monkey and human nasal microsomes to metabolise ADCP is much lower.
- ADCP is almost quantitatively metabolised to its corresponding N-oxide in rat, mouse, hamster and dog.
- Only traces of ADCP were detected upon incubation of monkey olfactory microsomes.
- No ADCP N-oxide was detected upon incubation with pooled human olfactory or respiratory microsomes.
- Roflumilast was metabolised to a more complex range of metabolites without any detectable formation of ADCP (except traces with rat liver microsomes) or its N-oxide in any of the species investigated. Metabolites of hitherto unknown structure, designated M7 and M9, were most prevalent. Mass spectrometry data indicated that the structure of M9 was consistent with that of the parent compound, suggesting that it may be a labile metabolite.

Conclusion:

In general, microsomes of all species metabolised Roflumilast to a series of metabolites without, however, formation of ADCP or its N-oxide. On the other hand, nasal microsomes of rat, mouse, hamster and dog did convert ADCP almost quantitatively to its corresponding N-oxide, which is in sharp contrast to monkey and man which both had a much lower rate of metabolism, specifically with nasal microsomes, and no detectable formation of ADCP N-oxide.

The cynomolgus monkey was found to most closely resemble man in the metabolism of Roflumilast and ADCP. Therefore, it is suggested that this species may be the most appropriate common laboratory animal species to use to model the effects of the test compound in man.

142/97 Study Protocol No.:	(b) (4)
Study Title:	Orientative investigation of the formation of N-oxide metabolites of B9302-107 and B9202-045 by microsomal fractions of nasal mucosa in various species *in vitro*.
Principal Investigator:	(b) (4)
Study Period:	5/1996 to 4/1997
Report No.:	142/97

Objectives:

To investigate the formation of N-oxide metabolites (B9502-044, B9502-054) during the in vitro bio-transformation of roflumilast (B9302-107) and dichloroaminopyridine (DCAP, B9202-045) mainly in microsomal fractions of nasal mucosa of rat, mouse, hamster and dog. To investigate the in vitro biotransformation in microsomal fractions of human respiratory tissue.

Results:

In all nasal tissues of the animals studied B9502-054 (N-oxide) was a major in vitro product of DCAP. Differences were more marked for B9302-107. The monooxygenase activities (from no „-" to strong „+++") are given in the following table.

Species	Tissue microsomal fraction of nasal mucosa	Formation of N-oxide	
		B9302-107 to B9502-044	B9202-045 to B9502-054
Rat	not differentiated	-	+ +
Mouse	not differentiated	+	+ +
Hamster	not differentiated	+	+ +
Dog	olfactory or respiratory	+ +	+ + +
Human	respiratory	-	-

Additionally, as shown by orientative investigations, the in vitro formation of the N-oxide of roflumilast was found to occur in the hepatic microsomes of rodents. A strong oxidation rate of DCAP and roflumilast was observed in liver samples of the hamster.

Conclusions:

In summary, formation of N-oxide could be demonstrated in vitro for most nasal microsomes studied. In contrast, no oxidative metabolism was obvious in human respiratory nasal tissue.

(b) (4)

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FHP015

Study Title: Study on the bioequivalence of 3 tablet strengths (100 μg, 250 μg, 500 μg) of roflumilast

Objectives: Assessment of bioequivalence between 3 different strengths of roflumilast Formula B/Konstanz tablets, differing by various amounts of active ingredients (roflumilast 100 μg, 250 μg and 500 μg) while the amount and ratio of excipients (65 mg) was the same.

Study Design: Open, randomized, 3-period, crossover study. Single dose of roflumilast 500 μg of Formula B/Konstanz, p.o. either 5 tablets of 100 μg, 2 tablets of 250 μg or 1 tablet 500 μg.

Study Population: Healthy subjects, N = 18 (M), aged 21 to 41 years, median: 28 years.

Data Analysis: Serial blood sampling for PK assessment (roflumilast, roflumilast N-oxide). Measurements of vital signs, ECG, clinical laboratory and monitoring of AE.

Pharmacokinetic Results: Summary statistics of pharmacokinetic parameters are shown the table below:

T-Table 2.7.1 - 9   Roflumilast and roflumilast N-oxide PK characteristics (geometric mean, 68% range) after a single dose of roflumilast 500 μg (Formula B/Konstanz) of either 5 tablets à 100 μg, 1 tablet à 500 μg or 2 tablets à 250 μg [FHP015 (67/99)]

	5 tablets à Rof 100 μg	1 tablet à Rof 500 μg	2 tablets à Rof 250 μg
Roflumilast			
AUC_{inf} [μg×h/L]	33.9 (25.4, 45.4)	33.8 (25.8, 44.2)	33.5 (26.8, 41.8)
C_{max} [μg/L]	8.18 (6.71, 9.97)	7.75 (5.81, 10.3)	7.81 (6.32, 9.66)
$t_{1/2}$ [h]	11.4 (7.47, 17.5)	9.70 (6.67, 14.1)	10.8 (7.79, 15.0)
t_{max} [h] *	0.53 ± 0.03	0.61 ± 0.06	0.64 ± 0.09
Roflumilast N-oxide			
AUC_{inf} [μg×h/L]	368 (284, 477)	382 (301, 484)	374 (300, 466)
C_{max} [μg/L]	9.70 (8.05, 11.7)	9.79 (8.05, 11.9)	9.84 (8.18, 11.8)
$t_{1/2}$ [h]	20.1 (16.3, 24.9)	22.3 (18.2, 27.3)	19.6 (16.4, 23.5)
t_{max} [h] *	8.56 ± 0.97	8.81 ± 1.00	6.39 ± 1.00

* t_{max}: mean±SE

T-Table 2.7.1 - 10   Roflumilast and roflumilast N-oxide test/reference ratios (point estimate [% of reference], 90% confidence interval) of AUC_{inf} and C_{max} after a single dose of roflumilast 500μg of either 5 tablets à 100 μg (test 1), 1 tablet à 500 μg (test 2) or 2 tablets à 250 μg (reference) [FHP015 (67/99)]

	5 tablets à Rof 100 μg (test 1)	1 tablet à Rof 500 μg (test 2)
Roflumilast		
AUC_{inf}	103 (97, 109)	103 (98, 110)
C_{max}	105 (94, 116)	99 (90, 110)
Roflumilast N-oxide		
AUC_{inf}	97 (93, 101)	102 (97, 106)

C_{max} of roflumilast N-oxide was not assessed

Conclusions: 3 different strengths of roflumilast Formula B/Konstanz tablets (100 μg, 250 μg and 500 μg, respectively) were bioequivalent.

FHP010

Study Title: Study on the effect of food intake on the pharmacokinetics of roflumilast after single oral dose administration of 0.5 mg to healthy volunteers

Objectives: Assessment of food effect on PK of roflumilast, roflumilast N-oxide and ADCP.

Study Design: Open label, randomized, 2-period crossover study. Single dose of roflumilast 500 µg, p.o. was administered under fed or fasted conditions.

Study Population: Healthy subjects, N = 12 (10M/2F), aged 22 to 304 years with the median of 27 years.

Data Analysis: Serial blood sampling for PK assessment (roflumilast, roflumilast N-oxide and ADCP). Measurements of vital signs, ECG, clinical laboratory and monitoring of AE.

Pharmacokinetic Results: Summary statistics of pharmacokinetic parameters are shown the table below:

T-Table 2.7.1 - 6   Roflumilast, roflumilast N-oxide and ADCP PK characteristics (geometric mean, 68% range) after a single dose of roflumilast 500 µg, p.o. either under fed or fasted conditions [FHP010 (11/98K)]

	Fed	Fasted
Roflumilast		
AUC_{inf} [µg×h/L]	34.8 (29.6, 41.0)	31.2 (24.6, 39.5)
C_{max} [µg/L]	3.84 (3.01, 4.90)	6.51 (4.97, 8.53)
$t_{\frac{1}{2}}$ [h]	11.1 (7.3, 17.0)	10.3 (6.4, 16.4)
t_{max} [h] *	1.96 ± 0.35	0.96 ± 0.19
Roflumilast N-oxide		
AUC_{inf} [µg×h/L]	304 (255, 362)	350 (283, 434)
C_{max} [µg/L]	8.40 (7.02, 10.0)	8.81 (7.07, 10.9)
$t_{\frac{1}{2}}$ [h]	20.6 (13.5, 31.5)	19.6 (13.7, 28.1)
t_{max} [h] *	12.0 ± 0.82	12.2 ± 0.76
ADCP		
AUC_{inf} [µg×h/L]	n.a.	n.a.
C_{max} [µg/L]	0.065 (0.045, 0.093)	0.075 (0.066, 0.084)
$t_{\frac{1}{2}}$ [h]	n.a.	n.a.
t_{max} [h] *	19.1 ± 5.72	26.6 ± 10.6

* t_{max}: mean±SE

T-Table 2.7.1 - 7   Roflumilast and roflumilast N-oxide test/reference ratios (point estimate [% of reference], 90% confidence interval) of AUC_{inf} and C_{max} after a single dose of roflumilast 500 µg either under fed (test) or fasted conditions (reference) [FHP010 (11/98K)]

	Roflumilast	Roflumilast N-oxide
AUC_{inf}	112 (100, 125)	91 (79, 104)
C_{max}	59 (49, 70)	95 (90, 101)

T-Table 2.7.1 - 8   AUC test/reference ratios (point estimate [% of reference], 90% confidence interval) of roflumilast N-oxide (test) and roflumilast (reference) after a single dose of roflumilast 500 µg either under fed or fasted conditions [FHP010 (11/98K)]

	Fed	Fasted
AUC ratio roflumilast N-oxide/roflumilast	911 (802, 1034)	1111 (1024, 1206)

Conclusions: Applying a bioequivalence range of 80 to 125%, a food effect was seen for roflumilast with respect to systemic exposure (12% increase under fed conditions) and peak exposure (41% decrease under fed conditions). For roflumilast N-oxide, a food effect was seen with respect to systemic exposure (9% decrease under fed conditions) but not with respect to

peak exposure. Under fed and fasted conditions, the formation of roflumilast N-oxide was similar (about 9-fold higher under fed and 11-fold higher under fasted conditions when compared with roflumilast). ADCP plasma concentrations were only detected at low levels, reflecting a low formation of this metabolite. A single dose of roflumilast 500 µg was very well tolerated, regardless whether the medication was taken under fed or fasted conditions.

JP704

Study Title: A clinical pharmacological (Phase I) study of APTA-2217 in healthy adult male volunteers (Effect of food intake, single oral dose)

Objectives: To compare the pharmacokinetics and to evaluate the safety of APTA-2217 after single oral administration of 500 mcg under fasting and fed (low fat diet) conditions in healthy adult male volunteers.

Study Design: Of the subjects who were determined eligible based on the screening examination results, 10 subjects and 2 substitutes were selected; 5 subjects were randomized to either Group A (the initial administration was given under fasting) or Group B (the initial administration was given after ingestion of standardized food). Study
medication was administered in Periods 1 and 2 according to the allocated food condition, and specified observations and tests were performed. During each study period, subjects were hospitalized for 8 days and 7 nights, and the minimum-dosing interval of the study drug between Period 1 and Period 2 was 10 days.

	Period 1	Period 2
Group A (5 subjects)	Administration of APTA-2217 500 mcg tablets under the fasting condition	Administration of APTA-2217 500 mcg tablets under the fed condition
Group B (5 subjects)	Administration of APTA-2217 500 mcg tablets under the fed condition	Administration of APTA-2217 500 mcg tablets under the fasting condition
During each study period subjects were hospitalized from 2 days before administration of roflumilast up to Day 6 for 8 days (8 days and 7 nights). The minimum-dosing interval of the study drug between Period 1 and Period 2 was 10 days.		

Study Population: Healthy subjects, N = 10 (M) with 5 for each treatment.

Data Analysis: PK assessment (roflumilast, roflumilast N-oxide) was conducted using a noncompartmental approach.

Pharmacokinetic Results:

Linear plot

Single logarithmic plot
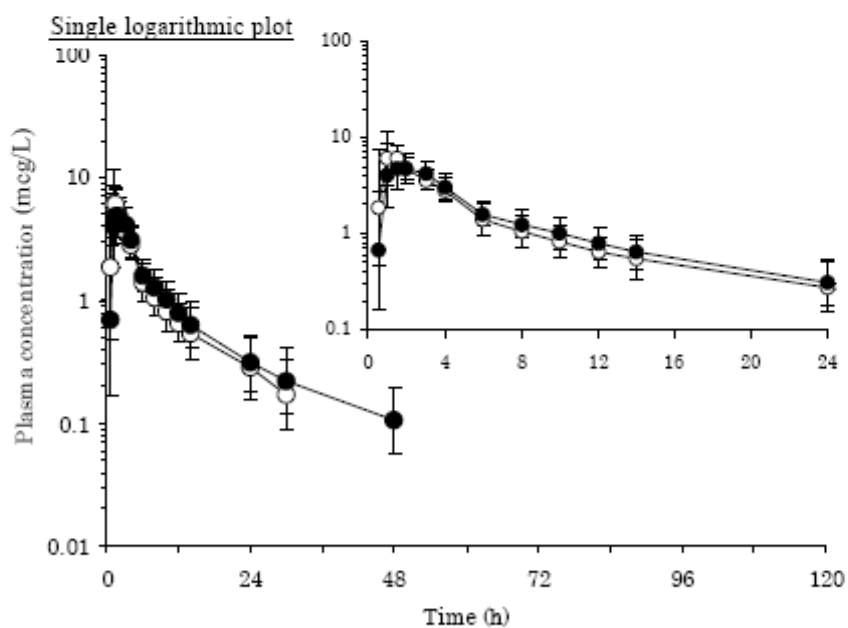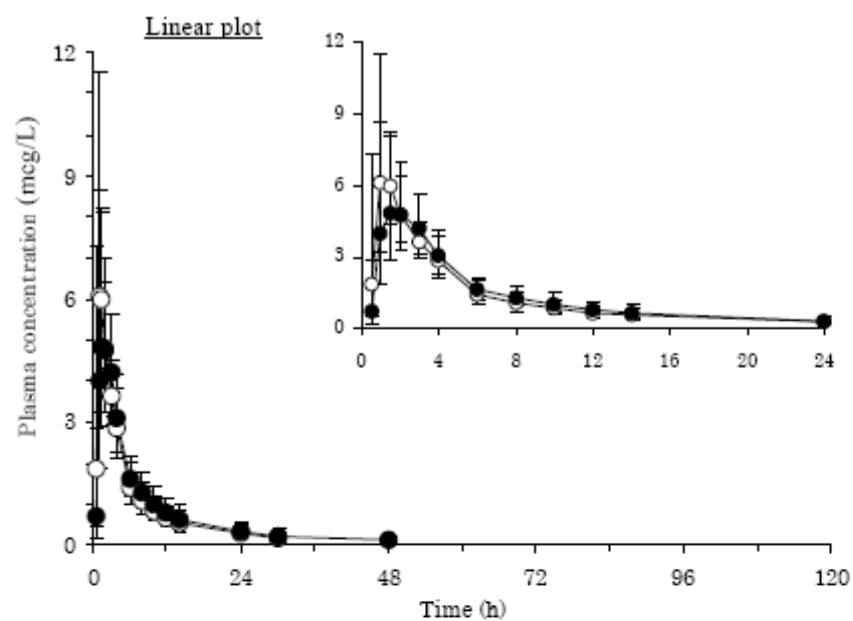
(Geometric mean, 68% range, n=10, however n=7 at 48hr post-dose under fed condition)
O: Administration under the fasting condition, ●: Administration under the fed condition

Figure 11.4-1 Time-course of plasma concentrations of roflumilast after single oral administration of APTA-2217

Figure 11.4-2 Time-course of plasma concentrations of roflumilast N-oxide after single oral administration of APTA-2217

Summary statistics of pharmacokinetic parameters are shown the table below:

	Roflumilast		Roflumilast N-oxide	
Condition	Fasting	Fed	Fasting	Fed
AUC(0-inf.) [mcg·h/L]	37.9 (26.6, 54.0)	39.3 (27.7, 55.9)	474.3 (345.5,651.1)	448.2 (332.4,604.4)
	log(1.038)[1] log(1.008) – log(1.069)[2]		log(0.945)[1] log(0.925) – log(0.965)[2]	
Cmax [mcg/L]	7.651 (4.964, 11.793)	6.643 (5.003,8.820)	12.558 (10.367,15.212)	10.496 (8.590, 12.824)
	log(0.868)[1] log(0.726) – log(1.038)[2]		log(0.836)[1] log(0.815) – log(0.857)[2]	
Tmax [h]	1.00 (0.50, 4.00)	1.75 (1.00, 3.00)	4.00 (4.00, 10.00)	6.00 (4.00, 10.00)
t1/2 [h]	11.87 (7.22,19.52)	11.44 (7.96, 16.43)	19.86 (15.48, 25.48)	20.18 (16.59, 24.56)
CLt or CLmet [L/h]	13.20 (9.26, 18.80)	12.70 (8.94, 18.05)	1.10 (0.80, 1.50)	1.16 (0.86, 1.57)
Vd/F [L]	225.95 (172.46, 296.03)	209.65 (173.13, 253.88)	31.40 (26.53, 37.16)	33.78 (27.90, 40.90)

Geometric mean (68 % range); Median (min, max) for T_{max}.
1) Difference of logarithmic transformed mean value. 2) 90% confidence intervals.

Conclusions: After single oral administration of APTA-2217 at 500 mcg to healthy adult male subjects under fasting or fed condition, the Cmax decreased and the Tmax was slightly delayed in the fed condition for roflumilast and roflumilast N-oxide; no change was noted in the AUC(0-inf). It was concluded that food has no relevant effect on the systemic absorption of APTA-2217.

FHP006

Study Title: Randomized study to investigate the absolute bioavailability of roflumilast in healthy volunteers

Objectives: Assessment of absolute bioavailability of roflumilast.

Study Design: Open, randomized, 2-period, crossover study. Single dose of roflumilast 500 μg (2 tablets of 250 μg), p.o., single short-term infusion over 15 minutes of roflumilast 150 μg, i.v.

Study Population: Healthy subjects, N = 13 (M), aged 25 to 44 years.

Data Analysis: PK assessment (roflumilast, roflumilast N-oxide) was conducted using a noncompartmental approach.

Pharmacokinetic Results: Summary statistics of pharmacokinetic parameters are shown the table below:

Table: Roflumilast and roflumilast N-oxide PK characteristics (geometric mean, 68% range) after a single dose of roflumilast 500 μg, p.o. or roflumilast 150 μg, i.v.

	Rof 150 μg i.v.	Rof 500 μg p.o.
Roflumilast		
AUC_{inf} [μg×h/L]	14.0 (9.71, 20.3)	37.2 (25.2, 54.9)
C_{max} [μg/L]	6.36 (5.03, 8.04)	8.32 (5.79, 11.9)
$t_{½}$ [h]	14.7 (10.0, 21.7)	15.7 (12.3, 19.9)
t_{max} [h] *	0.22 ± 0.01	0.98 ± 0.12
Cl [L/h/kg]	0.137 (0.097, 0.194)	---
$V_d$area [L/kg]	2.92 (2.38, 3.58)	---
Roflumilast -N-oxide		
AUC_{inf} [μg×h/L]	99.2 (80.0, 122)	400 (291, 550)
C_{max} [μg/L]	2.87 (2.30, 3.58)	13.1 (9.88, 17.3)
$t_{½}$ [h]	22.7 (14.8, 34.9)	20.6 (15.4, 27.5)
t_{max} [h] *	6.92 ± 0.95	8.83 ± 3.96

* t_{max}: mean±SE

Table 11.4.1.1

Pharmacokinetic characteristics of Roflumilast (B9302-107) and B9502-044 following single oral administration of 0.5 mg Roflumilast (B9302-107)

	B9302-107	B9502-044
$AUC_{(0-\infty)}$ [μg*h/l]	37.22 (25.20 - 54.98)	400.47 [1] (291.09 - 550.97)
C_{max} [μg/l]	8.328 (5.793 - 11.973)	13.107 (9.883 - 17.382)
$t_{½}$ [h]	15.70 (12.38 - 19.90)	20.60 [2] (15.40 - 27.56)
t_{max} [h]	0.98 ± 0.12	8.83 ± 3.96

[1] N = 6; [2] N = 8

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Table 11.4.1.2

Pharmacokinetic characteristics of Roflumilast (B9302-107) and B9502-044 following single intravenous administration of 0.15 mg Roflumilast (B9302-107)

	B9302-107	B9502-044
AUC $_{(0-\infty)}$ [μg*h/l]	14.06 (9.71 - 20.36)	99.22 [1] (80.07 - 122.96)
C$_{max}$ [μg/l]	6.364 (5.035 - 8.044)	2.875 (2.307 - 3.582)
t$_{½}$ [h]	14.79 (10.05 - 21.76)	22.73 [2] (14.81 - 34.90)
t$_{max}$ [h]	0.22 $\pm$ 0.01	6.92 $\pm$ 0.95
Cl [l/h/kg]	0.137 (0.097 - 0.194)	n.a.
Vd$_{area}$ [l/kg]	2.924 (2.389 - 3.580)	n.a.

[1] N = 8; [2] N = 11 n.a.: not ascertained

Conclusions: Absolute bioavailability of roflumilast was estimated to be 79%. After oral administration of roflumilast, the systemic exposure to roflumilast N-oxide was about 12-fold higher when compared with the systemic exposure to roflumilast, whereas after intravenous administration, the systemic exposure to roflumilast N-oxide was about 7-fold higher.

FHP001

Study Title: Safety and tolerability of the new phosphodiesterase inhibitor 89302-107 administered to healthy male volunteers as ascending single oral doses

Objectives: To assess safety and tolerability

Study Design single-blind, placebo-controlled, 4-period change-over with increasing single doses and interspersed placebo administration. Drug was given as a single oral dose at 0, 1, 2.5 and 5 mg.

Study Population: 4 healthy male volunteers, aged 21 - 30 (median = 28) years

Data Analysis: Serial blood sampling for PK assessment (roflumilast, roflumilast N-oxide). Measurements of vital signs, ECG, clinical laboratory and monitoring of AE.

Pharmacokinetic Results: PK was only measured in one subject given 2.5 mg.

Subject	Dose (mg)	t_{max} (h)	C_{max} (μg/l)	AUC (μg/l*h)	$t_{\frac{1}{2}}$ (h)
1	2.5	0.5	11.04	76.7	14.3

Conclusions: Single oral doses of 89302-107 were well tolerated up to and including 1.0 mg in healthy male volunteers. The 2.5 mg dose was safe, but drug related adverse events such as nausea, dizziness or headache were observed in all three volunteers. The early onset of nausea and dizziness corresponds to a rapid absorption of 89302-107 after oral intake of a tablet in this study. In conclusion, 1 mg 89302-107 can be recommended as a suitable single oral dose per volunteer in future clinical studies.

FHP002

Study Title: Safety and tolerability of the new phosphodieste- INN rase inhibitor (89302-107) administered to healthy male volunteers as ascending single oral doses

Objectives: Safety and tolerability after single-dose oral administration of ascending' dose levels of 89302-107; preliminary data on pharmacokinetics

Study Design Single-blind, placebo-controlled, ascending dose study with randomly interspersed placebo phases. Dose levels planned (with randomly interspersed placebo phases):
a) Dose group I (n=4 subjects): 1 mg, 2.5 mg and 5 mg 89302-107
b) Dose group II (n=4 sUbjects): 10 mg, 15 mg and 20 mg 89302-107
The study was terminated after the third period in dose group I, actually. The dose levels 1 mg and 2.5 mg 89302-107 were administered to 4 subjects each, the dose level 5 mg 1 89302-107 was administered to only 1 subject..

Study Population: 4 healthy male volunteers, aged 21 - 30 (median = 28) years

Data Analysis: Safety and tolerability was evaluated by repeated measurements of blood pressure, heart rate, ECG, clinical laboratory investigations and recording of adverse events. The pharmacokinetic profiles of 89302-107 were determined in 1 subject after dosing of 5 mg and in 2 subjects after dosing of 2.5 mg 89302-107.

Results: After administration of 1.0 mg 89302-107 one subject complained about diarrhea and one about headache, while two subjects reported no adverse events. Adverse events were more

frequent after administration of 2.5 mg 89302-107 and 5.0 mg 89302-107, so that it seemed that the limit of tolerability had been reached with 1.0 mg 89302-107. PK was only measured in two subjects given 2.5 mg and one in 5 mg.

2.5 mg:

Pharmacokinetic characteristics		
C_{max} (μg/l)	23.08	25.30
t_{max} (h)	3.00	2.00
$AUC_{(0 - 24h)}$ (μg/l.h)	148.96	193.19

5 mg:

Pharmacokinetic characteristics	
C_{max} (μg/l)	35.32
t_{max} (h)	4.00
$AUC_{(0 - 24h)}$ (μg/l.h)	421.45

Conclusions: 89302-107 when administered as ascending single oral doses to healthy male subjects was well tolerated at a dose level of 1 mg. Definitive conclusion on the PK cannot be made as small sample size. However, the exposure is dose related.

FHP005

Study Title: Safety, tolerability and orientative pharmacokinetics of roflumilast after increasing i.v. single doses

Objectives: Primary: safety and systemic and local tolerability of the roflumilast infusion solution Secondary: orientative pharmacokinetics for selection of the roflumilast dosage suitable for a planned bioavailability study

Study Design Single blind, 5-period ascending dose design with randomly interspersed placebo. Vials containing 8 mg/10 ml roflumilast (Batch No.: 037497) for dilution with the lipid emulsion Lipofundin® MGT 10% (Braun Melsungen, Satch No.: 039497)

Placebo (Lipofundin® MGT 10% emulsion) infusion over 15 minutes
0.01 mg roflumilast diluted in Lipofundin® MGT 10% emulsion, infused over 15 minutes
0.03 mg roflumilast diluted in Lipofundin® MGT 10% emulsion, infused over 15 minutes
0.07 mg roflumilast diluted in Lipofundin® MGT 10% emulsion, infused over 15 minutes
0.15 mg roflumilast diluted in Lipofundin® MGT 10% emulsion, infused over 15 minutes

Study Population: 4 healthy male volunteers, aged 21 - 30 (median = 28) years

Data Analysis: Safety and tolerability were assessed by repeated measurements of 12-lead EGG, blood pressure and heart rate as well as by safety measurements at pre and final check and continuous recording of adverse events.
Repeated blood samplings were taken up to 8 h after each dosing for pharmacokinetic purposes. Safety and tolerability were evaluated descriptively.
The following pharmacokinetic characteristics were determined: AUC, Cmax, tmax, t1l2.

Results: Local tolerability was very good. The mean and median values of blood pressure (SP) and heart rate (HR) were comparable under placebo and roflumilast treatment up to the dose level of 0.07 mg. The diastolic blood pressure tended to decline from 7.5 min until 30 min after start of infusion of 0.15 mg roflumilast, however, means and medians of diastolic blood pressure were still within the normal range. Subject No. 03 showed a remarkable decrease in diastolic blood pressure at 7.5 min after start of infusion with 0.15 mg roflumilast (BP: 117/37 mmHg, HR: 59 b/min; predose value: SP: 115/78 mmHg, HR 48 b/min), but at 15 min after start of infusion (=tmax), the value had
normalized (SP: 104/61; HR: 49 b/min).

Geom. means with 68%-range

	0.01 mg	0.03 mg	0.07 mg	0.15 mg
$AUC_{(0-\infty)}$ [µg/l*h]	n.a.	n.a.	n.a.	15.00 [2
C_{max} [µg/l]	0.426 [3	1.144	3.123	5.178
	(0.346-0.526)	(0.903-1.450)	(2.148-4.541)	(4.069-6.590)
$t_{1/2}$ [h]	n.a.	n.a.	11.4 [1	13.7 [2
Cl/kg [l/h]	n.a.	n.a.	n.a.	0.1578 [2
Vd_{area}/kg [l]	n.a.	n.a.	n.a.	3.112 [2

n.a. = not ascertainable   [1 N=1   [2 N=2   [3 N=3

Conclusions: Safety and tolerability was good. An influence of 0.15 mg roflumilast Lv. on diastolic blood pressure cannot be excluded and should be of interest in the subsequent bioavailability study. Cmax values after intravenous administration of 0.01,0.03, 0.07 and 0.15 mg roflumilast increased in proportion to the dose. Derived from the pharmacokinetic data of this study, the required intravenous dose for the planned bioavailability study is 0.15 mg.

FHP023

Study Title: Investigation of the safety, tolerability and pharmacokinetics of gradually increasing repeated oral doses (500 ug/d, 750 ug/d, 1000 ug/d) of roflumilast in healthy male and female subjects. A double blind randomized placebo controlled study (Study Code: BY217/FHP023)

Objectives: Primary: Safety and tolerability

Secondary: Pharmacokinetics of roflumilast (B9302-107) and metabolite B9502-044

Study Design The study was conducted according to a double-blind, parallel-group design with 2:1 randomization of gradually increasing roflumilast doses (N=12) and placebo (N=6):
Group I: roflumilast treatment for 21 consecutive days (N=12):
days 1-7: 500 ug/d roflumilast (2 tablets of 250 ug each per day)
days 8-14: 750 ug/d roflumilast (3 tablets of 250 ug each per day)
days 15-21: 1000 ug/d roflumilast (4 tablets of 250 ug each per day)
Group II: placebo treatment for 21 consecutive days (N=6):
days 1-7: 2 placebo tablets per day
days 8-14: 3 placebo tablets per day
days 15-21: 4 placebo tablets per day
12-lead resting ECG, blood pressure and heart rate were measured predose and 1 h, 2 h, 4 h, 8 hand 12 h post dose on days 1,7,8,14,15 and 21. Clinical laboratory was determined predose on days 1, 8, 15, and in the morning of day 22 (Additional safety measurements were performed at pre and final check.). Adverse events were monitored continuously
during the study. Repeated blood samples for pharmacokinetic purposes were taken on
days 7 and 14 (up to 24 h each) as well as on day 21 (up to 54 h).

Study Population: total: 18 (17 male, 1 female) roflumilast at increasing doses: 12 (11 male, 1 female) placebo: 6 (all male)

Data Analysis: Safety and tolerability: 12-lead resting ECG, blood pressure and heart rate were measured predose and 1 h, 2 h, 4 h, 8 hand 12 h post dose on days 1, 7, 8, 14, 15 and 21. Clinical laboratory (clinical chemistry, hematology, urinalysis) was determined predose on days 1, 8, 15, and in the morning of day 22. Adverse events were monitored continuously during the study. Pharmacokinetics: AUC and Cmax in steady state as respective extent and rate characteristics of roflumilast (B9302-107) and metabolite B9502044 based on plasma levels determined at the following time points: predose, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 hand 24 h after administration of 500 ug, 750 ug and 1000 ug roflumilast on study days 7, 14 and 21. Terminal half-life t1/2, was calculated additionally for the highest roflumilast dose level of 1000 ug in steady state. Therefore, additional blood samples were taken at 30 h, 48 h and 54 h following administration of 1000 μg roflumilast on day 21.

Roflumilast and metabolite 89502-044 plasma concentrations were determined by a validated assay using reversed-phase HPLG with fluorescence detection after post-column photochemical derivatization. Sample clean-up was performed using liquid/liquid extraction. The lower limit of quantitation (LLOQ) was 0.085 ug/1 for roflumilast and 0.5 ug/1 for metabolite 89502-044.

Results: With regard to safety, it can be stated that repeated doses of 1000 ug/d roflumilast were safe and well-tolerated when the daily dose was gradually increased in steps of 250 ug after one week of treatment each. There was no increase in the frequency and severity of adverse events when the roflumilast dosage was increased step by step from 500 ug/d to 1000 ug/d.

Table: Pharmacokinetic characteristics (geometric means / 68%-range) of roflumilast (89302-107) and the metabolite 89502-044 following a gradually increasing repeated oral dose of 500 ug/d (Days 1-7), 750 ug/d (Days 8-14) and 1000 ug/d (Days 15-21) roflumilast to healthy subjects (N=12)

Study day	PK characteristics	Roflumilast (B9302-107)	Metabolite B9502-044
Day 7	AUC [µgxh/l]	32.61 (23.96, 44.37)	347.17 (284.71, 423.33)
	C_{max} [µg/l]	4.740 (3.714, 6.050)	20.681 (17.234, 24.818)
	$t_{1/2}$ [h]	14.33 (9.00, 22.82)	not ascertainable
	t_{max} [h]	2.25 ± 0.56	4.08 ± 0.40
Day 14	AUC [µgxh/l]	50.82 (36.90, 70.00)	587.34 (462.32, 746.17)
	C_{max} [µg/l]	8.153 (6.042, 11.002)	33.720 (27.281, 41.677)
	$t_{1/2}$ [h]	13.70 (8.67, 21.67)	not ascertainable
	t_{max} [h]	1.71 ± 0.28	5.33 ± 0.43
Day 21	AUC [µgxh/l]	65.92 (49.49, 87.81)	799.93 (638.52, 1002.15)
	C_{max} [µg/l]	11.135 (8.289, 14.958)	50.618 (43.766, 58.541)
	$t_{1/2}$ [h]	14.66 (10.39, 20.67)	19.64 (15.08, 25.59)
	t_{max} [h]	1.60 ± 0.39	5.17 ± 0.30

Conclusions: Safety and tolerability: Repeated doses of 500 ug/d, 750 ug/d, and 1000 ug/d roflumilast were safe and well-tolerated when the dosage was gradually increased.
Pharmacokinetics: With respect to AUC and Cmax' a dose-proportional increase was observed with gradual increase of the dose from 500 ug/d to 1000 ug/d. The terminal half-life was not influenced by increasing the dose. After administration of the last dose, the terminal half-life was 14.7 h and 19.6 h for roflumilast and metabolite 89502-044, respectively.

FHP039

Study Title: Pharmacokinetics of roflumilast and roflumilast- N-oxide after single and repeated oral administration of 250 µg or 500 µg roflumilast - an open, randomized, two-period crossover study.

Objectives: The main aim of the present study was to investigate, in healthy volunteers, the intra-individual dose proportionality of single and repeated oral administration of 250 µg and 500 µg roflumilast as demonstrated by pharmacokinetics of roflumilast and its metabolites roflumilast-N-oxide, ADCP and ADCP N-oxide. Further, the study also provided information on the safety and tolerability of this roflumilast treatment.

Study Design: The trial was conducted as an open, randomized, two-period crossover monocenter study. It consisted of a screening examination (within 4 weeks before the first administration of study medication), two treatment periods of 12 days each, separated by a washout period of 10-14 days. Dose: 250 µg (Treatment A) and 500 µg (Treatment B). Drug

was administered orally with 240 ml water, once daily in the morning. Each of the two treatment periods lasts 12 days. Within each treatment period, one tablet of roflumilast (250 µg/day in Treatment A and 500 µg/day in Treatment B) was administered as a single dose on Study Day 1 and as repeated dose from Study Day 5 to Study Day 12.

For pharmacokinetics blood samples were drawn at the following time points following single or repeated oral doses of 250 and 500 µg of roflumilast:

• Study Day 1: at pre-dose, and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 30h, 48h, 72h, 96h after morning administration of study medication;

• Study Day 12: at pre-dose, and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 30h, 48h, 72h after morning administration of study medication.

Study Population: Nineteen healthy subjects (14 men, 5 women). Healthy subjects, Caucasian, aged 18-45 years.

Data Analysis: • Pharmacokinetics: Primary variables were the AUC and $t1/2$ of roflumilast (B9302-107) and roflumilast-N-oxide (B9502-044) measured in plasma samples after single and repeated oral administration of 250 µg or 500 µg roflumilast. Secondary variables were the Cmax and tmax for roflumilast and roflumilast N-oxide.

• Safety and tolerability: Physical examination including vital signs (blood pressure, pulse rate) as well as a 12-lead-ECG, and clinical laboratory investigations (clinical chemistry, hematology, urinalysis) were used as safety variables. In addition, adverse events were monitored during the entire study.

Results: Dose proportionality was found for roflumilast and roflumilast N-oxide, after the single dose (Study Day 1) and in steady state (Study Day 12), when referenced to the 250 µg dose.

Safety results: During treatment, a total of 79 AEs were reported by 18 subjects. Most AEs reported by the subjects were mild or moderate in intensity. Furthermore, 70% of the AEs reported during treatment with 250 µg roflumilast and 51% of those reported during treatment with 500 µg roflumilast were considered by the investigator as "unrelated" or "unlikely related" to the study drug. None of the symptoms experienced by the subjects were definitely related to the intake of roflumilast. The most frequently reported AE was headache which occurred in 47% of the subjects.
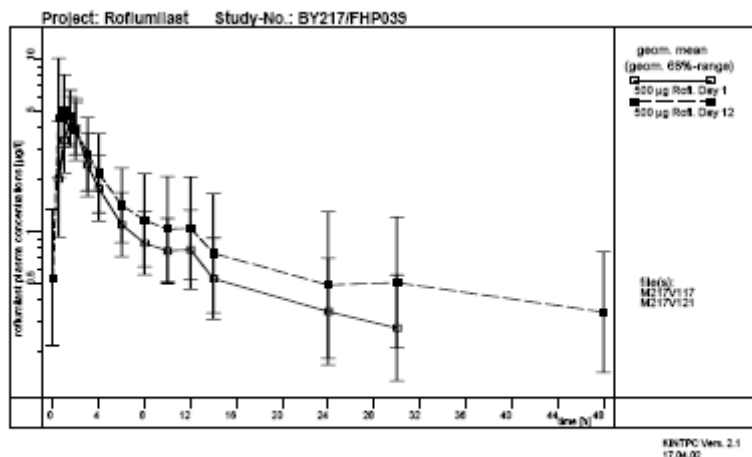
Figure 3: Individual roflumilast plasma concentrations in healthy male and female subjects following one single oral dose or multiple once-daily oral doses of 500 µg roflumilast on Study Days 1 or 12, semilog. scale

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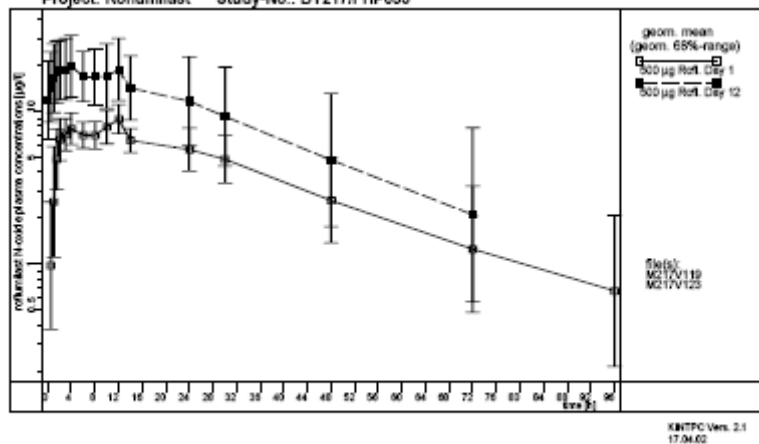
Figure 17: Individual roflumilast N-oxide plasma concentrations in healthy male and female subjects following one single oral dose or multiple once-daily oral doses of 500 µg roflumilast on Study Days 1 or 12, semilog. scale

Table 2: Roflumilast: Summary of pharmacokinetic characteristics in healthy male and female subjects following single and multiple oral doses of 250 µg and 500 µg roflumilast [geom. mean, 68% range; tmax: median (min, max)]

Pharmacokinetic Characteristic	250 µg roflumilast		500 µg roflumilast	
	Study Day 1	Study Day 12	Study Day 1	Study Day 12
AUC [µg/l x h]	18.1 [*]	17.0 [**]	35.0 [*]	33.7 [**]
(68% range)	(11.1, 29.7)	(10.5, 27.4)	(20.5, 59.8)	(19.3, 58.7)
C_{max} [µg/l]	2.92	3.06	5.27	6.01
(68% range)	(2.00, 4.25)	(2.04, 4.57)	(4.19, 6.63)	(3.75, 9.64)
t_{max} [h]	1.00	1.00	1.25	1.00
(min, max)	(0.50, 2.00)	(0.50, 1.50)	(0.50, 2.00)	(0.50, 2.00)
$t_{1/2}$ [h]	13.56	15.99	14.47	18.01
(68% range)	(7.26, 25.31)	(8.90, 28.74)	(7.86, 26.63)	(10.75, 30.19)

(*) following single administration (Study Day 1), AUC was calculated from 0-inf.
(**) in steady state (Study Day 12), AUC was calculated from 0-24 h

Table 5: Roflumilast N-oxide: Summary of pharmacokinetic characteristics in healthy male and female subjects following single and multiple oral doses of 250 µg and 500 µg roflumilast [geom. mean, 68% range; tmax: median (min, max)]

Pharmacokinetic Characteristic	250 µg roflumilast		500 µg roflumilast	
	Study Day 1	Study Day 12	Study Day 1	Study Day 12
$AUC_{(0-\infty)}$ [µg/l x h]	178.6	179.8	351.3	375.4
(68% range)	(115.8, 275.2)	(117.4, 275.2)	(235.5, 524.0)	(231.5, 608.7)
C_{max} [µg/l]	4.50	10.45	9.39	21.66
(68% range)	(3.50, 5.79)	(6.73, 16.23)	(7.48, 11.78)	(13.86, 33.85)
t_{max} [h]	12.00	8.00	11.00	4.00
(min, max)	(2.00, 12.00)	(2.00, 12.00)	(2.00, 12.00)	(1.00, 12.00)
$t_{1/2}$ [h]	22.13	23.13	23.16	21.16
(68% range)	(14.58, 33.58)	(15.87, 33.71)	(14.24, 37.66)	(14.08, 31.81)

Source of data: Section 14.2.1.1, Tables 19 and 27 (250 µg dose for Study Day 1 and Study Day 12, respectively), Tables 21 and 29 (500 µg dose for Study Day 1 and Study Day 12, respectively)

Conclusions: In the present study, a dose proportionality of roflumilast and roflumilast N-oxide was demonstrated after oral administration of a single dose and repeated once-daily doses of 250 µg and 500 µg roflumilast.

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In addition, laboratory values (including blood chemistry, hematology, urinalysis) and measurements of blood pressure, pulse rate, and ECG parameters did not reveal any clinically relevant alterations after administration of the study medication. Treatment with 250 μg or 500 μg once-daily doses of roflumilast was well tolerated and safe.

FHP040

Study Title: Dose proportionality of roflumilast after single oral administration of 125 *ug,* 250 *ug* or 500 *ug* roflumilast - an open, randomized, three-period change-over study.

Objectives: Primary: Dose proportionality of a single oral administration of 125 ug, 250 ug or 500 ug roflumilast as demonstrated by pharmacokinetics ofroflumilast and its major metabolite roflumilast-N-oxide
Secondary: Safety and tolerability

Study Design: The study was conducted according to an open, randomized, three-period cross-over design. It was planned to include 12 healthy subjects of either sex between 18 and 45 years of age. All subjects received three tablets: single doses of orally administrated 125 ug, 250 ug and 500 ug roflumilast in the morning of Day 1 of each period in a randomized order. So in total, each subject took 125 ug + 250 ug + 500 ug = 875 ug roflumilast in the course of the study. Five days per period, wash-out phase of at least 10 days between the treatment periods.

Study Population: Twelve subjects were included in the study. All subjects received all treatments according to protocol. Healthy subjects of either sex, between 18 and 45 years of age (both inclusive), were included in the study.

Data Analysis: ANOVA after logarithmic transformation; point estimates and 90% confidence intervals for the respective Test/Reference ratios.

Results:
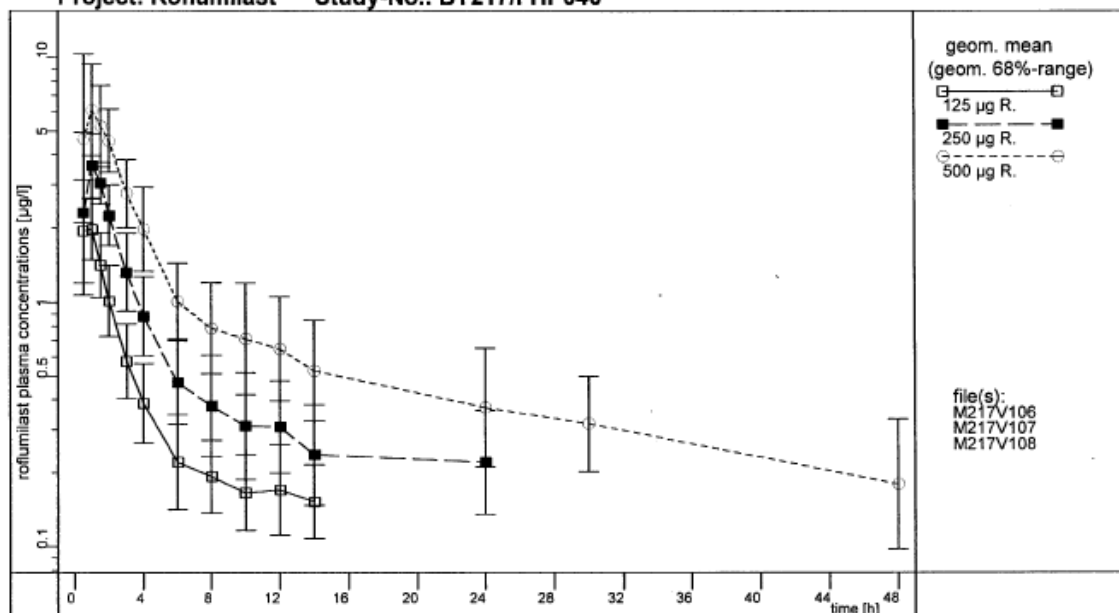
Figure 2: Mean roflumilast plasma concentrations in healthy male and female subjects following single oral doses of 125 µg, 250 µg and 500 µg roflumilast, semilog. scale

KINTPC Vers. 2.1
03.06.02

Table 11.4.1-1: Summary of pharmacokinetic characteristics of roflumilast in 12 healthy male and female subjects following single oral doses of 125 µg, 250 µg and 500 µg roflumilast [geom. mean, 68% range; t_{max}: median (min/max)].

Kinetic Characteristic Roflumilast	Dose of Roflumilast		
	125 µg	250 µg	500 µg
$AUC_{(0-\infty)}$ [µg/lxh]	6.6* (4.4, 10.0)	18.1** (10.4, 31.4)	40.4 (27.0, 60.3)
C_{max} [µg/l]	2.27 (1.71, 3.02)	3.99 (3.04, 5.22)	7.34 (4.76, 11.31)
t_{max} [h]	0.75 (0.50, 1.00)	1.00 (0.50, 1.50)	1.00 (0.50, 2.00)
$t_{1/2}$ [h]	8.43 (3.13, 22.71)	16.44 (8.16, 33.09)	18.2 (14.43, 23.19)

*n = 9   **n = 10

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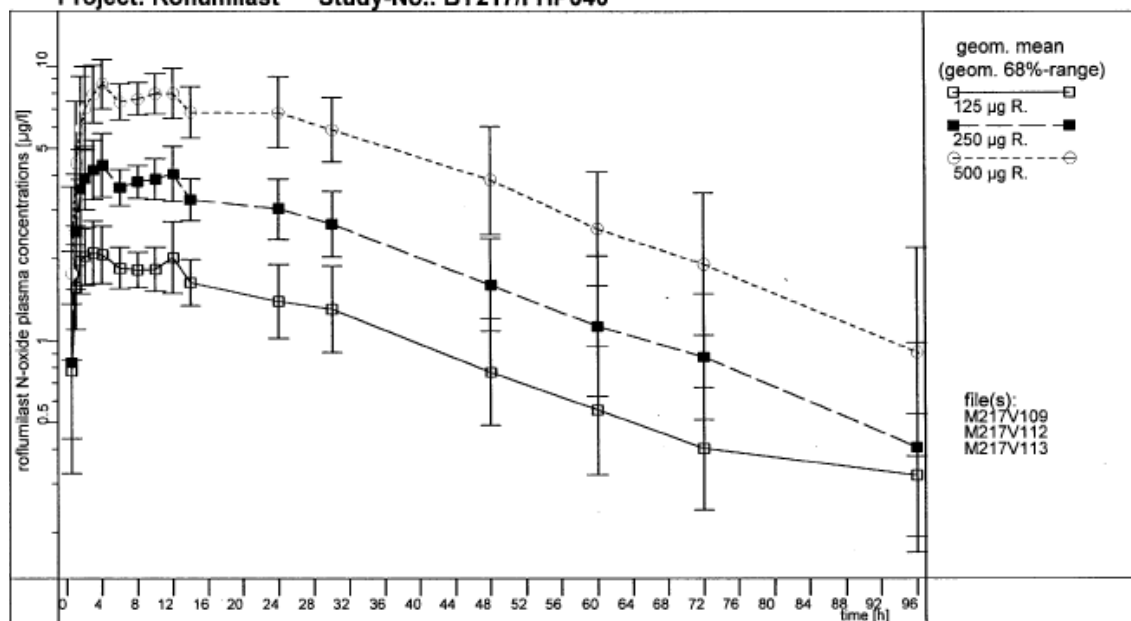
Figure 4: Mean roflumilast N-oxide plasma concentrations in healthy male and female subjects following single oral doses of 125 µg, 250 µg and 500 µg roflumilast, semilog. scale

KINTPC Vers. 2.1
03.06.02

Table 11.4.1-4: Summary of pharmacokinetic characteristics of roflumilast N-oxide in 12 healthy male and female subjects following single oral doses of 125 µg, 250 µg and 500 µg roflumilast [geom. mean, 68% range; t_{max}: median (min/max)].

Kinetic Characteristic	Dose of Roflumilast		
Roflumilast N-oxide	125 µg	250 µg	500 µg
$AUC_{(0-\infty)}$ [µg/lxh]	**96.6** (69.1, 135.2)	**187.4** (147.4, 238.1)	**435.9** (295.6, 642.8)
C_{max} [µg /l]	**2.37** (1.86, 3.01)	**4.81** (4.00, 5.78)	**9.40** (7.93, 11.13)
t_{max} [h]	**6.00** (1.50, 30.00)	**4.00** (3.00, 24.00)	**4.00** (1.50, 24.00)
$t_{1/2}$ [h]	**24.20** (18.75, 31.23)	**23.58** (15.48, 35.91)	**25.30** (16.16, 39.60)

Conclusions: There was no strict dose proportionality found for the 125 *ug* dose, most probably due to limitations by the lower limit of quantitation. For roflumilast N-oxide, dose proportionality was found for both Test doses when compared to the Reference dose of 250 *ug*

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roflumilast. The point estimates for the Testl/Reference ratios of the geom. means of AUC(0-inf) and Cmax for the 125 *ug* as well as for the 500 *ug* dose and their respective 90% confidence limits were inside the equivalence range.

A single dose of 125 *ug* or 250u*lg* or 500 *ug* roflumilast was well tolerated in 12 healthy subjects of either sex (4 male, 8 female) with regard to adverse events, vital signs, ECG parameters and laboratory values.

FHP036

Study Title: A study to investigate the distribution, metabolism, excretion (mass balance) and pharmacokinetics of [14C]-B9302-107 after oral and intravenous administration to six healthy male volunteers.

Objectives: The primary objectives were to investigate the absorption, absolute bioavailability and mass balance of [14C]-B9302-107 and to determine plasma concentrations and derived parameters of total radioactivity, parent compound (B9302-107) and its N-oxide metabolite (B9502-044) after oral and intravenous administration of [14C]-B9302-107.

The secondary objectives were to assess the safety and tolerability of B9302-1 07 after oral and intravenous administration and to identify the metabolic pathway of B9302-1 07 after oral and intravenous administration.

Study Design: Single-centre, single-dose, open-label, two-way crossover study in six healthy male volunteers with a washout period of at least 21 days between drug administrations.

Eligibility screening and follow-up consisting of clinical laboratory, full physical examination, ECG recording, drug screen, HBs Ag, anti-HCV and anti- HIV ~.

Observation period from -17h to 176h; stay in the clinical could be prolonged depending on excretion ofradioactivity in urine and faeces.

Blood sampling for pharmacokinetic parameters at t = 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose. Plasma was used for analysis of B9302-1 07, B9502-044 and radioactivity. Whole-blood was used for analysis of total radioactivity at t = 0, 0.5, 1, 1.5, 3, 6, 10, 24, 48, 72, 96, 120, 144, 168, 192 and 216 hours post-dose. Plasma for genotyping (CYP2D6, CYP2C19, NAT-2) prior to the first dose.

Urine sampling: pre-dose, and 0-4, 4-8, 8-12, and 12- 24 hours after drug administration and in 24 hours intervals until 216 hours post-dose.

Faeces sampling: pre-dose, thereafter in 24 hour intervals until 216 h post-dose.

Safety assessments: adverse events, vital signs; ECQ recordings telemetric monitoring.

Study Population: Six healthy male volunteers were enrolled. The age range from 18 to 45 years. Weight range from 50 to 100 kg. Single dose of 0.5 mg oral solution in PEG containing 1.89 MBq radioactivity and 0.3 mg intravenous solution containing 1.113 MBq radioactivity were given to the subjects.

Data Analysis: [14C}-radioactivity in plasma, whole blood, urine, faeces and medication by liquid scintillation counting; quick counts for [14C]-radioactivity in urine and faeces days 7 and 8; B9302-107 and its major metabolite B9502-044 by LC/MS/MS

Pharmacokinetic parameters: AUC, Cmax, tmax, t1l2, keh Ae urine, Ae faeces and Ae total (Ae for total radioactivity)

Safety parameters: vital sign, ECG recordings, clinical laboratory parameters, physical examination, adverse events. Descriptive analysis was performed.

Results: Pharmacokinetic characteristics of [^{14}C]-radioactivity, B9302-107 and B9502-044 in plasma and balance excretion of radioactivity (geometric mean) following a single oral dose of 0.5 mg and intravenous dose of 0.3 mg [^{14}C]-B9302-107 to healthy subjects (N=6).

PK Characteristics (unit)	[^{14}C]-radioactivity		B9302-107		B9502-044	
	po	iv	po	iv	po	iv
C_{max} (µgeq, or µg/l)	18.153	12.320	8.834	8.860	8.496	5.089
AUC/0-∞ (µgeq, or µg x h/l)	592.83	425.21	28.19	26.43	314.95	215.49
t_{max}(h)*	0.50	0.50	0.50	0.50	3.67	6.00
$t_{1/2}$(h)	46.79	44.81	13.41	10.96	17.77	17.55
A^e urine$^+$ (% of dose)	70.1	70.7	-	-	-	-
A^e faeces$^+$ (% of dose)	20.2	20.6	-	-	-	-
A^e total$^+$ (% of dose)	90.3	91.2	-	-	-	-
$F_{absorption}$$^{++}$	0.84	reference	-	-	-	-
$F_{bioavailability}$$^{++}$	-	-	0.64	reference	-	-

* Mean

Conclusions: Absorption following oral administration of 0.5 mg [14C]-B9302-107 was about 84 % based on dose normalized plasma AUC values and 99 % based on urinary excretion of total radioactivity.

The absolute bioavailability based on dose normalized plasma AUC values for unchanged B9302-107 was 64 %. Total recovery of radioactivity amounted to 90% of the dose, 70 % being excreted in urine and about 20 % in faeces after both routes of administration. Based on plasma

AUC, the sum of parent compound and metabolite B9502-044 accounted for 57 % and 58 % of total radioactivity AUC after iv and po administration, respectively, thus indicating the formation of other metabolites than B9502-044.

Oral and intravenous administration of [14C]-B9302-107 was safe and well tolerated.

Note: the human plasma and urine data were also analyzed for individual compound composition with the pooled sample and reported in 107/2002 and 212/2002.

FHP011

Study Title: A PET study to investigate the pharmacokinetics and distribution of [18F]B9302-1 07 into the lung, nose, stomach and brain after single oral administration of 0.5 mg to healthy volunteers

Objectives: To investigate the in vivo distribution in the lung, nose, stomach and brain of [18F]B9302-107 by positron emission tomography (PET) analysis and to investigate the pharmacokinetics of roflumilast (B9302-107) and its metabolites B9202-045 and B9502-044 after oral administration.

Study Design: Single dose, open-label study design. Repeated measurements of PET, pharmacokinetic and safety parameters were performed following oral administration. 0.5 mg of drug was given orally as oral suspension.

Study Population: Six healthy subjects were enrolled.

Data Analysis: PET variables: Descriptive evaluation of radioactivity in nose and stomach/intestines together with quantitative evaluation of B9302-107 concentration in nasal mucosa, brain, lung and heart

Pharmacokinetic variables: Plasma concentrations of parent compound roflumilast (B9302-107) and metabolites B9502-044 and B9202-045 AUC, C_{max}, $t1/2$, t_{max} of parent compound, and C_{max} and t_{max} only of metabolites

Safety: ECG, blood pressure, heart rate, adverse events, safety measurements at pre and final check.

Results:
The following table presents an overview of the pharmacokinetic characteristics for parent compound 89302-107, metabolite 89502-044 and metabolite 89202-045:

Characteristics	Parent compound B9302-107	Metabolite B9502-044	Metabolite B9202-045
$AUC_{(0-\infty)}$ [µg*h/l]	39.94 (29.38 - 54.30) [1]	not ascertained	Concentrations in all plasma samples below the LLOQ (0.04 µg/l)
C_{max} [µg/l]	5.361 (3.896 - 7.375)	10.626 (6.854 - 16.475)	
$t_{\frac{1}{2}}$ [h]	12.56 (9.20 - 17.13)	not ascertained	
t_{max} [h]	0.92 ± 0.08	5.83 ± 1.42	

Geometric means (68%-range); t_{max}: mean ± SEM
N=6; [1] N=5

The following table presents drug equivalent concentrations in plasma for parent compound 89302107 and metabolite 89502-044 in the 6 subjects in this study. The data is provided as geometric means:

Mean time of PET scan (minutes)	Mean plasma concentration (drug equivalent concentration in µg/l) (68%-range)
31	33.71 (25.39 - 44.77)
60	23.76 (17.99 - 31.39)
113	15.28 (11.46 - 20.36)
180	12.01 (8.97 - 16.07)
240	10.77 (9.21 - 12.59)
302	9.99 (8.29 - 12.04)
360	9.71 (7.62 - 12.37)
460	9.64 (7.75 - 12.00)

PET results

There was a rapid uptake of tracer from the intestines with significant extravascular localization in lung tissue, musculature (arms) and brain, although at different magnitudes with highest in lung tissue. No selective accumulation was found in the nasal mucosa.

Safety results

The study medication was well tolerated. 3 subjects reported a total of 3 AEs, all headaches, none of which were judged to be related to the study drug. No serious AEs occurred during the study.

Conclusions: From the PET studies it was shown that there was a rapid uptake of the study drug from the intestines. The study drug also localised in the extravascular space in lung, musculature and brain. No accumulation was found in the nasal mucosa.

Following single oral administration of 0.5 mg [18F]89302-107 as a suspension formulation to man, values of pharmacokinetic characteristics are comparable to the tablet formulation. The main conclusion of the work is that no specific accumulation could be observed in the nasal mucosa. The tissue-to-blood ratio is close to 1.0 (tissue-to-plasma ratio of 0.6), with no signs of increase from 2 hours after administration of drug.

There is a definite fraction of the drug that can be observed in brain, muscle and lung, and which is not related to the intravascular compartment. In the brain, the non-vascular concentration is about 8% of that of plasma, in muscle 15 % and in lung 45 %. The values for lung are here corrected for the density of the lung, with the assumption that the drug is not distributed in the air in the alveolus.

FHP004

Study Title: Safety and tolerability of the new phosphodiesterase inhibitor (B9302-1 07) administered to healthy male volunteers as ascending repeated oral doses over 7 days

Objectives: Primary: safety and tolerability
Secondary: preliminary data on pharmacokinetics and pharmacodynamics

Study Design: Placebo-controlled, single-blind, 3-period ascending dose investigation with a randomly interspersed placebo period and a subsequent 4th period in which all subjects received bid. treatment of roflumilast (The daily dose of roflumilast in the fourth period depended on the results of the preceding periods).
D0: 4 placebo tablets in the morning of days 1-7
D1: 2 placebo tablets and 2 tablets of 0.25 mg roflumilast in the moming of days 1-7 (daily dose: 0.5 mg/d roflumilast p.o.)
D2: 4 tablets of 0.25 mg roflumilast in the morning of days 1-7 (daily dose: 1.0 mg/d roflumilast p.o.)
D3: 2 tablets of 0.25 mg roflumilast in the morning and 2 tablets of 0.25 mg roflumilast in the evening of days 1-7 (daily dose: 1.0 mg/d roflumilast p.o.)

Safety and tolerabilitv: Repeated implementation of blood pressure, heart rate, ECG, clinical laboratory investigation, olfactometry, spermiogram, physical examination, and continuous recording of adverse events
Pharmacokinetics: Repeated blood sampling for determination of the pharmacokinetic profiles of roflumilast (B9302-107) and metabolite B9202-045 on day 7.
Analysis of parent compound B9302-107 was conducted by reversed-phase HPLC with fluorescence detection after post-column photochemical derivatization (LLOQ: 0.1 µ9/L). Analysis of metabolite B9202-045 was performed by GC-MS analysis (LLOQ: 0.04 µ9/L).
Pharmacodynamics: Repeated implementation of impedance cardiography and repeated blood sampling for the determination of TNFa in whole blood.

Study Population: Eleven healthy male subjects were enrolled (median age: 32 years; median body weight: 67.4 kg)

Data Analysis: Safety and tolerability: Descriptive
Pharmacokinetics: Calculated parameters were t_{112} (B9302-107 only), T_{max} (B9302-107 only), C_{max} and AUC using the KINT program (Version 2.1). Statistical ratio analysis of AUCs was calculated using the BioQPC program (Vers. 1.1.2). Results were given as point estimates with upper and lower 90% confidence limits.
Pharmacodynamics: Descriptive
Results:
Safety and tolerabilitv: Adverse events reported most frequently under treatment with 0.5 mg/d roflumilast were: diarrhea, increased frequency of defaecation, loose stool (5/11 subjects), headache (5/11 subjects), sleep disturbances (2/11 subjects), lumboischialgia, lumbalgia (2/11 subjects). Adverse events were more frequent and pronounced under treatment with 1.0 mg/d roflumilast. The adverse events reported most frequently were: nausea, anorexia (1.0 mg s.i.d.: 5/9 subjects: 0.5 mg b.i.d.: 8/8 subjects), headache (1.0 mg s.i.d.: 5/9 subjects: 0.5 mg b.i.d.: 6/8 subjects), gastrointestinal complaints such as diarrhea and abominal pain (1.0 mg s.i.d.: 5/9 subjects; 0.5 mg b.i.d.: 2/8 subjects), lumboischialgia, lumbalgia (1.0 mg s.i.d.: 4/9 subjects: 0.5 mg b.i.d.: 3/8 subjects).

Pharmacokinetics: Pharmacokinetic characteristics: geometric means (68% range); mean ±SEM for Tmax

Parent compond B9302-107 (roflumilast):

Dose	0.5 mg s.i.d. (N=10)	1.0 mg s.i.d. (N=8)	0.5 mg b.i.d. (N=4)
$t_{1/2}$ [h]	8.2 (6.7 - 10.0)	8.1 (6.1 - 10.6)	6.3 (4.1 - 9.7)
t_{max} [h]	2.60 ± 0.36	1.94 ± 0.33	1.13 ± 0.24
C_{max} [µg/l]	5.47 (3.98 - 7.53)	10.93 (7.36 - 16.22)	7.43 (4.74 - 11.64)
AUC [µg/l*h]	32.86 (20.63 - 52.37) [1]	61.46 (39.14 - 96.50) [1]	27.43 (18.96-39.70) [2]
Point estimate (90% conf. limits) 90% conf. limits	reference	0.98 (0.87 - 1.11)	0.99 (0.88 - 1.12)

Metabolite B9202-045:

Dose	0.5 mg s.i.d. (N=10)	1.0 mg s.i.d. (N=8)	0.5 mg b.i.d. (N=4)
$t_{1/2}$ [h]	n.a.	n.a.	n.a.
t_{max} [h]	n.a.	n.a.	n.a.
C_{max} [µg/l]	0.24 (0.14 - 0.43)	0.56 (0.35 - 0.91)	0.52 (0.29 - 0.96)
AUC [µg/l*h]	4.14 (2.22 - 7.70) [1]	10.15 (6.03 - 17.06) [1]	4.87 (2.69 - 8.81) [2]
Point estimate (90% conf. limits)	reference	1.14 (0.95 - 1.35)	1.13 (1.08 - 1.18)
Point estimate (90% conf. limits) of the AUC ratio metabolite/ parent compound	0.13 (0.10 - 0.16)	0.17 (0.14 - 0.20)	0.18 (0.13 - 0.24)

n.a.= not ascertained   [1] AUC(0-24h)   [2] AUC(0-12h)

Conclusions: Safety and tolerabilitv: The results suggested that the maximum tolerable dose for repeated dosing is reached with 0.5 mg/d roflumilast. Repeated administration of 0.5 mg/d roflumilast over 7 days was sufficiently tolerated in this study. Hence, it was concluded that 0.5 mg/d is the dosage of interest that would be investigated in further phase I studies and in phase II studies.

Pharmacokinetics: AUC and Cmax of parent compound 89302-107 and metabolite 89202-045 increased in proportion to the dose when 89302-107 was administered at dose levels of 0.5 mg s.i.d. and 1.0 mg s.i.d. Comparable values for AUC and Cmax of parent compound in the dosing interval were determined following administration of 0.5 mg 89302107 s.i.d. and 0.5 mg 89302-107 b.i.d. Comparison of AUCs of metabolite 89202-045 following administration of 0.5 mg 89302-107 s.Ld. and 0.5 mg 89302-107 b.i.d. showed an increase in AUC of 14% and 13%, respectively. No relevant differences in the AUC ratio of metabolite/parent compound at all three dose levels were calculated.

Pharmacodynamics: Results of impedance cardiography and of TNFa determination in whole blood did not lead to final conclusions.

FHP009

Study Title: Safety and tolerability of the new phosphodiesterase inhibitor B9302-1 07 administered to healthy male volunteers as repeated oral doses over 3 weeks - A double-blind randomized placebo-controlled crossover study

Objectives: Primary: safety and tolerability
Secondary: orientative data on pharmacokinetics and pharmacodynamics

Study Design: Placebo-controlled, randomized, double-blind, 2-period crossover investigation.

Safety and tolerability: Repeated implementation of blood pressure, heart rate, ECG, clinical laboratory investigation, olfactometry, and continuous recording of adverse events.

Pharmacokinetics: Blood samples were taken at 2 h after administration on study days 1, 7, 14 and 21, and the plasma was assayed for parent compound 89302-107 (roflumilast) and metabolite 89202-045. Analysis of the parent compound was conducted by reversed-phase HPLC with fluorescence detection after post-column photochemical derivatization. Sample clean-up was performed using liquid/liquid extraction. The lower limit of quantitation (LLOQ) was 0.1 ug/1.

Analysis of metabolite 89202-045 was performed by GC-MS analysis. LLOQ varied from 0.08 to 0.320 ug/1 depending on the volume of plasma available for extraction.

Study Population: fourteen healthy male subjects were enrolled (median age: 34 years)

Data Analysis: Safety and tolerability: Descriptive
Pharmacokinetics: PK variables were calculated using noncompartmental approach.
Pharmacodynamics: Descriptive

Results:
Safety and tolerability:
The adverse events reported most frequently under treatment with roflumilast were: back pain/lumboischialgia/lumbalgia (8 of 16 subjects), headache (3 of 16 subjects), loose stools/diarrhea (2 of 16 subjects) and common cold (2 of 16 SUbjects). The frequency of the above-mentioned symptoms under treatment with placebo was as follows: lumbalgia was reported by 2 of 16 Subjects, gastrointestinal complaints and headache were reported by 1 of 16 subjects each. Apart from these complaints some single events were reported under both treatments. In most of the cases with back pain/lumboschialgia/lumbalgia the symptoms subsided spontaneously under continued treatment with the study medication. Neurological examinations were performed by a nerve specialist and revealed normal findings. It should be noted that lumbalgia was also reported by two subjects under placebo treatment. Repeated implementation of safety measurements (ie. physical examination, blood pressure, heart rate, ECG, clinical laboratory, and olfactometry) did not reveal clinically relevant findings.

Pharmacokinetics: Geometric means with geometric 68% range of plasma concentrations [ug/l] of parent compound 89302-107 (roflumilast) and metabolite 89202-045 in the 2 h-samples on study days 1, 7, 14 and 21 following single or repeated oral administration of 0.5 mg 89302-107:

	Study day 1	Study day 7	Study day 14	Study day 21
parent compound B9302-107 (roflumilast):	(N=15)	(N=15)	(N=14)	(N=15)
geom. means	3.208	3.934	3.907	3.765
geom. 68% range	1.870-5.502	2.783-5.561	2.788-5.475	2.220-6.387
metabolite B9202-045:	(N=15)	(N=7)	(N=10)	(N=10)
geom. means	all values < D.L.	0.145	0.181	0.244
geom. 68% range		0.100-0.209	0.138-0.238	0.167-0.356

D.L.: detection limit

Pharmacodynamics: On day 1, the blood levels of TNFa determined at 2 h after roflumilast and placebo administration did not differ significantly. There is a relative high variability of individual TNFa concentrations. From day 1 to day 21, the median blood levels of TNFa (determined at 2 h after dosing) increased significantly under placebo treatment and decreased slightly under roflumilast treatment. On day 21, the median TNFa concentration in whole blood determined at 2 h after roflumilast administration (4833 pg/ml) was clearly lower than the median TNFa concentration obtained at 2 h after placebo administration (6265 pg/ml). The difference did not reach statistical significance at the 5%-level, two-sided, as the nonparametric 95%-confidence interval -calculated for the respective Test/Reference ratios after logarithmic transformation - ranged from 0.65 to 1.01 (parametric: 0.66 to 1.002); point estimate: 0.79 (parametric: 0.81).

Conclusions: Safety and tolerability: Adverse events seemed to be more frequent under treatment with roflumilast as compared to placebo. Nevertheless, repeated dosing of 0.5 mg/d roflumilast was safe and well tolerated. None of the adverse events was considered to be definitely related to the study medication. The etiology of some rather uncommon adverse events such as lumbalgia cannot be finally assessed yet, however, neurological
examinations revealed normal findings, so that a risk for the subjects could be excluded. This assessment is confirmed by the fact that most of these symptoms subsided spontaneously under continued treatment with the study medication.
Pharmacokinetics: Measurement of 89302-107 (roflumilast) and 89202-045 concentrations in the 2h plasma samples resulted in values which demonstrate compliance with the study protocol for all subjects throughout the study. All concentration values were in the expected range. Comparison of the mean concentrations of 89302-107 showed approximately constant values throughout the study. When mean concentrations of metabolite 89202-045 on study days 7, 14 and 21 were compared, a continuous increase in concentration throughout mthe duration of the study period (i.e. about 50% between days 7 and 21) could be observed. On study day 1, no metabolite 89202-045 was detectable in the 2h plasma samples of all subjects.
Pharmacodynamics: Determination of TNFa in whole blood did not lead to final conclusions in this study, however, 2 h after administration on day 21, the median blood level of TNFa was clearly lower under roflumilast treatment than under placebo treatment. The difference on day 21 is mainly related to an increase of median TNFa concentration under placebo treatment. Nevertheless, the results give hints that roflumilast may cause a suppression of TNFa, taking into account that under both treatments the median TNFa concentration may be on a hiaher level on dav 21 as compared to day 1 due to interfering variables.

CP-043

Study Title: Investigation of pharmacokinetics of roflumilast and roflumilast N-oxide after single morning or evening oral administration of 500 µg roflumilast in healthy subjects - an open, randomized, two-period crossover study

Objectives: The main aim of the present study was to compare, in healthy volunteers, the "morning" and "evening" pharmacokinetics of roflumilast and roflumilast N-oxide after a single

oral administration of 500 µg roflumilast in the morning or in the evening. Further, the study also provided information on the safety and tolerability of this roflumilast treatment.

Study Design: The study was conducted according to an open, randomized, two-period crossover design. Subjects received either Treatment A (500 µg roflumilast s.i.d. at Study Day 1 in the **morning)** or the Treatment B (500 µg roflumilast s.i.d. at Study Day 1 in the **evening**). The treatment periods were separated by a washout period of at least 10 days. Blood samplings for pharmacokinetic purposes were performed at pre-dose, and 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 30h, 48h, 72h and 96h after morning or evening oral administration.

Study Population: 16 subjects participated in the study.

Data Analysis: Pharmacokinetic characteristics were evaluated using the validated 'KINTPC' program (Version 2.0).

Results:

Table 5:   Summary of pharmacokinetic characteristics of roflumilast and roflumilast N-oxide in healthy male and female volunteers following a single oral dose of 500 µg roflumilast in the morning or evening [geometric mean, (68% range); t_{max}: median (min, max)].

Pharmacokinetic characteristics	Roflumilast (morning, Reference)	Roflumilast (evening, Test)	Roflumilast N-oxide (morning, Reference)	Roflumilast N-oxide (evening, Test)
AUC [µg/lxh]	40.6 (29.2, 56.4)	38.9 (29.0, 52.2)	377.9 (291.9, 489.3)	386.2 (294.3, 506.8)
C_{max} [µg/l]	3.79 (2.71, 5.32)	3.06 (2.15, 4.34)	6.61 (5.03, 8.67)	6.79 (5.16, 8.93)
t_{max} [h]	1.50 (0.50, 4.00)	2.00 (0.50, 8.00)	12.00 (6.00, 48.00)	12.00 (8.00, 48.00)
$t_{1/2}$ [h]	20.09 (14.28, 28.26)	20.03 (13.45, 29.85)	26.96 (19.49, 37.29)	28.09 (18.56, 42.51)

Table 6: Point estimates and 90%-confidence limits for the Test/Reference ratios of geometric means of $AUC_{(0-inf)}$ and C_{max} values of roflumilast and roflumilast N-oxide following a single oral administration of 500 μg roflumilast in the morning (Reference) or in the evening (Test).

Pharmacokinetic Characteristic	Roflumilast Point estimate	Roflumilast 90% confidence limit	Roflumilast N-oxide Point estimate	Roflumilast N-oxide 90% confidence limit
$AUC_{(0-inf)}$	0.96	0.90 – 1.03	1.02	0.97 – 1.07
C_{max}	0.81	0.66 – 0.98	1.03	0.96 – 1.10

Source of data: Section 14.2.1.3

Conclusions: For the parent compound roflumilast, the primary variable AUC(0-inf) representing the systemic exposure as well as the secondary variable t1/2 were not affected by morning or evening administration of roflumilast. However, the roflumilast mean maximum plasma concentration Cmax after roflumilast intake in the evening was lowered in comparison to Cmax after morning administration of roflumilast, whereas tmax was slightly increased, an effect that may relate to differences between stomach or intestinal content of the study volunteers. For roflumilast N-oxide, the pharmacokinetic characteristics of the primary and secondary variables were equivalent.

JP701

Study Title: A Clinical Pharmacological (Phase I) study of APTA-2217 in healthy male volunteers. Single oral dose.

Objectives: To evaluate the pharmacokinetics (PK) and safety of APTA-2217 after single oral dose administration of 125, 250, 500 or 1000 mcg to healthy adult male Japanese volunteers under fasting conditions.

Study Design:

	Period 1	Period 2	Period 3	Period 4
Group A (n=12) (+2 substitutes)	125 mcg: n=9 placebo: n=3		500 mcg: n=9 placebo: n=3	
Group B (n=12) (+2 substitutes)		250 mcg: n=9 placebo: n=3		1000 mcg: n=9 placebo: n=3
During each study period subjects were hospitalized from 2 days before administration of roflumilast up to Day 5 for 7 days (7 days and 6 nights).				

Study Population: fourteen healthy male subjects were enrolled (median age: 34 years)

Data Analysis: Criteria for evaluation:

Pharmacokinetic variables

(1) Plasma concentration [roflumilast and the major metabolite (roflumilast N-oxide)]

(2) Urine excretion [roflumilast and the major metabolite (roflumilast N-oxide)]

(3) Pharmacokinetic parameters [roflumilast and the major metabolite (roflumilast N-oxide)] Cmax, AUC, Tmax and t1/2 of roflumilast and the major metabolite (roflumilast N-oxide), and CLt, Vd/F, Rate of urine excretion and CLr as reference data, were calculated.

(4) Metabolic activity index   cortisol levels in plasma and urine, 6β-hydroxycortisol in urine

Safety variables

(1) Adverse events

(2) Adverse events suspected to be causally related to the investigational drug.

Statistical method:

(1) Pharmacokinetics

Plasma and urinary concentration of roflumilast and its active metabolite (roflumilast N-oxide) were measured after administration of each dose. The summary statistics of pharmacokinetic parameters (AUC(0-inf), tmax, Cmax, t1/2, CLt, Vd/F) was calculated and dose-proportionality of Cmax and AUC(0-inf.) was evaluated.

(2) Safety

The incidence of all adverse events and adverse events suspected to be causally related to the investigational drug was calculated for each dose.

Results:

The pharmacokinetic parameters of plasma concentrations of roflumilast and roflumilast N-oxide after oral administrations of single doses of 125, 250, 500 or 1000 mcg of APTA-2217 to healthy adult males under fasting conditions were evaluated.

Dose	125 mcg	250 mcg	500 mcg	1000 mcg	
Roflumilast					
AUC$_{(0\text{-inf.})}$ [mcg·h/L]	9.7 (6.1, 15.3)	20.0 (16.4, 24.4)	38.3 (26.0, 56.4)	80.8 (64.2, 101.8)	
C$_{max}$ [mcg/L]	2.059 (1.666, 2.545)	3.924 (3.164, 4.867)	7.242 (5.622, 9.330)	12.637 (10.416, 15.332)	
t$_{max}$ [h]	1.00 (0.50, 2.00)	1.00 (1.00, 1.50)	1.00 (0.50, 3.00)	1.00 (0.50, 3.00)	
t$_{1/2}$ [h]	9.33 (4.71, 18.49)	9.80 (7.83, 12.26)	14.58 (10.56, 20.13)	17.27 (10.66, 27.98)	
CLt [L/h]	12.94 (8.16, 20.52)	12.51 (10.26, 15.25)	13.06 (8.86, 19.24)	12.37 (9.82, 15.59)	
Vd/F [L]	174.23 (123.91, 244.99)	176.93 (146.14, 214.19)	274.65 (216.61, 348.24)	308.35 (209.34, 454.19)	
Geometric mean (68 % range); Median (min, max) for t$_{max}$.					

Dose	125 mcg	250 mcg	500 mcg	1000 mcg
Roflumilast N-oxide				
$AUC_{(0-inf.)}$ [mcg·h /L]	128.9 (90.1, 184.6)	222.7 (179.4, 276.3)	494.3 (353.0, 692.1)	925.6 (733.3, 1168.4)
C_{max} [mcg/L]	3.189 (2.787, 3.649)	5.760 (4.927, 6.734)	11.344 (9.663, 13.317)	23.188 (20.056, 26.810)
t_{max} [h]	4.00 (3.00, 4.00)	4.00 (4.00, 10.00)	4.00 (4.00, 10.00)	4.00 (4.00, 4.00)
$t_{1/2}$ [h]	22.65 (15.85, 32.36)	18.70 (15.03, 23.26)	23.03 (17.19, 30.85)	20.57 (16.68, 25.38)
CLmet [L/h]	1.01 (0.70, 1.44)	1.17 (0.94, 1.45)	1.05 (0.75, 1.47)	1.12 (0.89, 1.42)
Vd/F [L]	32.93 (26.63, 40.72)	31.49 (28.76, 34.49)	34.94 (28.24, 43.24)	33.34 (29.61, 37.54)

Geometric mean (68 % range); Median (min, max) for t_{max}.

The 95 % confidence interval of the regression coefficient for Cmax of both roflumilast and roflumilast N-oxide did not include 1. However, it was considered that dose-proportionality for Cmax of roflumilast and roflumilast N-oxide was almost obtained because both the point estimates of ratios of Cmax and the 95 % confidence interval were approximately 2 (1.83 [95 % CI: 1.72 ~ 1.95] for roflumilast, 1.94 [95 % CI: 1.89 ~ 2.00] for roflumilast N-oxide), when the dose was doubled.

For AUC(0-inf) of roflumilast and roflumilast N-oxide, the 95% confidence interval of the regression coefficient included 1, thus it was considered that there was dose-proportionality. t1/2 of roflumilast was prolonged with dose increases, and significant differenceswere found between doses in statistical analyses. A possible cause is as follows: the terminal elimination phase could not be evaluated in 125 mcg and 250 mcg,

and as a result, t1/2 of roflumilast of those doses was shortened. For t1/2 of roflumilast N-oxide, statistically significant differences between doses were noted, however, the respective geometric means were close, and it was considered that there were no marked differences between doses. For CLt of roflumilast and Clmet of roflumilast N-oxide, it was considered that there were no marked differences between doses. For Vd/F of roflumilast and roflumilast N-oxide, the result of the comparison among doses was similar to the result of t1/2.

Conclusions: The Cmax and AUC0-inf of roflumilast and roflumilast N-oxide after administration of single oral doses of 125 mcg up to 1000 mcg APTA-2217 to healthy adult male volunteers increased in proportion to the dose. The t1/2 and Vd/F of roflumilast were prolonged and increased with dose increases, and significant differences were found between doses in statistical analyses. The fact that the terminal elimination phase could not be evaluated in 125 mcg and 250 mcg was considered to be the cause for this. For t1/2 and Vd/F of roflumilast N-oxide, significant differences were noted, however, the respective geometric means were close, and it was considered that there were no marked differences between doses. Apparent total clearance (CLt and CLmet) and renal clearance of both roflumilast and roflumilast N-oxide were almost constant for all doses. Cumulative urinary excretion rates of roflumilast and roflumilast N-oxide were small and the dose-proportional increase was not observed. As CLm of cortisol was an indicator for the metabolic activities of CYP3A4 in each subject and the CLm was

partially correlated to the extra renal clearance of APTA-2217, the individual differences of the metabolic activity (CYP3A4) among the subjects were considered to be partially responsible for the inter-subject difference of the pharmacokinetics of APTA-2217.

FHP018

Study Title: Pharmacokinetics of roflumilast after single dose oral administration of 0.5 mg to healthy elderly subjects.

Objectives: Primary: pharmacokinetics of a single oral dose of 0.5 mg roflumilast (B9302-107) in healthy male or female subjects aged ~ 65 years
Secondary: safety and tolerability; pharmacokinetics of the metabolite B9502-044

Study Design: The study was conducted according to an open, single-dose, one-period design. Roflumilast was given as 0.5 mg oral dose (2 tablets or 0.25 mg each). Blood samples for pharmacokinetic purposes were taken predose, and at 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 30 h, 48 h, 54 h and at 72 h after oral administration.

Data Analysis: Pharmacokinetics:
Primary variable: AUC(0-inf) and Cmax as respective extent and rate characteristics of roflumilast. Secondary pharmacokinetic variables: t'h and tmax of roflumilast and pharmacokinetic characteristics of the metabolite 89502-044
Safety and tolerability:
Measurements of ECG, blood pressure and pulse rate, physical examination and clinical laboratory investigations (clinical chemistry, hematology, urinalysis) during the screening visit and the post study examination; additional reasurements of ECG, blood pressure and pulse rate at predose, and at 1 h and 2 h after dosing; adverse events

Results:
Pharmacokinetic characteristics (geometric means 68%-range) of roflumilast (B9302-107) and metabolite B9502-044 following a single oral dose of 0.5 mg roflumilast to elderly subjects (N=12)

Study BY217/FHP018	Roflumilast (B9302-107)	B9502-044
$AUC_{(0-\infty)}$ [μgxh/l]	53.23 (38.81, 73.01)	421.64 (351.96, 505.11)
C_{max} [μg/l]	4.681 (3.345, 6.551)	8.561 (7.239, 10.126)
$t_{½}$ [h]	22.53 (17.71, 28.67)	29.78 (21.93, 40.44)
t_{max} [h] [1]	2.17 ± 0.39	9.67 ± 1.47

[1] t_{max}: mean ± SEM

Following oral administration of 0.5 mg roflumilast to elderly subjects, the geometric mean of the maximum plasma concentrations Cmax of roflumilast was 4.681 ug/l (68%-range: 3.345,

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6.551 ug/I) and was attained at a mean value of 2.17 h. Following the individual maxima, roflumilast was eliminated biphasically with a terminal half-life of 22.53 h (68%-range: 17.71, 28.67 h). The geometric mean of the AUC(0-inf) was 53.23 ugxh/l (68%-range: 38.81, 73.01 ugxh/l). The geometric mean of the maximum plasma concentrations Cmax of metabolite 89502-044 was 8.561 ug/l (68%-range: 7.239, 10.126 ug/I) and was attained at a mean value of 9.67 h. Following the individual maxima, 89502-044 was eliminated with a geometric mean terminal half-life of 29.78 h (68%-range: 21.93, 40.44 h). The geometric mean of the AUC(0-inf) was 421.64 ugxh/l (68%-range: 351.96, 505.11 ugxh/l).

Conclusions: Pharmacokinetics:
The primary aim of this study was to evaluate the pharmacokinetics of roflumilast (89302-107) after single oral administration of 0.5 mg roflumilast to elderly healthy subjects. These data have been compared to historical data obtained from study 8Y217/FHP010, where healthy young volunteers had also received 0.5 mg roflumilast as a single oral dose. With respect to AUC, a distinct increase was observed in elderly Subjects as compared to young subjects. This increase was more pronounced for roflumilast than for the metabolite 89502-044. This increase of AUC was the result of a prolongation of the half-life, being 22.5 hand 29.8 h in elderly Subjects and 11.1 h and 20.6 h in young volunteers for roflumilast and metabolite 89502-044, respectively. Only minor changes were observed in Cmax in the elderly subjects when compared to young subjects. These findings suggested that the prolongation of the half-life in elderly subjects was the result of a reduction in clearance.
Safety and tolerability:
Single administrations of 0.5 mg roflumilast were safe and tolerable in healthy elderly subjects.

FHP024

Study Title: Investigation of the pharmacokinetics of a single oral dose of 500 mcg roflumilast in healthy middle-aged subjects (>45 and <65 years).

Objectives: Primary: Pharmacokinetics of roflumilast (B9302-107) and metabolite
B9502-044 Secondary: Safety and tolerability

Study Design: The study was conducted according to an open, one period design. Each subject received 500 ug roflumilast as a single dose (2 tablets of 250 ug roflumilast each) after a standard breakfast.
Blood samples for determination of the pharmacokinetics of roflumilast (B9302-107) and metabolite B9502-044 were taken predose and at 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 30 h, 48 h, 54 hand 72 h post dose. 12-lead resting ECG, blood pressure and pulse rate were measured predose and 1 h, 2 h, 4 h, 8 hand 12 h post dose as well as during the screening examination and the post-study examination.
Clinical laboratory (clinical chemistry, hematology, urinalysis) was determined during the screening examination and the post-study examination. Adverse events were monitored continuously during the study. Renal creatinine clearance was determined during the study.

Study Population: Twelve healthy male subjects were enrolled. 10 males and 2 female. Age range from 45 to 65 years of age.

Data Analysis: Pharmacokinetics: AUC and Cmax were estimated as extent and rate characteristics of roflumilast, respectively, and AUC and Cmax of the active metabolite 89502-044. Additionally, t1/2 and tmax of roflumilast, and t1/2 and tmax of the active metabolite 89502-044 were calculated. The renal creatinine clearance was determined during the study in order to evaluate whether or to what extent the pharmacokinetic characteristics of roflumilast were dependent on renal clearance.
Safety and tolerability: 12-lead resting ECG, blood pressure and heart rate were obtained at predefined time point, clinical laboratory (clinical chemistry, hematology, urinalysis) during the screening examination and the post-study examination. Adverse events were monitored continuously during the study.

Results: Pharmacokinetic characteristics (geometric means/68%-range) of roflumilast (89302-107) and the metabolite 89502-044 after a single dose of 500 ug in healthy subjects aged >45 years and <65 years (N=12)

Pharmacokinetic characteristics	Roflumilast Geometric mean (68%-Range)	B9502-044 Geometric mean (68%-Range)
$AUC_{(0-\infty)}$ (µgxh/l)	40.41 (27.44, 59.50)	383.96 (291.27, 506.15)*
C_{max} (µg/l)	5.427 (3.752, 7.851)	8.526 (6.664, 10.907)
$t_{1/2}$ (h)	16.64 (10.89, 25.43)	30.87 (20.65, 46.14)
t_{max} (h)	1.23 ± 0.13	10.08 ± 2.47
t_{max} mean ± SEM		*N = 8

Conclusions: Pharmacokinetics:
Compared to historical data obtained from studies with elderly healthy subjects or young healthy subjects who received the same dose of 500 ug roflumilast as a single oral dose, AUCs of roflumilast and metabolite 89502-044 of middle-aged subjects were lower than the corresponding AUCs of elderly subjects and higher than the corresponding AUCs of young healthy subjects. With respect to Cmax of roflumilast, changes observed in the middle-aged were moderate in comparison to the elderly (about 16%) and core pronounced in comparison to the young (about 41 %). Cmax of metabolite 89502-044 remained virtually unchanged. The elimination half-life of roflumilast and the metabolite 89502-044 increased by about 50% in the middle aged as compared to the young. Although these findings suggest a pharmacokinetic age dependency of roflumilast and its major metabolite 89502-044, their clinical relevance should be studied in prolonged treatment and larger patient populations.
Safety and tolerability:
A single dose of 500 ug roflumilast was well tolerated in subjects aged >45 years and <65 years with regard to adverse events, vital signs, ECG parameters and laboratory values.

FHP025

Study Title: Investigation of the pharmacokinetics of 250 ug roflumilast in healthy elderly subjects (~ 65 years) after single dosing and in steady state

Objectives: Primary: Pharmacokinetics of roflumilast (B9302-107) and metabolite B9502-044 Secondary: Safety and tolerability

Study Design: The study was conducted according to an open, one period design. It was planned to include 18 healthy subjects of either sex (15 male, 3 female), aged ~ 65 years into the study. Each subject received 250 mcg roflumilast as a single dose (Day 1) and for 8 consecutive days (Days 4-11).
Blood samples for determination of the pharmacokinetics of roflumilast (B9302-107) and metabolite B9502-044 were taken predose and at 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 30 h, 48 h, 54 hand 72 h post dose on Day 1 (after single dosing) as well as predose and at 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h, and 24 h post dose on Day 11 (day 8 of multiple
dose roflumilast treatment) 12-lead resting ECG, blood pressure and pulse rate were measured predose and 1 h, 2 h, 4 h, 8 hand 12 h post dose on Days 1 and 11 as well as during the screening examination and the post-study examination. Clinical laboratory (clinical chemistry, hematology, urinalysis) was determined during the screening examination and the post-study examination. Adverse events were monitored continuously during the study.

Study Population: Healthy subjects of either sex, aged ~ 65 years entered the study. A total of 18 subjects (14 male and 4 female) were enrolled.

Data Analysis: Pharmacokinetics: AUC(0-inf), AUC(0-24h) in steady-state, and Crnax were estimated as extent and rate characteristics of roflumilast, respectively, and AUC and Cmax of the active metabolite 89502-044. Additionally, ty, and trnax of roflumilast and of the active metabolite 89502-044 were calculated. The renal creatinine clearance was determined during the study in order to evaluate whether or to what extent the pharmacokinetic characteristics of roflumilast were dependent on renal clearance. All pharmacokinetic parameters were estimated for single and multiple dosing. Safety and tolerability: 12-lead resting ECG, blood pressure and heart rate were obtained at predefined time point, clinical laboratory (clinical chemistry, hematology, urinalysis) during the screening examination and the post-study examination. Adverse events were monitored continuously during the study.

Results: Pharmacokinetic characteristics (Geometric means/680/0-range) of roflumilast (89302-107) and the metabolite 89502-044 in elderly subjects ~ 65 years; N=18) after a single oral dose of 250 ug (Day 1) and after eight consecutive days of 250 ug roflumilast o.d. (Day 11)

	Roflumilast (B9302-107) Geometric mean (68%-range)		B9502-044 Geometric mean (68%-range)	
	Day 1	Day 11	Day 1	Day 11
$AUC_{(0-\infty)}$ (µgxh/l) $AUC_{(0-24h)}$ (µgxh/l)	27.20 (20.94, 35.35)*	28.71 (19.69, 41.85)	210.60 (195.2, 227.3)°	254.93 (196.2, 331.2)
C_{max} (µg/l)	2.900 (2.146, 3.918)	3.538 (2.628, 4.763)	3.596 (2.857, 4.525)	13.612 (10.47, 17.69)
$t_{½}$ (h)	21.00 (15.31, 28.81)	18.86 (13.15, 27.06)#	38.66 (24.88, 60.08)§	n.a.
t_{max} (h)[1]	1.64 ± 0.27	2.43 ± 0.37	15.65 ± 2.27	6.44 ± 1.12
[1]t_{max} mean ± SEM	*N = 17	#N = 7	°N = 8 §N = 14	

Conclusions: Pharmacokinetics:

The primary aim of this study was to compare the pharmacokinetics of roflumilast after single and multiple oral administration of 250 ug roflumilast to elderly healthy subjects.

Equivalence was demonstrated for roflumilast and metabolite 89502-044 with respect to the primary characteristic AUC. With respect to Cmax, equivalence could formally not be demonstrated for roflumilast. In addition, equivalence could not be demonstrated for Cmax of metabolite 89502-044. However, explorative evaluation of t1/2, for roflumilast showed confidence limits for this characteristic within the equivalence range.

Safety and Tolerability:

Single doses and repeated doses of 250 ug roflumilast were well tolerated when given to healthy subjects aged >=65 years.

CP-050

Study Title: Steady-state pharmacokinetics of 500 µg roflumilast of healthy elderly (≥ 65 years) subjects compared with healthy young (18 to 45 years) and healthy middle aged (46 to 64 years) subjects. An open, three parallel group comparison.

Objectives: Primary: Pharmacokinetics of roflumilast and roflumilast N-oxide under steady state conditions in healthy elderly subjects (aged ≥ 65 years), compared to healthy young subjects (aged 18 to 45 years), and to healthy middle aged subjects (aged 46 to 64 years). Secondary: Safety and tolerability.

Study Design: The study was conducted according to an open, three parallel group comparison with multiple-dose administrations of roflumilast in healthy young, middle aged and elderly subjects.

The trial consisted of the following phases:
Run-in period: Days -1 to 0
Treatment period: Days 1 to 15
PK profile period: Days 15 to 21

All subjects were confined in the clinic from Day – 1 until Day 1 and from the evening of Day 14 until the morning of Day 16. Subjects were not confined from the evening of Day 1 until the evening of Day 14. During this time they visited the clinic every day for all study related procedures (i.e. administration of study medication). All subjects received 500 µg roflumilast once a day during the period of 15 days. There was no placebo treatment group.

Study Population: Young: 22 healthy subjects, 19 to 44 years of age (11 male, 11 female)
Middle aged: 22 healthy subjects, 46 to 64 years of age (11 male, 11 female)
Elderly: 22 healthy subjects, 65 to 76 years of age (12 male, 10 female)

Data Analysis: Primary Variables: AUCT and t½ of roflumilast and of roflumilast N-oxide on Day 15. Blood samplings for pharmacokinetic purposes were performed on Day 15 at pre-dose, and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 14h, 24h, 26h, 48h, 72h, 96h, 120h and 144h after morning administration of study medication.

 Descriptive analysis and ANOVA will be used to do the analysis.
Results:
Plasma concentrations of roflumilast/ roflumilast N-oxide were determined by using a validated liquid chromatography-mass spectrometry/ mass spectrometry (LC-MS/MS) assay. The limit of quantification in plasma (LLOQ) was 0.04 ng/ml using a sample volume of 0.5 ml.
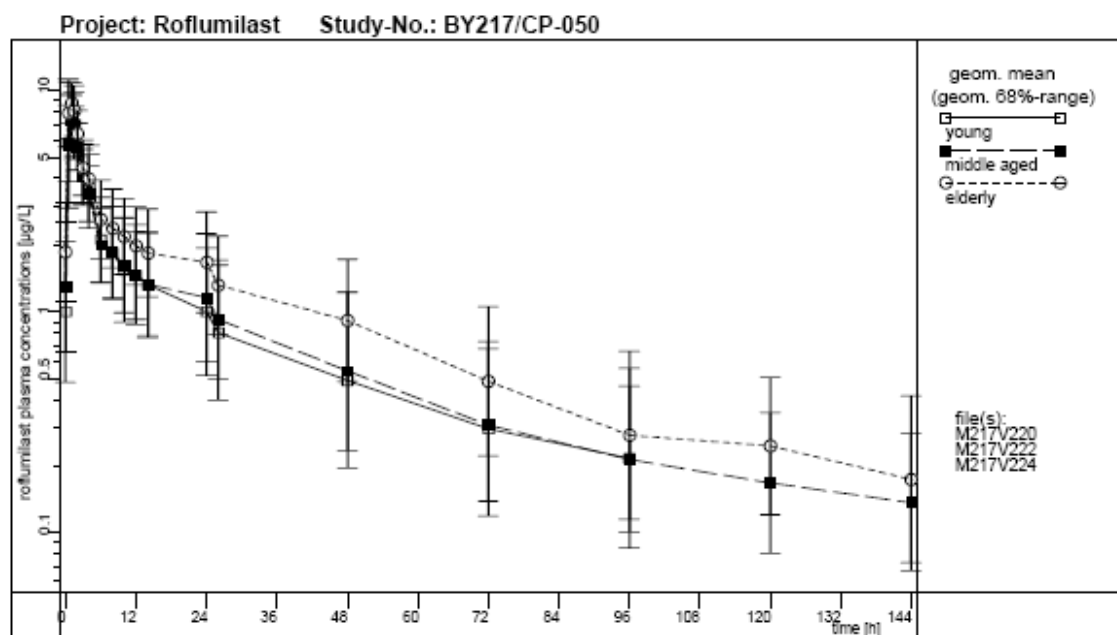
Figure 11.4.4 – 2:   Geom. Mean steady state plasma concentrations of roflumilast in young, middle aged and elderly female and male subjects following once daily oral administration of 500 µg roflumilast on Day 15, **semi log scale** (0 to 144h)
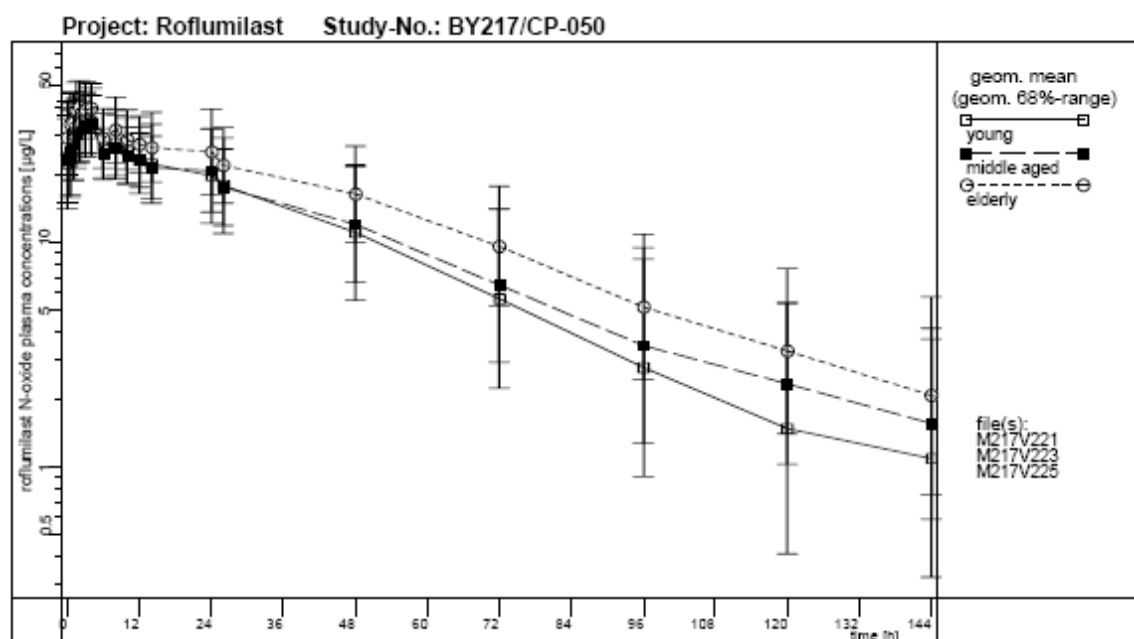
Figure 11.4.4 – 5:   Geom. Mean steady state plasma concentrations of roflumilast N-oxide in young, middle aged and elderly female and male subjects following once daily oral administration of 500 μg roflumilast on Day 15, semi log scale (0 to 144h)

Summary of pharmacokinetic characteristics of roflumilast in healthy male and female subjects after 15 days of once-daily oral doses of 500 μg roflumilast [geometric mean, (68% range); tmax: median (min/max)]:

Roflumilast		C_{max} [ug/L]	AUCT [h*ug/L]	CLss/FBW [L/h/kg]	$t_{1/2}$ [h]	t_{max} [h]
Elderly	Value	10.17	67.20	0.1016	30.98	1
(n=22)	Range	12.29 - 8.42	93.11 - 48.50	0.1397 - 0.0739	41.93 - 22.88	1.5 - 0.5
Middle aged	Value	8.17	52.48	0.1260	28.78	1.00
(n=22)	Range	10.97 - 6.09	76.48 - 36.01	0.1814 - 0.0875	39.80 - 20.81	0.5 - 2
Young	Value	8.74	53.10	0.1264	30.29	1.00
(n=19)	Range	11.54 - 6.62	76.49 - 36.86	0.1844 - 0.0866	46.40 - 19.77	4 - 0.5

Summary of pharmacokinetic characteristics of roflumilast N-oxide in healthy male and female subjects after 15 days of once-daily oral doses of 500 μg roflumilast [geometric mean, (68% range); tmax: median (min/max)]:

Roflumilast N-oxide		C_{max} [ug/L]	AUCT [h*ug/L]	$t_{1/2}$ [h]	t_{max} [h]
Elderly	Value	42.75	717.47	34.903	2
(n=22)	Range	56.89 - 32.12	991.32 - 519.27	47.89 - 25.44	10 - 1.5
Middle aged	Value	34.88	593.11	31.64	3
(n=22)	Range	47.88 - 25.41	820.88 - 428.54	44.64 - 22.43	8 - 1.5
Young	Value	37.73	605.39	29.72	3
(n=19)	Range	53.14 - 26.79	871.81 - 420.38	44.34 - 19.92	8 - 1.5

Comparison of pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide in the elderly vs. young population: Data analyzed suggests that roflumilast exposure in the elderly was 27 % higher then in the young population. This difference reflected the 20% lower CLss/FBW in the elderly. There was no difference in the t½. Similar differences between these two populations were observed for roflumilast N-oxide. Exposure in the elderly was 19 % higher than in the young population. Elderly had also 17% longer t 1/2.

Comparison of pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide in the middle aged vs. young population: In contrast to the elderly, comparison of roflumilast exposure and CLss/FBW between the middle aged and the young population showed no difference. However, estimated t1/2 in the middle aged population was 5 % shorter than in the young population. The same pattern of similarities and differences, as observed for roflumilast, was also observed for roflumilast N-oxide exposure. Comparison of the exposure between these populations showed no difference. However, a 6 % prolongation of t½ in the middle aged population was observed.

Table 11.4.4 – 5: Roflumilast – Summary of pharmacokinetic parameter estimates in healthy female and male (gender comparison) subjects on day 15th following multiple once-daily oral dose of 500 µg roflumilast [geometric mean, (68 % range); t_{max}: median (min/max)] for the young, middle aged and young age group

	Elderly		Middle aged		Young	
	Female	Male	Female	Male	Female	Male
C_{max} [ug/l]	11.16 12.62 – 9.871	9.41 11.54 – 7.67	9.57 12.09 – 7.58	6.97 9.12 – 5.32	8.89 11.35 – 6.96	8.61 11.82 – 6.27
AUCT [h*ug/l]	76.75 107.12 – 54.99	60.15 80.20 – 45.12	70.17 85.12 – 57.84	39.25 51.61 – 29.84	63.31 94.62 – 42.36	45.32 58.39 – 35.17
CLss/FBW [l/h/kg]	0.0957 0.1375 – 0.0666	0.1068 0.1418 – 0.0804	0.1025 0.1312 – 0.0803	0.1548 0.2203 – 0.1087	0.1142 0.1739 – 0.0749	0.1385 0.1925 – 0.0996
$t_{½}$ [h]	38.5 50.0 – 29.64	25.84 31.58 – 21.14	34.32 43.94 – 26.8	24.14 32.66 – 17.84	31.47 43.03 – 23.01	29.26 49.4 – 17.32

Table 11.4.4 – 6: Roflumilast N-oxide – Summary of pharmacokinetic parameter estimates in healthy female and male (gender comparison) subjects on day 15th following multiple once-daily oral dose of 500 µg roflumilast [geometric

mean, (68% range); t_{max}: median (min/max)] for the young, middle aged and young age group

	Elderly		Middle aged		Young	
	Female	Male	Female	Male	Female	Male
C_{max}[ug/l]	52.81 64.75 − 43.08	35.84 44.57 − 28.82	43.09 55.4 − 33.51	28.23 35.25 − 22.6	43.31 62.09 − 30.21	33.31 44.44 − 24.97
AUCT[h*ug/l]	879.03 1127.456 − 685.34	605.76 803.99 − 456.41	731.14 931.13 − 574.1	481.136 623.25 − 371.42	703.85 1063.13 − 465.98	528.59 690.85 − 404.44
$t_½$[h]	43.07 60.52 − 30.65	29.28 34.04 − 25.19	39.47 49.56 − 31.42	25.36 34.19 − 18.81	35.38 51.63 - 24.24	25.4 36.69 - 17.58

Conclusions: Comparison of pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide in the elderly vs. young population suggests that roflumilast exposure in the elderly was 27 % higher then in the young population. This difference reflected the 20 % lower CLss/FBW in the elderly. There was no difference in the t½. Similar differences between these two populations were observed for roflumilast N-oxide. Exposure in the elderly was 19 % higher than in the young population. Elderly had also 17 % longer t1/2. Comparison of pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide in the middle aged vs. young population suggests that, in contrast to the elderly, comparison of roflumilast exposure and CLss/FBW between the middle aged and the young population is not different. However, estimated t1/2 in the middle aged population was 5% shorter than in the young population. For roflumilast N-oxide exposure, there was no difference between these populations. However, a 6 % prolongation of t½ in the middle aged population was observed.

With respect to tolerability in healthy subjects, an age-depended gender related increase in adverse events cannot be excluded. Overall however, the application of 500 μg roflumilast for 15 days was safe in young, middle aged and elderly healthy subjects.

CP-067

Study Title: A Study of the Effect of Fluvoxamine on the Pharmacokinetics of Roflumilast and Roflumilast-N-Oxide.

Objectives: 1. To evaluate the effect of fluvoxamine on the pharmacokinetics (PKs) of roflumilast 2. To evaluate the effect of fluvoxamine on the PKs of roflumilast-N-oxide
3. To investigate the safety and tolerability of roflumilast and coadministration of roflumilast and fluvoxamine.

Study Design: This was an open-label, nonrandomized, 1-sequence, 2-period, 2-treatment study in 16 healthy volunteers.

Treatment schedule.			
Study Day 1	Study Days 8-14	Study Day 15	Study Days 16-21

Roflumilast 500 μg PO	Fluvoxamine 50 mg PO QD	Roflumilast 500 μg PO Fluvoxamine 50 mg PO	Fluvoxamine 50 mg PO QD

Study Population: A total of 16 subjects were enrolled into the study.

Data Analysis: PK parameters including log-transformed maximum observed plasma concentration (Cmax), area under the plasma concentration-time profile (AUC), and oral clearance (CL/F) values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (roflumilast with fluvoxamine) as a percentage of reference (roflumilast alone) were generated.

Descriptive analysis and ANOVA will be used to do the analysis.

Results: PK results for roflumilast and roflumilast-N-oxide are summarized in the following figure and tables.

Figure S1. Mean Roflumilast (Left Panels) and Roflumilast-N-Oxide (Right Panels) Plasma ConcentrationTime Profiles Following Single Oral 500-μg Roflumilast Doses Alone (Filled Symbols) and With Steady-State Fluvoxamine (Open Symbols) (Study A5821013)

Table S3. Summary of Roflumilast Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Fluvoxamine (Protocol A5821013)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Fluvoxamine (Test, N = 14)	Roflumilast Alone (Reference, N = 16)		
Cmax, ng/mL	7.94	7.12	112	100 to 124.53
$AUC_{(0-tlqc)}$, ng·hr/mL	119	50.8	234	207 to 265
$AUC_{(0-\infty)}$, ng·hr/mL	141	55.2	256	218 to 301
CL/F, L/hr	3.53	9.06	39.0	33.2 to 45.9
Tmax, hr	1.16	1.28		Not Applicable
t½, hr	64.8	33.1		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Table S4. Summary of Roflumilast-N-Oxide Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Fluvoxamine (Protocol A5821013)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Fluvoxamine (Test, N = 14)	Roflumilast Alone (Reference, N = 16)		
Cmax, ng/mL	8.42	10.5	80.3	73.6 to 87.7
$AUC_{(0-tlqc)}$, ng·hr/mL	868	635	137	126 to 148
$AUC_{(0-\infty)}$, ng·hr/mL	1190	780	152	132 to 175
Tmax, hr	29.5	10.4		Not Applicable
t½, hr	78.5	44.0		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

In the presence of steady-state fluvoxamine, roflumilast time to maximum observed plasma concentration (Tmax) and Cmax values were similar to those observed when roflumilast was administered alone. Mean Tmax was less than 10 minutes earlier and mean Cmax was 12% higher with steady-state fluvoxamine. In contrast, mean roflumilast AUC values with steady-state fluvoxamine were more than double those observed when roflumilast was administered alone, and mean CL/F decreased by approximately 60%. Mean roflumilast terminal half-life (t½) with steady-state fluvoxamine was nearly twice as long as that for roflumilast administered alone.

In the presence of steady-state fluvoxamine, mean Tmax for roflumilast-N-oxide was almost 3 times later and Cmax was 20% lower than when roflumilast was administered alone. Mean roflumilast-N-oxide AUC(0-tlqc) and AUC(0-∞) values with steady-state fluvoxamine increased by 37% and 52%, respectively, relative to those observed when roflumilast was administered alone. Mean roflumilast-N-oxide t½ increased by about 80% with steady-state fluvoxamine.

Conclusions: Based on AUC values, steady-state fluvoxamine administration increases roflumilast exposure more than 2-fold, and increases roflumilast-N-oxide exposure by approximately 50%. Steady-state fluvoxamine administration had little effect on roflumilast Cmax, but roflumilast-N-oxide Cmax decreased by about 20% and occurred about 3 times later. Single oral 500-µg roflumilast doses were safe and well-tolerated, with and without coadministration with fluvoxamine.

FHP021

Study Title: Comparison of pharmacokinetics of a single dose of 500 µg roflumilast p.o. in healthy nonsmokers and smokers.

Objectives: Primary: Pharmacokinetics of a single oral dose of 500µg roflumilast in healthy subjects, smokers compared to non-smokers
Secondary: Safety and tolerability of roflumilast

Study Design: The study was conducted according to an open, single dose, one period, parallel group design. To each smoking subject, a non-smoking subject of the same sex, and comparable in age, height and weight was allocated (matched pairs). One tablet of 500 µg roflumilast was given orally to the subjects as single dose. Blood samples for the determination of roflumilast and the active metabolite B9502-044 (roflumilast- N-oxide) were taken at pre-dose and at 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 8h, 10h, 12h, 24h, 30h, 48h, 54h and 72h post-dose.

Study Population: A total of 24 subjects with 12 smokers and 12 non-smokers were enrolled into the study.

Data Analysis: PK parameters including log-transformed maximum observed plasma concentration (Cmax), area under the plasma concentration-time profile (AUC), and oral clearance (CL/F) values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (smoking) as a percentage of reference (non-smoking) were generated. Descriptive analysis and ANOVA will be used to do the analysis.

Results: Roflumilast and metabolite B9502-044 plasma concentrations were determined by a validated assay using reversed-phase HPLC with fluorescence detection after post-column photochemical derivatization. Sample clean-up was performed using liquid/liquid extraction. The lower limit of quantitation (LLOQ) was 0.085 µg/l for roflumilast and 0.5 µg/l for metabolite B9502-044.

Pharmacokinetic characteristics (geometric means/ 68%-range) of roflumilast and the metabolite B9502-044 following a single oral dose of 500µg roflumilast to healthy smokers (n = 12):

	Roflumilast	B9502-044
$AUC_{(0-\infty)}$ [µg*h/l]	37.33 (26.03, 53.54)	459.10 (344.03, 612.67)
C_{max} [µg/l]	7.829 (6.435, 9.523)	10.234 (8.538, 12.268)
$t_{\frac{1}{2}}$ [h]	12.93 (8.78, 19.04)	26.13 (18.65, 36.59)
t_{max} [h][1]	0.90 ± 0.17	8.38 ± 1.30

[1] t_{max}: mean ± SEM

Pharmacokinetic characteristics (geometric means/ 68%-range) of roflumilast and the metabolite B9502-044 following a single oral dose of 500µg roflumilast to healthy non-smokers (n = 12):

	Roflumilast	B9502-044
$AUC_{(0-\infty)}$ [µg*h/l]	42.56 (25.57, 70.85)	391.02 (294.38, 519.37)
C_{max} [µg/l]	7.460 (5.611, 9.920)	8.958 (7.753, 10.350)
$t_{\frac{1}{2}}$ [h]	14.46 (7.67, 27.26)	24.84 (16.80, 36.72)
t_{max} [h][1]	0.94 ± 0.17	12.50 ± 2.18

[1] t_{max}: mean ± SEM

Point estimates (90%-confidence intervals) of pharmacokinetic characteristics of roflumilast and its metabolite B9502-044 following a single oral administration of 500µg roflumilast to healthy smokers (Test) and to healthy non-smokers (Reference):

Pharmacokinetic characteristics	Point estimates (90%-CI)	
	Roflumilast	B9502-044
$AUC_{(0-\infty)}$	0.877 (0.644, 1.196)	1.174 (0.950, 1.451)
C_{max}	1.049 (0.884, 1.246)	--
$t_{\frac{1}{2}}$	0.894 (0.619, 1.292)	1.052 (0.810, 1.366)
t_{max}	-0.042 (-0.446, 0.363)	--

Conclusions: Following single oral administration of 500µg roflumilast to 12 healthy smokers, the pharmacokinetic characteristics were found to be comparable to the corresponding values of a control group of healthy non-smokers. The smoking habit did not affect the pharmacokinetics of roflumilast in healthy subjects.

FHP027

Study Title: The possible effect of steady-state roflumilast on digoxin pharmacokinetics in healthy subjects - an open, randomized, two-period crossover design.

Objectives: The primary objective was the possible effect of steady state roflumilast on digoxin pharmacokinetics. Secondary objectives were the pharmacokinetics of roflumilast and roflumilast-N-oxide, as well as safety and tolerability.

Study Design: The study was conducted according to an open, randomized, two-period crossover design. Subjects received either Treatment A (digoxin 250 µg o.d. on Days 1 and 14,

and Roflumilast 500 µg o.d. on Days 1 to 14) or Treatment B (digoxin 250 µg o.d. on Day 1). The treatment periods were separated by a washout period of at least 10 days. Blood sampling for determination of pharmacokinetic parameters was done on Day 1 of Treatment A and on Days 13 and 14 of Treatment B. Clinical laboratory parameters were determined before start of each treatment, on Days 12 and 19 of Treatment A and on Days 1 and 6 of Treatment B.

Study Population: A total of 16 subjects were enrolled into the study. The median age of the 16 subjects was 39 years; their median weight was 72.5 kg, their median height was 174 cm, and their median Broca index was 0.99. In total, 11 subjects were male, 5 subjects were female.

Data Analysis: PK parameters including log-transformed maximum observed plasma concentration (Cmax), area under the plasma concentration-time profile (AUC), and oral clearance (CL/F) values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (smoking) as a percentage of reference (non-smoking) were generated. Descriptive analysis and ANOVA will be used to do the analysis.

Results: Concentrations of digoxin in plasma were determined using a validated radioimmunoassay (RIA) using 125I-digoxin tracer and specific rabbit anti-digoxin antibodies. Digoxin standard curves were valid up to 1000 ng/l and the lower limit of quantitation was 20 ng/l. A good reproducibility of the assay was found within this range, based on a between-assay coefficient of variation of the trend parameters (B0/TA, NSB/B0, ED10, ED50, ED90; Slope, Intercept) being <20%.

Concentrations of roflumilast and roflumilast N-oxide in plasma were determined using a validated liquid chromatographic method employing liquid-liquid extraction and MS/MS detection. Roflumilast and roflumilast N-oxide standard curves were valid up to 109.57 ng/ml and the lower limit of quantitation was 0.10 ng/ml. The intra-day precision of the calibration standards ranged from 1.51% to 8.74% concerning roflumilast and from 1.91% to 5.81% referring to roflumilast N-oxide. For the quality control samples the intra-day precision concerning roflumilast ranged from 2.13% to 4.43% and from 3.27% to 4.93% referring to roflumilast N-oxide, respectively. The intra-day accuracy of roflumilast obtained from back calculated calibration standards was found to be within the range of –13.09% to +18.02%, while the accuracy of the calibration standards of roflumilast N-oxide ranged from –12.18% to +14.44%. The intra-day accuracy of the roflumilast quality control samples ranged from –9.75% to +4.62% and from –9.84% to +1.68% in case of roflumilast N-oxide. The inter-day precision of the roflumilast quality control samples ranged from 7.63% to 12.56%, the inter-day accuracy from –0.83% to 9.55%. In case of roflumilast N-oxide the inter-day precision ranged from 4.84% to 8.01%, the inter-day accuracy from –5.22% to 2.53%.

Plasma concentration-time profiles of digoxin are shown in the figure below**.**
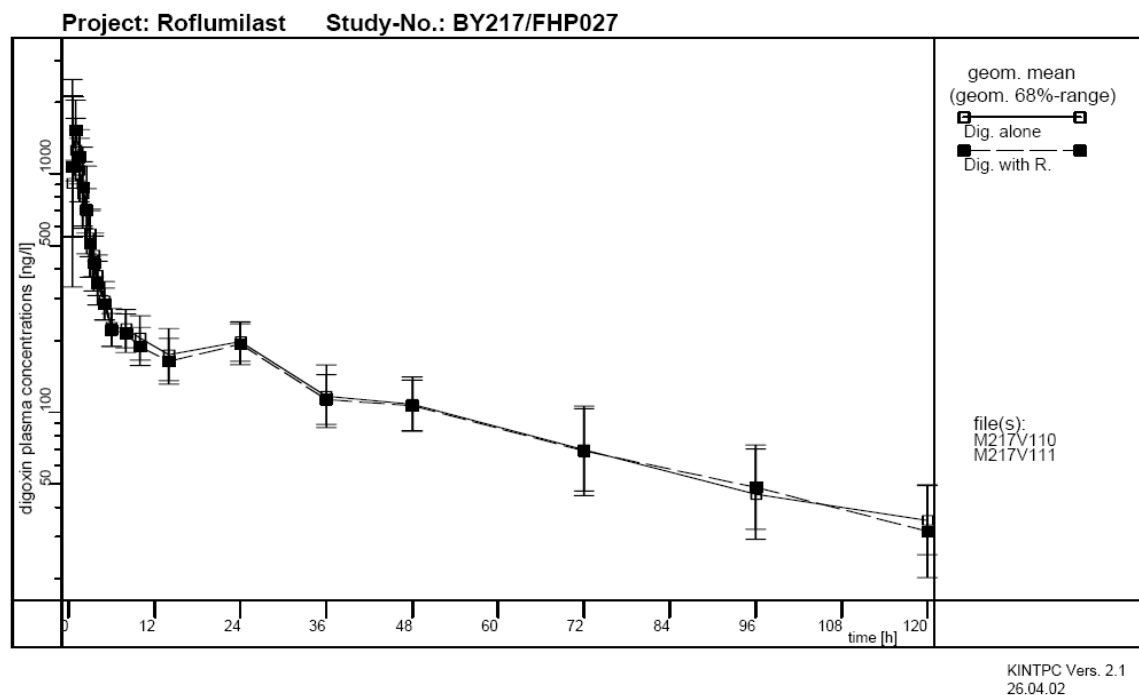
Figure 3: Mean digoxin plasma concentrations in healthy male and female subjects following one single oral dose of 0.25 mg of digoxin alone or in combination with multiple once-daily oral doses of roflumilast (0.5 mg), semilog. scale, 0-120h

The plasma concentration–time curves of digoxin appeared to be nearly super-imposable after digoxin treatments with and without concomitant roflumilast administration. A summary of the statistical evaluation is given in Table 6, displaying the effect of concomitant roflumilast administration on digoxin pharmacokinetics, based on point estimates and 90%-confidence intervals for the Test/Reference ratios of digoxin geometric mean AUC(0-∞) and Cmax values.

Table 5: Summary of pharmacokinetic characteristics of digoxin in healthy male and female subjects following single 250 µg oral doses of digoxin alone (Reference) or in combination with multiple once-daily doses of 500 µg roflumilast (Test); geometric means, (68% range); t_{max}: median (min, max).

Pharmacokinetic characteristic	250 µg Digoxin	250 µg Digoxin + 500 µg roflumilast
$AUC_{(0-\infty)}$ [ng/lxh] (68% range)	17046.8 (13304.8, 21841.3)	16205.9 (12664.0, 20738.3)
C_{max} [ng/l] (68% range)	1509.79 (1168.71, 1950.42)	1733.11 (1362.05, 2205.26)
t_{max} [h] (min, max)	0.75 (0.50, 2.00)	1.00 (0.50, 2.00)
$t_{1/2}$ [h] (68% range)	40.47 (31.93, 51.30)	37.80 (25.67, 55.67)

Source of data: Section 14.2.1.1 (Tables 15 and 17)

Table 6: Point estimates and 90%-confidence limits for the Test/Reference ratios of digoxin $AUC_{(0-\infty)}$ and C_{max} values following single 250 µg oral doses of digoxin alone (Reference) or in combination with multiple once-daily doses of 500 µg roflumilast (Test).

Pharmacokinetic Characteristic	Point estimate	90% confidence limit
$AUC_{(0-\infty)}$	1.01	0.92 - 1.11
C_{max}	1.15	0.99 – 1.34

Source of data: Section 14.2.1.3

The extent of digoxin absorption, as characterized by the area under the curve AUC(0-∞), was also not significantly influenced by concomitant roflumilast treatment. The point estimate for the Test/Reference ratio (1.01) as well as the corresponding 90% confidence limits (0.92 - 1.11) were within the equivalence range of 0.8 to 1.25 (Table 6). These findings indicate that the systemic exposure of digoxin is not significantly influenced by concomitant roflumilast treatment. The pharmacokinetic variables tmax and t1/2 for digoxin were not significantly influenced by concomitant roflumilast treatment (Table 5).

Plasma concentration-time profiles of roflumilast and roflumilast N-oxide are shown in the figures below.
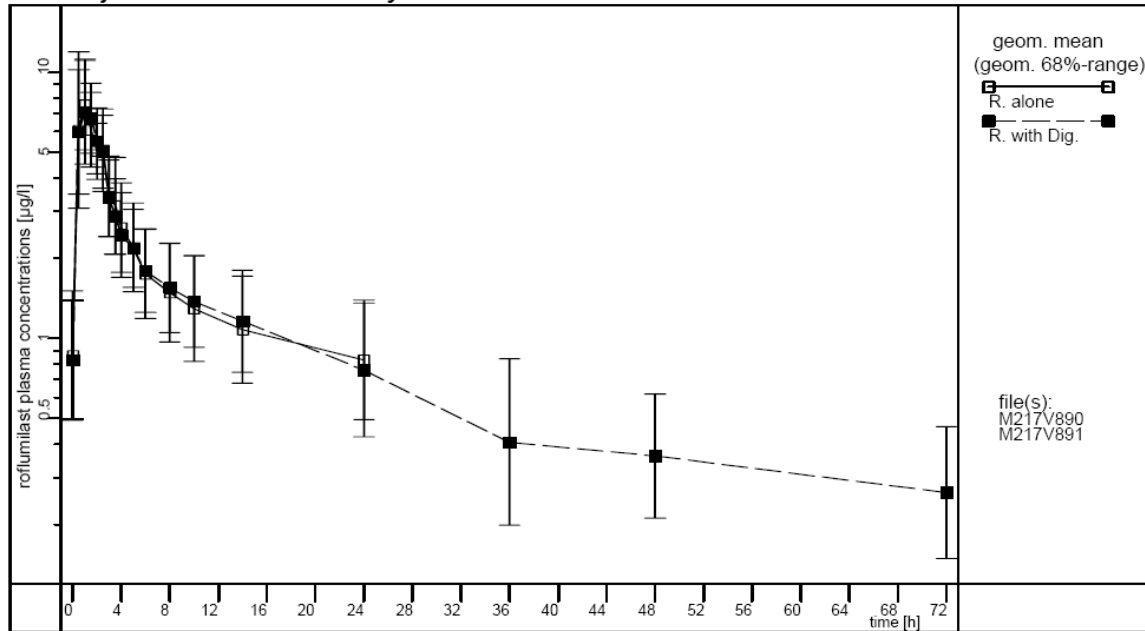
Figure 6: Mean roflumilast plasma concentrations in healthy male and female subjects following multiple once-daily oral doses of 0.50 mg roflumilast alone or in combination with one single oral dose of digoxin (0.25 mg), semilog. scale, 0-72 h. Study Subject #10 was excluded from the evaluation of geom. mean data

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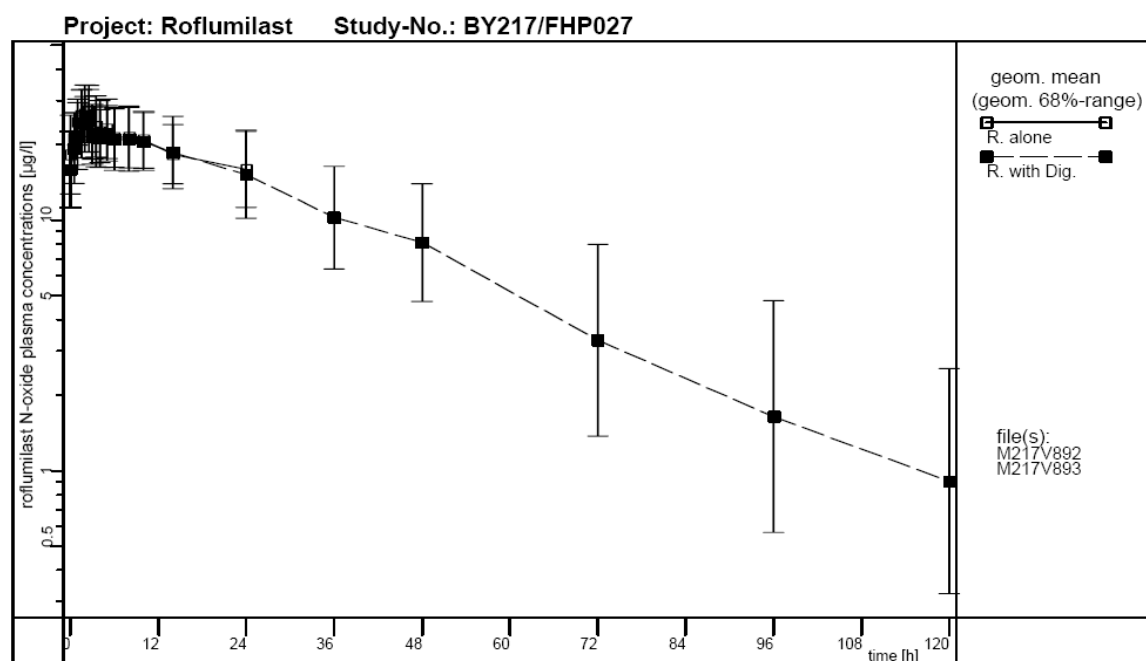
Figure 10: Mean roflumilast N-oxide plasma concentrations in healthy male and female subjects following multiple once-daily oral doses of 0.50 mg roflumilast alone or in combination with one single oral dose of digoxin (0.25 mg), semilog. scale, 0-120 h. Study Subject #10 was excluded from the evaluation of geom. mean data

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Table 7:   Summary of pharmacokinetic characteristics of roflumilast and its metabolite roflumilast N-oxide in healthy male and female subjects following the 13th (Reference) and the 14th (Test) of multiple once-daily oral doses of 500 µg roflumilast [geometric mean, (68% range); tmax: median (min, max)]. The individual results of all study subjects except Subject #10 were included.

Pharmacokinetic Characteristic	Roflumilast (R. alone) (Day 13)	Roflumilast (R. with Dig.) (Day 14)	Roflumilast N-oxide (R. alone) (Day 13)	Roflumilast N-oxide (R. with Dig.) (Day 14)
$AUC_{(0-24 h)}$ [µg/lxh] (68% range)	44.9 (33.9, 59.4)	45.6 (33.2, 62.7)	466.4 (353.7, 615.0)	464.8 (342.7, 630.3)
C_{max} [µg/l] (68% range)	9.51 (6.90, 13.11)	8.92 (6.75, 11.78)	29.32 (23.36, 36.80)	26.01 (19.62, 34.49)
t_{max} [h] (min, max)	1.00 (0.50, 3.00)	1.00 (0.50, 2.50)	2.50 (1.50, 8.00)	2.00 (1.00, 8.00)
$t_{1/2}$ [h] (68% range)	14.44 (9.08, 22.96)	18.12 (12.07, 27.21)	34.53 (23.29, 51.19)	22.75 (17.10, 30.27)

R.: roflumilast; Dig.: digoxin

Source of data: Section 14.2.1.1 (Tables 26, 27, 28 and 29)

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Table 8: Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast AUC(0-24 h) values following the 13th (Reference) and the 14th (Test) of multiple once-daily oral doses of 500 µg roflumilast. The individual results of all study subjects were included.

Pharmacokinetic Characteristic	Roflumilast		Roflumilast N-oxide	
	Point estimate	90% confidence limit	Point estimate	90% confidence limit
AUC$_{(0-24 h)}$	1.01	0.96 - 1.07	0.97	0.92 - 1.02
C$_{max}$	0.95	0.80 – 1.13	0.90	0.84 – 0.96

Source of data: Section 14.2.1.3

The point estimates for the Test/Reference ratio of the geometric mean AUC(0-24 h) found for roflumilast (1.01) and roflumilast N-oxide (0.97) as well as their respective 90% confidence limits were within the equivalence range (0.8 - 1.25). Point estimates for the Test/Reference ratio of Cmax (0.95 for roflumilast and roflumilast N-oxide (0.90) as well as the respective 90% confidence intervals were also within the equivalence range of 0.70 to 1.43 indicating that the extent of roflumilast absorption and roflumilast N-oxide formation is not significantly affected by concomitant digoxin administration.

In the present study, tmax remained unaffected by concomitant digoxin treatment. For t1/2 of roflumilast, a prolongation from 14.44 h (without digoxin) to 19.33 h with concomitant digoxin treatment was found. For roflumilast N-oxide a decrease of t1/2 from 34.53 h (without digoxin) to 24.27 h was seen. However, these alterations were not significant. For both components the geometric mean values for t1/2 of the digoxin-roflumilast period were within the 68% range of the geometric mean from the digoxin period.

Conclusions: For digoxin, the primary variables AUC(0-∞) representing the systemic exposure as well as Cmax were not influenced by concomitant treatment with roflumilast. Point estimates for the Test/Reference ratios for AUC(0-∞) and Cmax as well as their 90% confidence intervals were within the respective equivalence ranges. The secondary variables (tmax and t1/2) were unaffected by concomitant roflumilast treatment, also. No significant influence on the pharmacokinetic parameters AUC(0-24 h), Cmax and tmax was found for roflumilast and its metabolite roflumilast N-oxide by concomitant digoxin treatment. For t1/2 of roflumilast, a slight prolongation was found, whereas a decrease of t1/2 was found for roflumilast N-oxide. However, these alterations of the terminal elimination half-lives were not significant. Point estimates for the Test/Reference ratios for AUC(0-24 h) and Cmax as well as their 90% confidence intervals were within their equivalence ranges.

CP-044

Study Title: A Study of the Effect of Maalox Administration on the Single-Dose Pharmacokinetics of Roflumilast and Roflumilast-N-Oxide (Protocol A5821015)

Objectives: To evaluate the effect of Maalox administration on the pharmacokinetics of roflumilast; ˌ To evaluate the effect of Maalox administration on the pharmacokinetics of roflumilast- N-oxide; and ˌ To investigate the safety and tolerability of coadministration of roflumilast and Maalox.

Study Design: This was an open-label, randomized, 6-sequence, 3-period, 3-treatment, 3-way crossover study in 30 healthy volunteers. Subjects received treatment according to the following schedule (Table S1).

Table S1. Study Treatment (Protocol A5821015)

Group (Sequence)	Day 1	Day 15	Day 29
A	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg Maalox 30 mL
B	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL after 2 hours
C	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg
D	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg
E	Roflumilast 500 µg Maalox 30 mL after 2 hours	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL
F	Roflumilast 500 µg	Roflumilast 500 µg Maalox 30 mL	Roflumilast 500 µg Maalox 30 mL after 2 hours

Study Population: Thirty healthy volunteers (14 males and 16 females) entered the study. Twenty-seven subjects completed the study. There were two subject withdrawals due to adverse events, and one subject who withdrew consent.

Data Analysis: Pharmacokinetic blood samples were collected serially for 120 hours following the Day 1, 15, and 29 roflumilast doses. Plasma concentrations of roflumilast and roflumilast N-oxide were measured using a validated liquid chromatography/mass spectrometry (LC/MS/MS) method. Pharmacokinetic parameters including log-transformed Cmax, AUC, and CL/F values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for the test treatments (roflumilast with Maalox, and roflumilast with Maalox after 2 hours) as a percentage of reference (roflumilast alone) were generated. Lack of an effect of Maalox on roflumilast were concluded if the 90% confidence intervals for both Cmax and AUC(0-∞), based on log-transformed data, were entirely contained within the interval of 80% to 125%.

Results: Pharmacokinetic results for roflumilast and roflumilast N-oxide are summarized in the following figure and tables.

Figure S1. **Mean Roflumilast (Left Panels) and Roflumilast-N-Oxide (Right Panels) Plasma Concentration-Time Profiles Following Single Oral 500-μg Roflumilast Doses Alone (Filled Circles), With Maalox (Open Circles), and With Maalox After 2 Hours (Open Squares) (Protocol A5821015)**

Table S4. Summary of Roflumilast Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference), With Maalox, and With Maalox After 2 Hours (Protocol A5821015)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Maalox (Test)	Roflumilast Alone (Reference)		
N	30	28		
Cmax, ng/mL	6.55	7.37	88.8	80.4 to 98.1
AUC(0-tlqc), ng*hr/mL	54.5[a]	52.4	104	100 to 108
AUC(0-∞), ng*hr/mL	58.0[a]	55.6	104	100 to 109
CL/F (L/hr)	8.62[a]	8.98	95.9	92.2 to 99.9
tmax	1.84	1.56		Not Applicable
t½	28.5[a]	28.4		Not Applicable
	Roflumilast With Maalox After 2 hr (Test)	Roflumilast Alone (Reference)		
N	29	28		
Cmax, ng/mL	7.21	7.37	97.8	88.5 to 108
AUC(0-tlqc), ng*hr/mL	54.6	52.4	104	100 to 108
AUC(0-∞), ng*hr/mL	58.2	55.6	105	100 to 109
CL/F (L/hr)	8.59	8.98	95.6	91.9 to 99.5
tmax	1.62	1.56		Not Applicable
t½	30.3	28.4		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
a   N = 29.

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Table S5. Summary of Roflumilast N-Oxide Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference), With Maalox, and With Maalox After 2 Hours (Protocol A5821015)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Maalox (Test)	Roflumilast Alone (Reference)		
N	30	28		
Cmax, ng/mL	9.70	10.6	91.6	86.9 to 96.6
AUC(0-tlqc), ng*hr/mL	550[a]	558	98.5	95.2 to 102
AUC(0-∞), ng*hr/mL	616[a]	617	99.8	96.1 to 104
tmax	9.03	5.92		Not Applicable
t½	33.2[a]	31.7		Not Applicable
	Roflumilast With Maalox After 2 hr (Test)	Roflumilast Alone (Reference)		
N	29	28		
Cmax, ng/mL	10.7	10.6	101	95.4 to 106
AUC(0-tlqc), ng*hr/mL	556	558	99.6	96.3 to 103
AUC(0-∞), ng*hr/mL	629	617	102	98.1 to 106
tmax	6.83	5.92		Not Applicable
t½	35.3	31.7		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.
a   N = 29.

Roflumilast: Based on AUC(0-∞) values, extent of roflumilast absorption with Maalox administered either concurrently or 2 hours after roflumilast was similar to that for roflumilast alone. Based on Cmax and tmax values, rate of roflumilast absorption with Maalox administered either concurrently or 2 hours after roflumilast was similar to that for roflumilast administered alone. The 90% confidence intervals for treatment ratios of mean AUC(0-∞) and Cmax values, based on log-transformed data, were all within the 80% to 125% range. Mean tmax values for the 3 treatments were between 1.5 and 2.0 hours. Mean roflumilast t½ was similar across all treatments, averaging about 29 hours.

N-Oxide: Results for roflumilast N-oxide were similar to those for the parent compound. Based on AUC(0-∞) values, total exposure for roflumilast N-oxide with Maalox administered either concurrently or 2 hr after roflumilast was similar to that for roflumilast administered alone. The 90% confidence intervals for treatment ratios of mean AUC(0-∞) and Cmax values, based on log-transformed data, were all within the 80% to 125% range. Mean roflumilast N-oxide tmax was about 3 hr (53%) later when roflumilast was administered with Maalox, and about 1 hour (15%) later when Maalox was administered after 2 hours, compared to that for roflumilast alone.

Mean roflumilast N-oxide t½ was similar across all treatments, averaging about 33 hours.

Conclusions: Administration of 30 mL Maalox either concurrently with, or 2 hr after, a single 500-µg roflumilast oral tablet dose has no clinically important effect on the pharmacokinetics of

roflumilast or roflumilast N-oxide. The pharmacokinetic results for the parent drug and metabolite meet the usual bioequivalence criterion.

FHP014

Study Title: Investigation of a possible pharmacokinetic interaction between roflumilast and salbutamol in healthy male subjects (Study Code: BY217/FHP014)

Objectives: Primary: Investigation of a possible pharmacokinetic interaction of salbutamol (Sultanol® N, Mol 100 I-lg) on roflumilast in fasted state. Secondary: Investigation of a possible pharmacokinetic interaction of roflumilast on salbutamol (Sultanol® N, MOl 100 I-lg) in fasted state Investigation of a possible pharmacokinetic interaction of of salbutamol (Sultanol® N, MOl 100 I-Ig) on the pharmacological active metabolite of roflumilast (B9502-044) in fasted state Safety and tolerability

Study Design: The study was conducted according to a randomized, open, three-period, change-over design with random allocation of the eligible subjects to the 6 treatment sequences of a Latin Square and its mirror image. In one study period the subjects received roflumilast alone (Test 1), in another study period they received salbutamol alone (Test 2), and in a third study period both drugs were given together (Reference).

Repeated blood samples for pharmacokinetic purposes were taken up to 72 h after roflumilast administration and up to 24 h after salbutamol inhalation, beginning each after the morning administration on day 7. Safety measurements were performed on day 7 of each study period and at pre and final check.

Roflumilast was given 0.5 mg/d orally. Salbutamol was given 200 µg by aerosol inhalation three times a day from day 1 to 7.

Study Population: Thirteen subjects for each treatment for roflumilast, salbutamol, and roflumilast plus salbutamol. Healthy male subjects (median age: 24 years; median weight: 85 kg).

Data Analysis: For each of the drugs assayed geometric means and 90%-confidence limits were given for the respective Test/Reference ratios.
Roflumilast:
Equivalence of the pharmacokinetic characteristics of roflumilast was concluded if the 90%-confidence interval was entirely within the equivalence range of 0.80 to 1.25 concerning AUC(0-24h) and 0.70 to 1.43 concerning Cmax '
Metabolite 89502-044:
AUC(0-24h) and Cmax of the pharmacologically active metabolite 89502-044 were analysed in analogy to the corresponding characteristics of roflumilast. An extended equivalence range of

0.67 to 1.50 for the pharmacokinetic characteristics of the active metabolite 89502-044 was chosen because of the in-vivo formation of the metabolite.

Salbutamol:

AUC(0-6h), Cmax and elimination half-life of salbutamol were analysed in analogy to the corresponding characteristics of roflumilast. An extended equivalence range of 0.67 to 1.50 for the pharmacokinetic characteristics of salbutamol was chosen recognizing that inhalation technique plays a major part in determining lung deposition.

Results: The concentration-time profiles of roflumilast, roflumilast N-oxide, and salbutamol are shown in the following three figures, respectively.
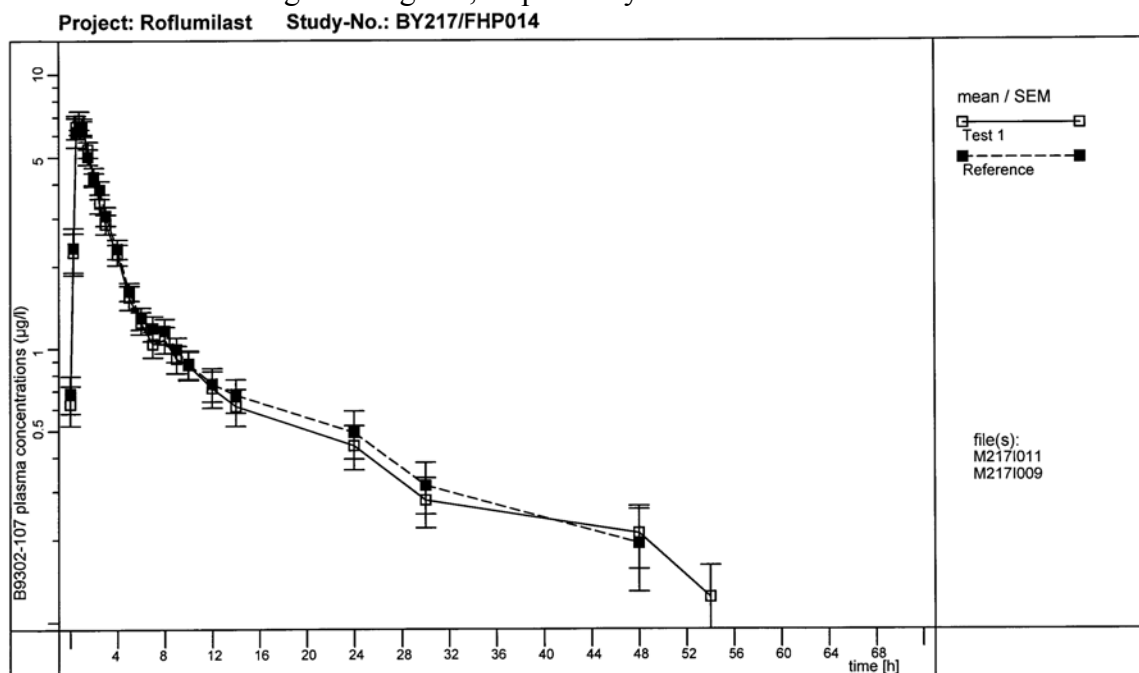
Fig. 1: Mean (SEM) plasma concentrations of roflumilast in healthy male subjects (N=12) after the 7th oral dose of 0.5 mg roflumilast on Day 7 with (Reference) or without (Test 1) a concomitant inhalative treatment of 600 µg salbutamol/day

Project: Roflumilast   Study-No.: BY217/FHP014
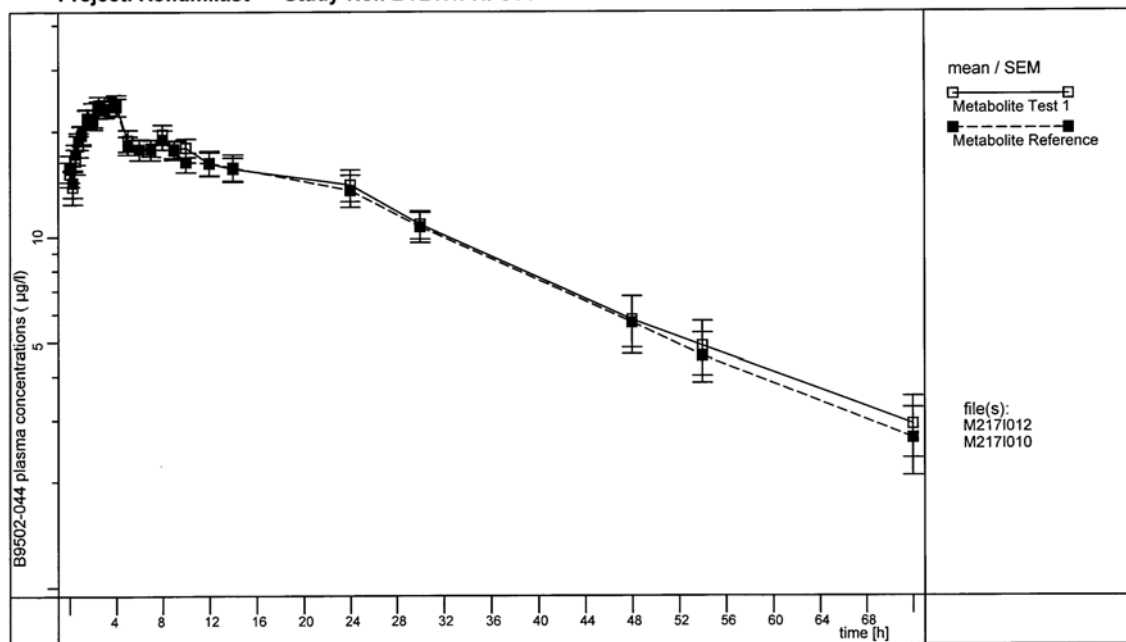
Fig. 2:   Mean (SEM) plasma concentrations of metabolite B9502-044 in healthy male subjects
(N=12) after the 7th oral dose of 0.5 mg roflumilast on Day 7 with (Reference) or without
(Test 1) a concomitant inhalative treatment of 600 µg salbutamol/day

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Project: Roflumilast   Study-No.: BY217/FHP014
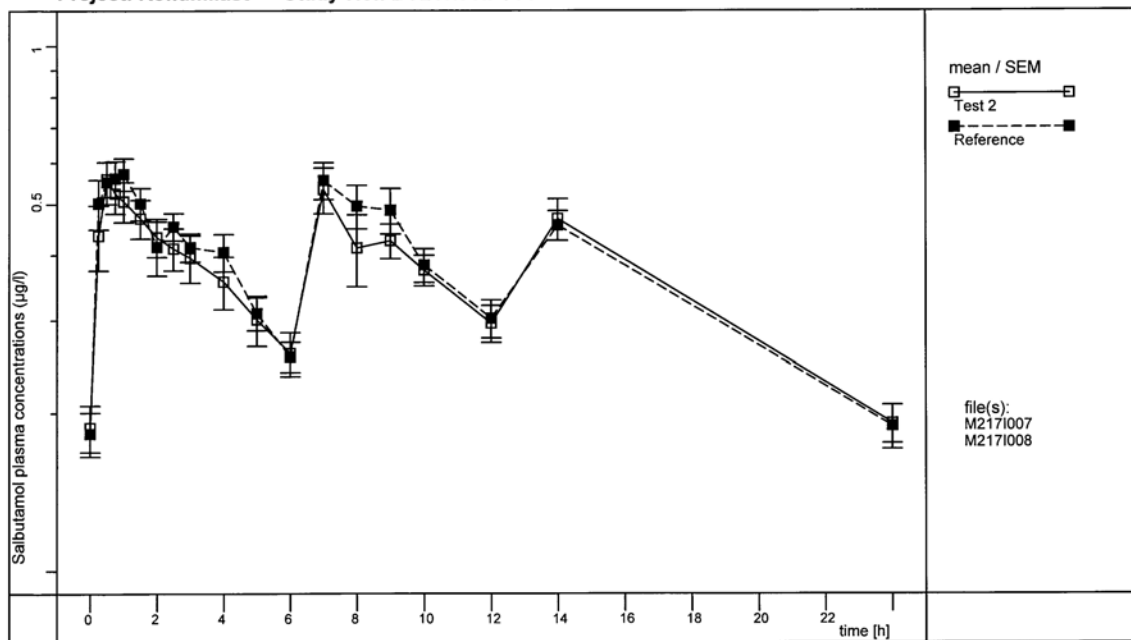
Fig. 3:   Mean (SEM) plasma concentrations of salbutamol in healthy male subjects (N=12)
after the 7th oral dose of 0.5 mg roflumilast on Day 7 with (Reference) or without (Test 2)
a concomitant inhalative treatment of 600 µg salbutamol/day

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The summary statistics of the pharmacokinetic characteristics for parent compound roflumilast, its active metabolite 89502-044 and salbutamol are summarized in the following table.

Table 1: Pharmacokinetic characteristics (geometric means/68%-range)

Kinetic characteristics	Roflumilast (Test 1)	Roflumilast (Reference)	B9502-044 (Test 1)	B9502-044 (Reference)	Salbutamol (Test 2)	Salbutamol (Reference)
$AUC^{1)}$ (µg/lxh)	30.85 (22.17, 42.93)	32.82 (24.64, 43.72)	400.62 (315.16, 509.26)	393.88 (306.45, 506.26)	2.188 (1.504, 3.183)	2.407 (1.883, 3.075)
C_{max} (µg/l)	7.232 (5.580, 9.372)	6.976 (5.289, 9.202)	24.408 (19.934, 29.887)	23.836 (19.697, 28.844)	0.578 (0.442, 0.755)	0.619 (0.465, 0.823)
$t_{max}^{2)}$ (h)	0.75 (0.50, 1.00)	0.75 (0.50, 1.00)	3.00 (2.00, 4.00)	3.00 (1.50, 4.00)	0.63 (0.25, 3.00)	0.75 (0.25, 4.00)
$t_{1/2}$ (h)	16.65 (11.87, 23.36)	14.25 (9.61, 21.13)	20.54 (14.88, 28.35)	21.07 (16.66, 26.64)	4.03 (2.97, 5.47)	3.32 (2.52, 4.38)

1) $AUC_{(0-24h)}$ for roflumilast and B9502-044
   $AUC_{(0-6h)}$ for salbutamol
2) t_{max}: median (min, max)

Statistical analysis of the PK variables are shown in the following three tables.

Table 2a: Summary of Equivalence Assessment: Roflumilast

Pharmacokinetic characteristics	Reference: geometric mean (N=12) (68%-range)	Test 1: geometric mean (N=12) (68%-range)	Equivalence ratio (Test/Reference) Point estimate (90%-confidence interval)
roflumilast	with salbutamol	without salbutamol	
$AUC_{(0-24h)}$ (µg/lxh)	32.74* (24.23, 44.24)	30.66* (21.83, 43.05)	0.94 (0.83, 1.05)
C_{max} (µg/l)	6.98 (5.27, 9.24)	7.23 (5.56, 9.41)	1.04 (0.91, 1.19)
$t_{1/2}$ (h)	14.24* (9.40, 21.58)	16.53* (11.71, 23.33)	1.16 (1.00, 1.34)

* n = 11

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Table 2b: Summary of Equivalence Assessment: B9502-044

Pharmacokinetic characteristics	Reference: geometric mean (N=12) (68%-range)	Test 1: geometric mean (N=12) (68%-range)	Equivalence ratio (Test/Reference) Point estimate (90%-confidence interval)
B9502-044	with salbutamol	without salbutamol	
$AUC_{(0-24h)}$ (µg/lxh)	393.88 (305.16, 508.39)	400.62 (312.22, 514.05)	1.02 (0.94, 1.10)
C_{max} (µg/l)	23.84 (19.95, 28.48)	24.41 (19.82, 30.07)	1.02 (0.97, 1.08)
$t_{1/2}$ (h)	21.07 (16.81, 26.40)	20.54 (14.89, 28.33)	0.97 (0.82, 1.16)

Table 2c: Summary of Equivalence Assessment: Salbutamol

Pharmacokinetic characteristics	Reference: geometric mean (N=12) (68%-range)	Test 2: geometric mean (N=12) (68%-range)	Equivalence ratio (Test/Reference) Point estimate (90%-confidence interval)
salbutamol	with roflumilast	without roflumilast	
$AUC_{(0-6h)}$ (µg/lxh)	2.401 (1.834, 3.142)	2.195* (1.480, 3.253)	0.91 (0.81, 1.03)
C_{max} (µg/l)	0.619 (0.462, 0.829)	0.578 (0.437, 0.765)	0.93 (0.79, 1.11)
$t_{1/2}$ (h)	3.323 (2.516, 4.389)	4.033 (2.950, 5.512)	1.21 (1.02, 1.45)

* n = 11

Note: The geometric means and geometric 68%-ranges in the Tables 2a – 2c were calculated by means of the analysis of variance of the crossover design, whereas the values given in Table 1 were directly calculated from the individual data without reference to the crossover design.

Conclusions: Lack of interaction was demonstrated for roflumilast with respect to the primary characteristics AUC and Cmax since the 90% confidence intervals are entirely in the clinically stipulated equivalence range.   Lack of interaction was also shown for the secondary characteristics AUC and Cmax of 89502-044 and salbutamol.

CP-059

Study Title: Investigation on the cardiovascular and pharmacokinetic interaction between oral roflumilast and inhaled formoterol in healthy subjects

Objectives: The aim of the study was to investigate a potential cardiovascular interaction between multiple doses of oral roflumilast and inhaled formoterol in healthy subjects.

Study Design: This single center study had an open, randomized, controlled, multiple-dose, parallel-group design. Healthy male subjects were assigned to Treatment A or Treatment B. Subjects in Treatment A received 500 μg/d roflumilast from Day 2 to Day 18 and 48 μg/d formoterol from Day 12 to Day 18. Subjects in Treatment B received 48 μg/d formoterol from Day 2 to Day 18 and 500 μg/d roflumilast from Day 9 to Day 18.

Blood samplings for pharmac1okinetic measurements were performed for Treatment A on Days 9 and 10 (trough levels), Day 11, and Day 18 and for Treatment B on Days 6 and 7 (trough levels), Day 8, and Day 18. Blood samples were taken at pre-dose, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, and 24 h after administration of study medication (the two last sampling times refer to roflumilast only).

Study Population: In total, 27 healthy young male subjects were included in the study. Twelve subjects were assigned to Treatment A and 15 subjects to Treatment B. In this study a total of 27 male Caucasian subjects were included (12 in Treatment A and 15 in Treatment B [including three protocol violators in Treatment B]). Their median (range) age was 33 years (25, 44) in Treatment A and 33 years (21, 44) in Treatment B; body height was 184 cm (169, 192) in Treatment A and 180 cm (168, 185) in Treatment B; body weight was 83 kg (66, 95) in Treatment A and 75 kg (61, 97) in Treatment B; body mass index was 25 kg/m2 (23, 28) in Treatment A and 24 kg/m2 (21, 30) in Treatment B.

Data Analysis: Pharmacokinetic parameter estimates were obtained with a non-compartmental analysis approach using WinNonLin professional, version 4.01. Pharmacokinetic parameter estimates for formoterol, roflumilast, and roflumilast N-oxide were determined using an extravascular model. No statistical analyses of pharmacokinetic parameter estimates were performed.

Results: Comparisons of the geometric mean plasma concentration-time profiles of formoterol, roflumilast, and roflumilast N-oxide are displayed in the following figures and tables.

T-Figure 5: Geometric mean formoterol plasma concentration [ng/L] - time curves (linear scale)
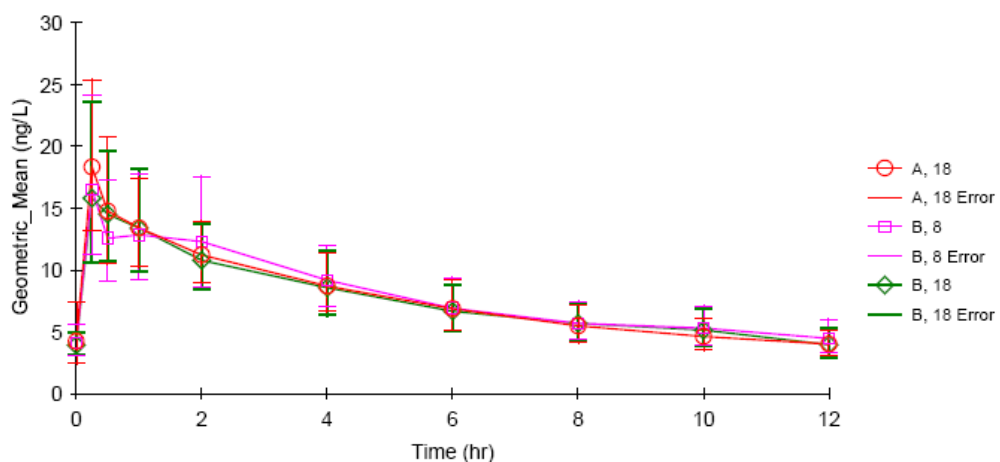
Error = 68% range, F = Treatment B, Day 8 (24 µg bid [2 puffs of 12 µg] formoterol [i.e. 48 µg/d] at steady state, N = 13), FR = Treatment B, Day 18 (24 µg bid [2 puffs of 12 µg] formoterol [i.e. 48 µg/d] and 500 µg roflumilast at steady state, N = 12), RF = Treatment A, Day 18 (500 µg roflumilast and 24 µg bid [2 puffs of 12 µg] formoterol [i.e. 48 µg/d] at steady state, N = 12). Data source: Section 15.2.1.1

A summary of the pharmacokinetic parameter estimates of inhaled formoterol with and without concomitant roflumilast treatment is shown in T-Table 6.

T-Table 6: Summary of pharmacokinetic parameter estimates of formoterol following inhalation of 24 µg with and without concomitant 500 µg roflumilast treatment

Treatment	A		B			
Day	18		8		18	
Variable	AUC_{tau} [h*ng/L]	C_{max} [ng/L]	AUC_{tau} [h*ng/L]	C_{max} [ng/L]	AUC_{tau} [h*ng/L]	C_{max} [ng/L]
N	12	12	13	13	12	12
Mean	95.82	19.36	100.38	17.81	95.68	18.05
SD	22.52	4.79	28.67	6.44	22.77	5.02
Min	60.01	10.9	57.58	8.09	56.24	7.79
Median	96.97	20.5	92.59	16.4	95.53	17.9
Max	129.89	24.2	150.82	30.4	138.1	25.6
Geometric mean	93.28	18.76	96.72	16.74	93.13	17.25
Upper 68%	119.34	24.6	128.49	24.31	119.16	24.16
Lower 68%	72.91	14.3	72.81	11.53	72.79	12.32

Treatment A: Day 18: 500 µg roflumilast and 24 µg bid (2 puffs of 12 µg) formoterol (i.e. 48 µg/d) at steady state.

Treatment B: Day 8: 24 µg bid (2 puffs of 12 µg) formoterol (i.e. 48 µg/d) at steady state, Day 18: 48 µg formoterol and 500 µg roflumilast at steady state.

AUC = area under the plasma concentration-time profile, C_{max} = maximum plasma concentration, formoterol tau (dosing interval) 12 h, N = number of subjects in a treatment period, SD = standard deviation.

Data Source: Section 15.2.1.1

T-Figure 7: Geometric mean roflumilast plasma concentrations [µg/L] - time curves (linear scale)

Analyte=Roflumilast
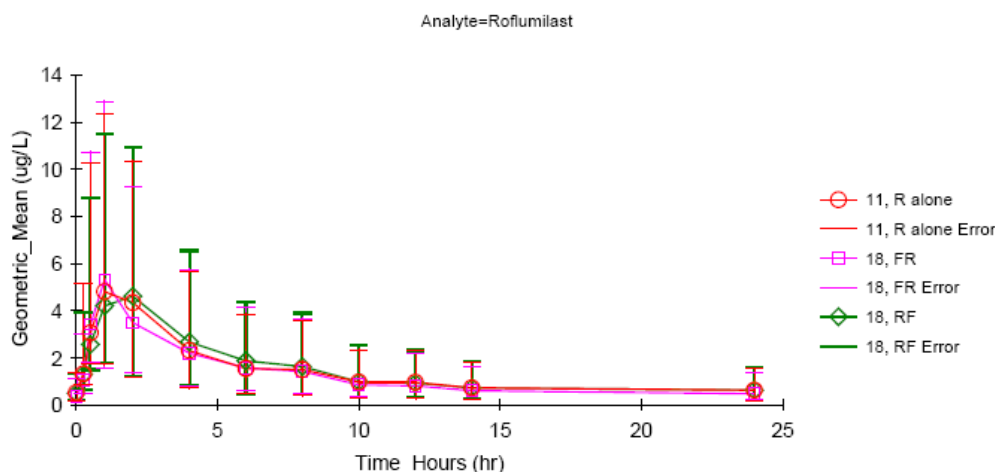
Error = 68% range, FR = Treatment B, Day 18 (24 µg bid [2 puffs of 12 µg] formoterol [i.e. 48 µg/d] and 500 µg roflumilast at steady state), R = Treatment A, Day 11 (500 µg roflumilast at steady state), RF = Treatment A, Day 18 (500 µg roflumilast and 24 µg bid [2 puffs of 12 µg] formoterol [i.e. 48 µg/d] at steady state). N = 12 for all measurements.
Data source: Section 15.2.1.2

T-Table 7: Summary of the pharmacokinetic parameter estimates of roflumilast at steady state following administration of 500 µg roflumilast alone and with concomitant inhalation of 24 µg formoterol

Analyte	Roflumilast								
Treatment	A			B			A		
Day	11			18					
Variable	AUCtau [hr*ug/L]	CLss F [L/hr]	Cmax [ug/L]	AUCtau [hr*ug/L]	CLss F [L/hr]	Cmax [ug/L]	AUCtau [hr*ug/L]	CLss F [L/hr]	Cmax [ug/L]
N	12	12	12	12	12	12	12	12	12
Mean	36.97	14.34	7.3	34.3	16.91	6.21	38.29	13.98	6.72
SD	10.19	3.32	2.98	13.64	6.76	1.92	11.89	3.36	2.32
Min	26.9	8.06	4.76	16.47	8.97	3.44	27.83	7.24	4.37
Median	34.92	14.33	6.5	32.3	15.49	5.82	33.46	14.96	6.08
Max	62.05	18.59	15.5	55.76	30.36	8.49	69.09	17.97	13
Geometric Mean	35.85	13.95	6.89	31.84	15.7	5.92	36.9	13.55	6.43
Upper 68%	46.12	17.95	9.62	47.78	23.56	8.22	48.44	17.78	8.63
Lower 68%	27.86	10.84	4.94	21.22	10.46	4.27	28.11	10.32	4.79

Treatment A: Day 11: 500 µg roflumilast at steady state, Day 18: 500 µg roflumilast and 24 µg bid (2 puffs of 12 µg) formoterol (i.e. 48 µg/d) at steady state.
Treatment B: Day 18: 24 µg bid (2 puffs of 12 µg) formoterol (i.e. 48 µg/d) and 500 µg roflumilast at steady state.
CLssF = apparent oral clearance, AUC = area under the plasma concentration-time profile, C_{max} = maximum plasma concentration, N = number of subjects in a treatment period, roflumilast tau (dosing interval) 12 h.
Data Source: Section 15.2.1.2

T-Figure 9: Geometric mean roflumilast N-oxide plasma concentrations [µg/L] - time curves (linear scale)
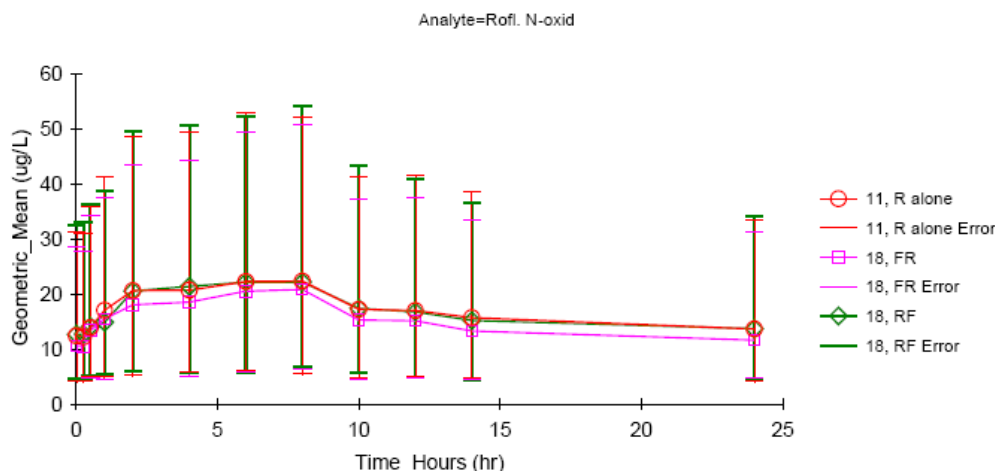
Analyte=Rofl. N-oxid

T-Table 8: Summary of the pharmacokinetic parameter estimates of roflumilast N-oxide at steady state following administration of 500 µg roflumilast alone and with concomitant inhalation of 24 µg formoterol

Analyte	Rofl. N-oxid					
Treatment	A		B		A	
Day	11		18			
Variable	AUCtau [hr*ug/L]	Cmax [ug/L]	AUCtau [hr*ug/L]	Cmax [ug/L]	AUCtau [hr*ug/L]	Cmax [ug/L]
N	12	12	12	12	12	12
Mean	439.73	24.33	393.25	23.12	437.45	24.83
SD	153.34	7.45	137.95	7.3	155.96	7.57
Min	281.9	15.6	215.82	13.3	218.33	12.3
Median	394.96	21.55	382.59	21.95	387.78	23.35
Max	731.48	37.9	597.76	34.6	785.4	40
Geometric Mean	417.33	23.35	369.85	22.04	414	23.74
Upper 68%	582.18	31.35	537.86	30.54	584.58	32.64
Lower 68%	299.15	17.39	254.32	15.91	293.19	17.27

Treatment A: Day 11: 500 µg roflumilast at steady state, Day 18: 500 µg roflumilast and 24 µg bid (2 puffs of 12 µg) formoterol (i.e. 48 µg/d) at steady state.
Treatment B: Day 18: 24 µg bid (2 puffs of 12 µg) formoterol (i.e. 48 µg/d) and 500 µg roflumilast at steady state (N = 12 for all measurements).
AUC = area under the plasma concentration-time profile, C_{max} = maximum plasma concentration, N = number of subjects in a treatment period, roflumilast N-oxide tau (dosing interval) 24 h based on roflumilast dosing.
Data Source: Section 15.2.1.3

Conclusions: The pharmacokinetic parameter estimates of roflumilast, roflumilast N- xide (in Treatment A), and formoterol (in Treatment B) were similar whether the respective medication was administered alone or in combination.

FHP017

Study Title: Investigation of a possible pharmacokinetic interaction between roflumilast and budesonide in healthy male subjects (Study Code: BY217/FHP017)

Objectives: Primary: Investigation of a possible pharmacokinetic interaction of budesonide (Pulmicort® Turbohaler® 400 I-lg) on roflumilast in fasted state
Secondary: Investigation of a possible pharmacokinetic interaction of roflumilast on budesonide (Pulmicort® Turbohaler® 400 I-lg) in fasted state Investigation of a possible pharmacokinetic interaction of budesonide (Pulmicort® Turbohaler® 400 I-lg) on the pharmacological active metabolite of roflumilast (B9502-044) in fasted state Safety and tolerability

Study Design: The study was conducted according to a randomized, open, three-period, change-over design with random allocation of the eligible subjects to the 6 treatment sequences of a Latin Square and its mirror image. In one study period the subjects received roflumilast alone (Test 1), in another study period they received budesonide alone (Test 2), and in a third study period both drugs were given together (Reference).
Repeated blood samples for pharmacokinetic purposes were taken up to 54 h after roflumilast administration and up to 12 h after budesonide inhalation. Safety measurements were perfomed on day 7 of each study period and at pre and final check.

Roflumilast was given as oral dose 0.5 mg/day.
Budesonide was given as 0.8 mg as powder inhalation by power inhalator twice daily.

The study duration is 7 days.

Study Population: Twelve subjects were enrolled and treated in the study.

Data Analysis: Pharmacokinetic parameter estimates were obtained with a non-compartmental analysis approach using WinNonLin professional, version 4.01. Pharmacokinetic parameter estimates for budesonide, roflumilast, and roflumilast N-oxide were determined using an extravascular model. No statistical analyses of pharmacokinetic parameter estimates were performed.

Results: Roflumilast and B9502-044 plasma concentrations were determined by a validated assay using reversed-phase HPLC with fluorescence detection after post-column photochemical derivatisation. Sample clean-up was performed using liquid/liquid extraction. The lower limit of

quantitation (LLOQ) was 0.1 and 0.5 µg/1 for B9302-107 and B9502-044, respectively. Analysis of budesonide in serum was conducted using a validated LC/MS/MS-method. The LLOQ was 0.025 µg/1.

Plasma concentration-time profiles of roflumilast, budesonide, and roflumilast N-oxide are shown in the following figure.
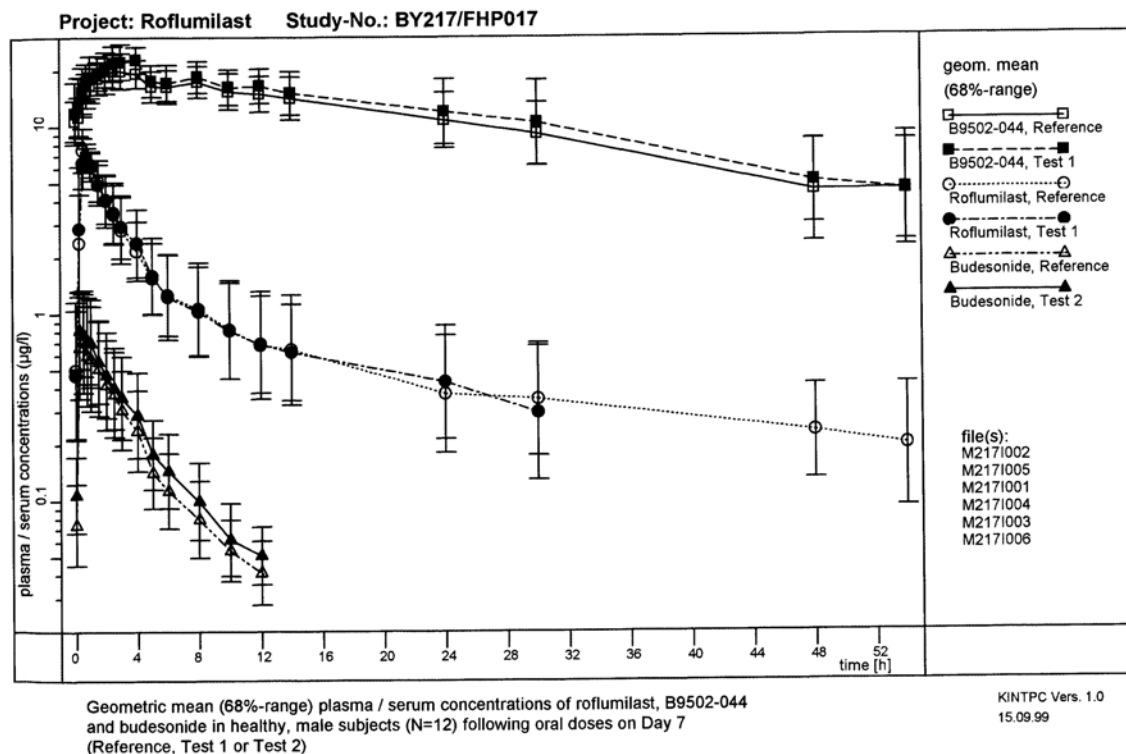
Geometric mean (68%-range) plasma / serum concentrations of roflumilast, B9502-044 and budesonide in healthy, male subjects (N=12) following oral doses on Day 7 (Reference, Test 1 or Test 2)

The summary statistics of the pharmacokinetic characteristics for parent compound roflumilast, its active metabolite 89502-044 and budesonide are summarized in the following table:

	Roflumilast		Metabolite B9502-044		Budesonide	
	Reference (Rofl. + Bud.)	Test 1 (Rofl. alone)	Reference (Rofl. + Bud.)	Test1 (Rofl. alone)	Reference (Rofl. + Bud.)	Test 2 (Bud. alone)
AUC [1)] [μg*h/l]	32.40 (21.42, 49.01)	32.47 (21.97, 47.98)	358.69 (285.40, 450.81)	389.32 (304.98, 496.98)	2.48 (1.51, 4.07)	2.92 (1.82, 4.69)
C_{max} [μg/l]	7.961 (6.475, 9.787)	7.391 (6.297, 8.676)	20.866 (16.731, 26.024)	23.782 (19.709, 28.696)	0.754 (0.418, 1.362)	0.874 (0.537, 1.420)
C_{max}/AUC [1/h]	0.2457 (0.1664, 0.3627)	0.2276 (0.1539, 0.3366)	0.0582 (0.0534, 0.0634)	0.0611 (0.0540, 0.0691)	0.3041 (0.2549, 0.3628)	0.2995 (0.2545, 0.3524)
t_{max} [2)] [h]	0.50 (0.50, 1.50)	0.50 (0.50, 1.50)	2.75 (1.50, 4.00)	3.50 (2.00, 4.00)	0.50 (0.25, 1.00)	0.25 (0.25, 0.75)
$t_{\frac{1}{2}}$ [h]	12.49 (8.29, 18.81)	14.71 (11.26, 19.23)	22.56 (18.19, 27.98)	19.89 (15.96, 24.78)	2.83 (2.00, 4.00)	3.26 (2.66, 4.00)

[1)] $AUC_{(0-24h)}$ for roflumilast and B9502-044; $AUC_{(0-12h)}$ for budesonide
[2)] t_{max}: median (min, max)

Point estimates and 90%-confidence intervals for the ratios of the respective population medians for roflumilast (Test 1: roflumilast alone; Reference: roflumilast and budesonide), its active metabolite B9502-044 (Test 1: roflumilast alone; Reference: roflumilast and budesonide), and budesonide (Test 2: budesonide alone; Reference: roflumilast and budesonide) are given in the following table:

	AUC	C_{max}	$t_{\frac{1}{2}}$
Roflumilast	**1.00** (0.92, 1.09)	**0.93** (0.84, 1.03)	**1.18** (0.99, 1.41)
Metabolite B9502-044	**1.09** (1.01, 1.17)	**1.14** (1.07, 1.22)	**0.92** (0.81, 1.04)
Budesonide	**1.18** (0.96, 1.44)	**1.16** (0.91, 1.48)	**1.15** (0.93, 1.43)

Conclusions: Lack of interaction was demonstrated for roflumilast with respect to the primary characteristics AUC and Cmax.

FHP026

Study Title: Investigation of a possible pharmacokinetic interaction between roflumilast and theophylline in healthy subjects

Objectives: Primary: Pharmacokinetic interaction between theophylline and roflumilast
Secondary: Pharmacokinetics of roflumilast and roflumilast-N-oxide; safety and tolerability of both, theophylline and roflumilast

Study Design: The study was conducted according to an open, randomized two-period crossover design.
• Blood samples for determination of the pharmacokinetics of theophylline were taken on study days 5 and 10 at predose and at 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 22h, 24h after morning oral administration.

• Blood samples for determination of the pharmacokinetics of roflumilast and roflumilast-Noxide were taken on study days 5 and 10 at predose and at 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, IOh, 12h, 14h, 16h, 18h, 24h after morning oral administration.

Treatment A: theophylline-roflumilast period: 375 mg theophylline capsule BID from day 1 to 10. Roflumilast was given as oral dose 0.5 mg/day from day 6 to 10.
Treatment B: Roflumilast period. 0.5 mg roflumilast tablets was given once daily on study days 1 to 5 orally.

Study Population: Twelve subjects were enrolled and treated in the study.

Data Analysis: Pharmacokinetic parameter estimates were obtained with a non-compartmental analysis approach using WinNonLin professional, version 4.01. Pharmacokinetic parameter estimates for theophylline, roflumilast, and roflumilast N-oxide were determined using an extravascular model. No statistical analyses of pharmacokinetic parameter estimates were performed.

Results:

Concentrations of theophylline in plasma were determined using a validated liquid chromatographic method employing protein precipitation as sample preparation and UV detection. Theophylline standard curves were valid up to 31.75 Ilg/ml and the lower limit of quantitation was 0.51 Ilg/ml. Quality control samples (QCs) were incorporated into each run during the sample analysis period to demonstrate good method performance. The intra-day precision of the calibration standards ranged from 0.53 to 4.01%, for QC samples, intra-day precision ranged from 0.41 to 3.04%. The intra-day accuracy obtained from back calculated calibration standards was found to be within the range of -l1.98 to +5.61%. The intra-day accuracy of quality control samples ranged from -8.30% to +2.37%. The inter-day precision of the quality control samples ranged from 1.93 to 3.86%, the inter-day accuracy from -5.00 to -0.55%.
The intra-day accuracy of roflumilast obtained from back calculated calibration standards was found to be within the range of -13.09% to +18.02%, while the accuracy of the calibration standards ofroflumilast N-oxide ranged from -12.18% to +14.44%. The intra-day accuracy of the roflumilast quality control samples ranged from -9.75% to +4.62% and from -9.84% to +1.68% in case ofroflumilast N-oxide. The inter-day precision of the roflumilast quality control samples ranged from 7.63% to 12.65%, the inter-day accuracy from -0.83% to 9.55%. In case of roflumilast N-oxide the inter-day precision ranged from 4.84% to 8.01%, the inter-day accuracy from -5.22% to 2.53%.

Plasma concentration time profile of theophylline with and without roflumilast.
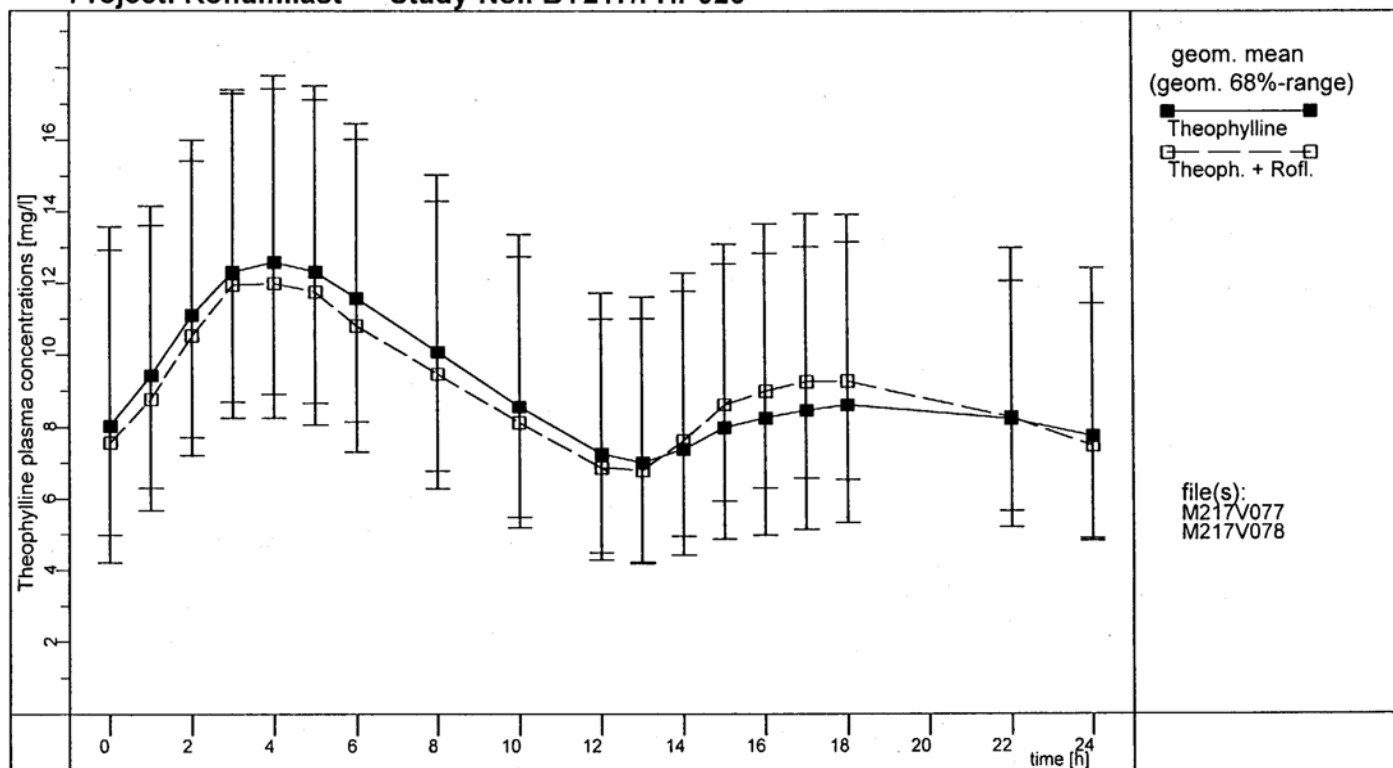
Figure 3: Mean theophylline plasma concentrations in healthy male and female subjects following multiple twice-daily oral doses of theophylline (2 X 375 mg) alone or in combination with multiple doses of 500 μg roflumilast (linear scale)

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Table 5: Summary of pharmacokinetic characteristics of theophylline in healthy male (n=12) and female subjects (n=14) following multiple twice-daily oral doses of 375 mg theophylline alone or in combination with 500 μg multiple once-daily doses of roflumilast [geometric mean, (68% range); t_{max}: median (min/max)].

Pharmacokinetic characteristics	Theophylline alone day 5 and 6	Theoph. with roflumilast day 10 and 11
$AUC_{(0-24h)}$ [mg/lxh]	222.9 (148.6, 334.4)	219.3 (150.5, 319.5)
C_{max} [mg/l]	12.83 (9.15, 18.00)	12.36 (8.80, 17.34)
t_{max} [h]	4.00 (3.00, 24.00)	4.00 (3.00, 16.00)
PTF [%]	65.94 (46.62, 93.26)	64.11 (47.75, 86.07)
$t_{1/2}$ [h]	8.89 (6.21, 12.73)	8.91 (6.66, 11.92)

A summary of the statistical evaluation is given in Table 6, displaying the effect of concomitant roflumilast administration on theophylline pharmacokinetics, based on point estimates and 90%-confidence intervals for the test/reference ratios of theophylline AUC(0-24h).

Table 6: Point estimates and 90%-confidence limits for the test/reference ratios of theophylline $AUC_{(0-24h)}$ and %PTF values following multiple 375 mg twice-daily doses of theophylline alone (reference, study day 5 and 6) or in combination with 500 μg multiple once-daily doses of roflumilast (test, study day 10 and 11).

Pharmacokinetic Characteristic	Point estimate	90% confidence limit
$AUC_{(0-24h)}$	0.98	0.93 – 1.04
%PTF	0.97	0.88 - 1.07

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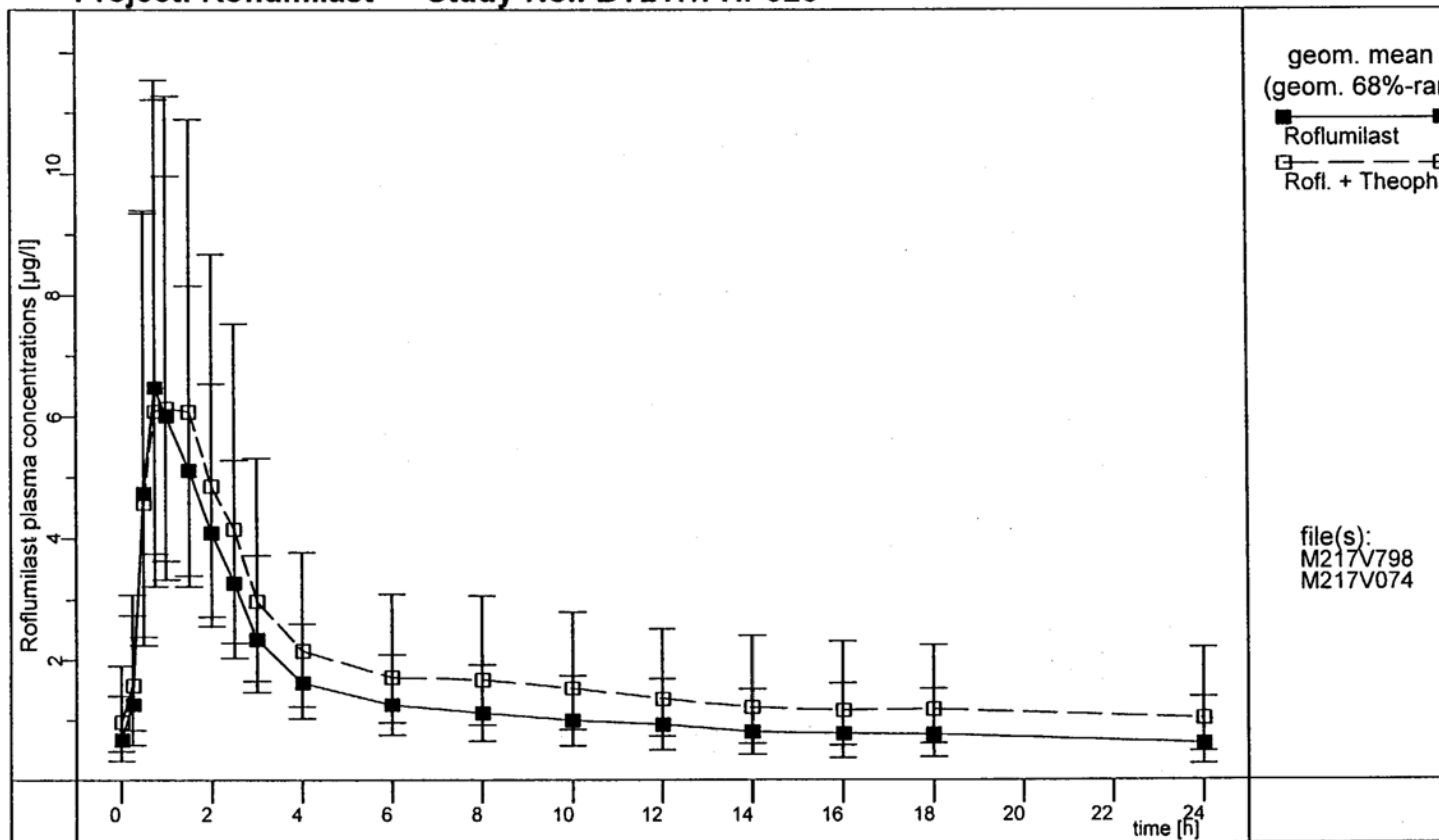
Figure 6: Geom. mean roflumilast plasma concentrations in healthy male and female subjects following multiple once daily oral doses of 500 μg roflumilast alone or in combination with multiple twice-daily oral doses of theophylline (2 X 375 mg), linear scale

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Table 7: Summary of pharmacokinetic characteristics of roflumilast and roflumilast N-oxide in healthy male and female subjects following once-daily oral doses of 500 μg roflumilast alone or in combination with twice-daily oral doses of 375 mg theophylline [geometric mean (68% range); t_{max}: median (min/max)].

Pharmacokinetic Characteristics	Roflumilast		Roflumilast N-oxide	
	(Roflumilast period, reference)	(Theophylline-roflumilast period, test)	(Roflumilast period, reference)	(Theoph. Roflumilast period, test)
$AUC_{[0-24h]}$ [μg/lxh]	33.7 (20.8, 54.5)	44.3 (25.1, 78.2)	401.7 (278.9, 578.5)	433.3 (303.4, 618.6)
C_{max} [μg/l]	7.00 (4.29, 11.43)	7.39 (3.99, 13.68)	24.06 (16.64, 34.78)	24.36 (17.62, 33.68)
t_{max} [h]	0.75 (0.50, 2.50)	0.75 (0.50, 2.00)	2.25 (1.50, 10.00)	2.00 (1.50, 4.00)
PTF [%]	443.59 (279.50, 704.01)	341.99 (228.05, 512.87)	65.08 (43.49, 97.40)	52.91 (38.88, 72.00)
$t_{1/2}$ [h]	17.60 (11.09, 27.92)	17.19 (12.29, 24.04)	26.09 (19.90, 34.21)	19.11 (13.76, 26.54)

Table 8: Point estimates and 90%-confidence limits for the test/reference ratios of roflumilast and roflumilast N-oxide $AUC_{(0-24h)}$ and %PTF values following multiple 500 μg once-daily doses of roflumilast alone (reference, study days 5 and 6) or in combination with 375 mg multiple twice-daily doses of theophylline (test, study days 10 and 11).

Pharmacokinetic Characteristics	Roflumilast		Roflumilast N-oxide	
	Point estimate	90% confidence limit	Point estimate	90% confidence limit
$AUC_{(0-24h)}$	1.28	1.09 – 1.51	1.07	0.98 – 1.16
%PTF	0.78	0.66 – 0.92	0.82	0.73 – 0.91

Conclusions: For theophylline, the AUC(0-24h) and Cmax were not influenced by concomitant treatment of roflumilast. Roflumilast N-oxide was not significantly influenced by concomitant theophylline treatment. AUC of roflumilast was 28% highter after co-administration of theophylline.

CP-060

Study Title: Pharmacokinetic and clinical safety drug-drug interaction study between roflumilast 500 μg repeated oral dose and montelukast 10 mg single oral dose alone and repeated dose with roflumilast in healthy male subjects. Open three fixed period study

Objectives: Primary objectives:
• To investigate the effects of steady-state roflumilast (500 μg p.o.) co-administration on the single-dose pharmacokinetics of montelukast (10 mg p.o.)

• To investigate the effects of steady-state montelukast (10 mg p.o.) co-administration on the steady-state pharmacokinetics of roflumilast (500 µg p.o.)
Secondary objectives:
• To assess the effects of steady-state roflumilast (500 µg p.o.) co-administration on the safety and tolerability of montelukast following a single oral dose of montelukast (10 mg)
• To assess the effects of steady-state montelukast (10 mg p.o.) co-administration on the safety and tolerability of steady-state roflumilast (500 µg p.o.)

Study Design: This study was conducted according to an open, non-randomized, three- period, one sequence design. It consisted of a screening examination, Period 1 (2 days) with single-dose montelukast (10 mg p.o. on Day 1), Period 2 (12 days) with repeated once-daily doses of roflumilast (500 µg p.o. on Days 3-14), Period 3 (9 days) with repeated doses of montelukast (10 mg p.o.) co-administered once-daily with roflumilast (500 µg p.o. on Days 15-22), and a post-study examination (on Day 23).
Repeated once-daily doses of 500 µg roflumilast were administered for a total of 20 days within Periods 2 and 3 (on Days 3-22), while repeated once-daily doses of 10 mg montelukast were administered for a total of 8 days in Period 3 (on Days 15-22).
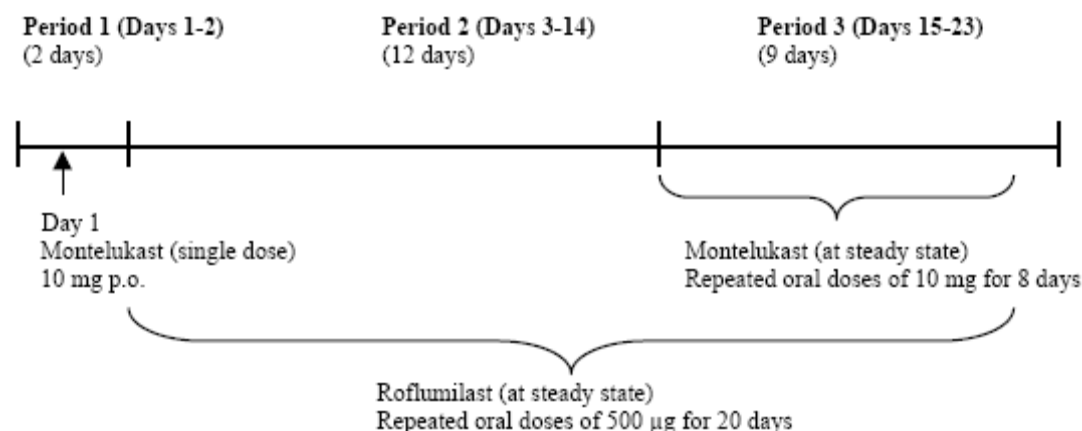
The evaluation of the pharmacokinetic parameter estimates of montelukast, roflumilast and roflumilast N-oxide were based on their plasma levels determined at the following time points: at pre-dose, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 16 h and 24 h after oral administration of study medication.
The 24 h pharmacokinetic measurements were made on the days indicated below:
 Study Day 1: after a single oral dose of 10 mg montelukast administered alone
 Study Day 14: after daily oral doses of 500 µg roflumilast administered alone for 12 days (steady-state)
 Study Day 15: after oral co-administration of single-dose montelukast (10 mg) and steady-state roflumilast (500 µg)
 Study Day 22: after 8 days oral co-administration of 10 mg montelukast (steady-state) and 500 µg roflumilast (steady-state)

Trough values were determined on Study Days 12, 13, 14 (Period 2) for roflumilast and roflumilast N-oxide as well as on Study Days 20, 21, 22 (Period 3) for montelukast, roflumilast, and roflumilast N-oxide.

Study Population: A total of 24 male subjects were enrolled and treated in the study. All subjects were of Caucasian origin. Median [min, max] value for age was 26 [18-44] years, for body weight was 78 [62-97] kg, and for height was 182 [170-192] cm.

Data Analysis: The primary pharmacokinetic parameter estimates (AUC, Cmax, 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 least-squares means (LSM). Each pharmacokinetic parameter estimate was log-transformed prior to analysis and a 90% CI was computed for the difference (Test-Reference) between the LSMs. Point estimates and confidence limits were then exponentiated resulting in approximate 90% CIs in the original scale for the ratios of geometric means. Percentage ratios of geometric means for AUC, Cmax, and CL/F of montelukast, roflumilast, and roflumilast N-oxide of the respective Test/Reference were calculated as stated above.

Results: Plasma concentrations of montelukast were determined by using a validated High Performance Liquid Chromatography (HPLC) assay with fluorescence detection. The limit of quantitation in plasma (LLOQ) was 5 ng/mL for montelukast using a sample volume of 0.2 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. Roflumilast standard curves were valid up to 20 ng/mL and roflumilast N-oxide standard curves were valid up to 40 ng/mL. The LLOQ was 0.10 ng/mL using a sample volume of 0.4 mL.

Figure 3: Geom. mean montelukast plasma concentrations (semilog. scale) following oral administration of 10 mg montelukast alone (Reference) and in combination with 500 µg roflumilast at steady state
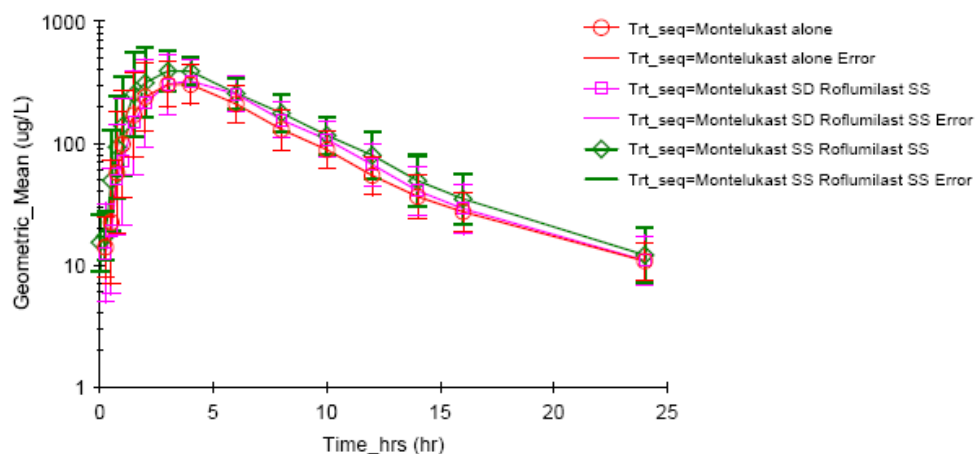
Data source: Section 15.2.1.1; geometric mean displayed with error bars (68% range); SD = single dose, SS = steady state

Pharmacokinetic parameter estimates of montelukast after single oral dose of 10 mg administered alone (montelukast Reference) and together with 500 µg roflumilast at steady state (montelukast Test); geometric means, 68%-range

Parameter	Montelukast (N=24)	
	SD alone (Day 1)	SD with steady-state roflumilast (Day 15)
AUC	2499.721*	2733.523*
(hr*µg/L)	1800.707, 3470.085	1971.099, 3790.854
CL/F	4.000	3.658
(L/hr)	2.881, 5.553	2.638, 5.073
C_{max}	347.481	376.202
(µg/L)	233.857, 516.311	257.013, 550.665

*$AUC_{(0-\infty)}$; ** AUC_{tau}
SD = single dose; SS = steady state

Point estimates and 90%-confidence interval for the Test/Reference ratios of the primary pharmacokinetic parameter estimates for montelukast after single oral dose of 10 mg montelukast alone (Reference) and together with once-daily doses of 500 µg roflumilast (Test)

Montelukast SD alone (Reference, N=24)	Montelukast SD, Roflumilast SS (Test, N=24)	
	Ratio (% Ref)	90% CI
AUC	109.353	94.598, 126.410
CL/F	91.447	79.108, 105.711
C_{max}	108.266	91.401, 128.242

SD = single dose; SS = steady state

Figure 5: Geom. mean roflumilast plasma concentrations (semilog. scale) following multiple once-daily oral doses of 500 µg roflumilast alone or in combination with steady-state 10 mg montelukast.

Analyte=Roflumilast
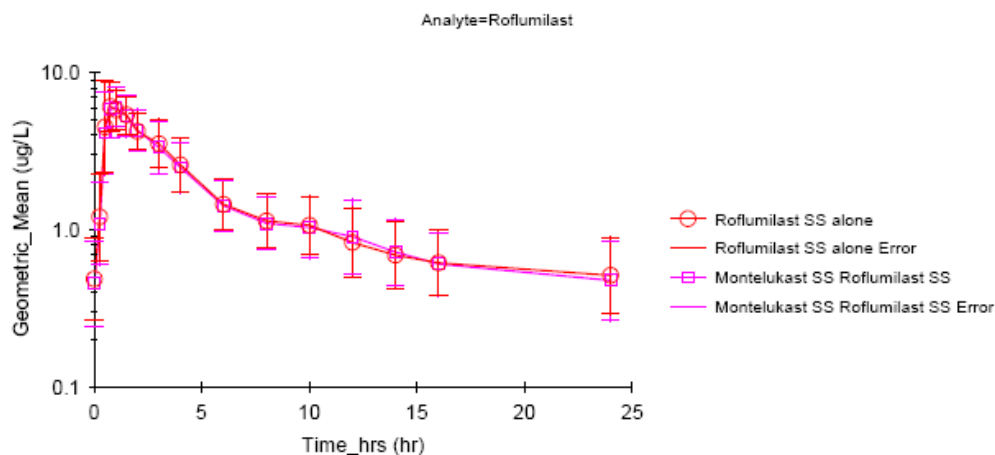
Data source: Section 15.2.1.2; geometric mean displayed with error bars (68% range); SS = steady state

Figure 7: Geom. mean roflumilast N-oxide plasma concentrations (semilog. scale) following multiple once-daily oral doses of 500 µg roflumilast administered alone or in combination with steady-state 10 mg montelukast.

Analyte=Rofl. N oxid
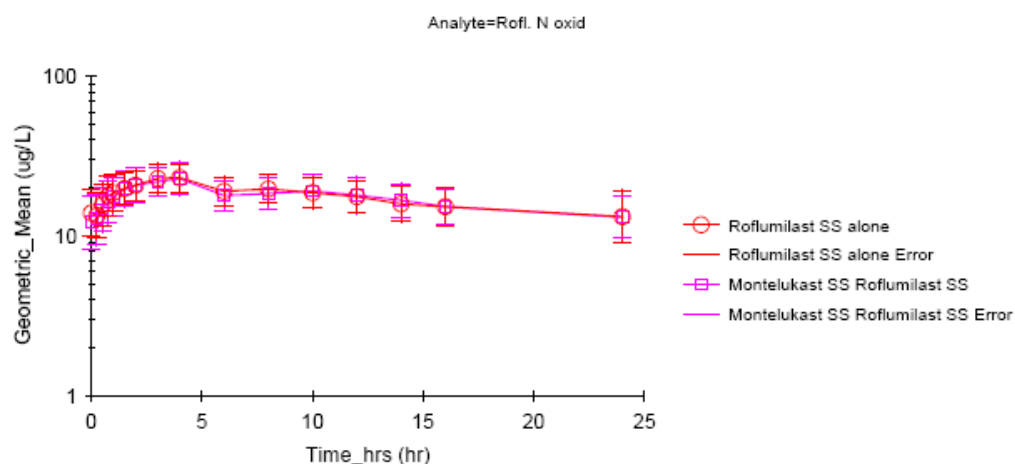
Data source: Section 15.2.1.3; geometric mean displayed with error bars (68% range); SS = steady state

Pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide after steady-state administration of 500 µg roflumilast alone (roflumilast/roflumilast N-oxide Reference) and with concomitant steady-state montelukast treatment (10 mg/day, Test)
geometric means, 68%-range

	Roflumilast (N=24)		Roflumilast N-oxide (N=24)	
	Roflu SS alone	Roflu SS with montelukast SS	Roflu SS alone	Roflu SS with montelukast SS
AUC_{last}	35.216	34.524	417.205	412.004
(hr*µg/L)	26.037, 47.632	25.448, 46.836	328.513, 529.841	324.418, 523.236
CLss_F	14.198	14.483	NA	NA
(L/hr)	10.502, 19.194	10.675, 19.650	NA	NA
C_{max}	7.29	6.973	23.767	23.463
(µg/L)	5.336, 9.959	5.223, 9.310	19.420, 29.087	18.624, 29.560

CLss_F: apparent oral clearance at steady state; Roflu SS = roflumilast at steady state

NA = not applicable

Point estimates and 90%-confidence interval for the Test/Reference ratios of the primary pharmacokinetic parameter estimates for roflumilast and roflumilast N-oxide after steady-state administration of 500 µg roflumilast alone (Reference) and together with steady-state montelukast treatment (10 mg/day, Test)

	Roflumilast (N=24)		Roflumilast N-oxide (N=24)	
	Ratio (% Ref)	90% CI	Ratio (% Ref)	90% CI
Test: montelukast SS, roflumilast SS; Reference: roflumilast SS alone				
AUC_{last}	98.035	84.632, 113.560	98.753	87.952, 110.881
CLss_F	102.005	88.059, 118.159	NA	NA
C_{max}	95.646	82.681, 110.644	98.720	88.875, 109.654

SS = steady state; CLss_F: apparent oral clearance at steady state; NA = not applicable

Conclusions: The pharmacokinetic parameter estimates CL/F, AUC, and Cmax indicate that multiple oral administration of 10 mg montelukast do not alter the steady-state pharmacokinetics of roflumilast (500 µg) and roflumilast N-oxide. In contrast, steady-state roflumilast co-administration results in a clinically insignificant increase (9%) in the single dose AUC of montelukast. This is reflected by a 9% decrease in montelukast apparent clearance.

CP-029

Study Title: Potential influence of roflumilast on pharmacodynamics and pharmacokinetics of R- and S-warfarin and vice versa in healthy male subjects - a double-blind, placebo controlled, randomized, crossover study.

Objectives: Primary: Influence of steady-state roflumilast on the pharmacodynamics of warfarin [Prothrombin Time (PT) and coagulation factor VII clotting activity].
Secondary: Influence of steady-state roflumilast on the pharmacokinetics of R- and S-warfarin. Influence of single-dose warfarin on the pharmacokinetics of roflumilast and roflumilast-N-oxide at steady state. Safety and tolerability.

Study Design: The study was conducted according to a double-blind, placebo-controlled, randomized, crossover design.

The study medication consisted of:
Treatment A: 500 µg (tablet) roflumilast on Days 1 to 12, and 25 mg warfarin sodium on Day 8 (Phases 2 or 3).
Treatment B: Placebo (tablet) on Days 1 to 12, and 25 mg warfarin sodium on Day 8 (Phases 2 or 3).
Treatment C: 25 mg warfarin sodium on Day -14 of the first study period ("Priming" period).

Study Population: A total of 24 male subjects were enrolled and treated in the study and 21 subjects completed the study.

Table 2: **Mean values and ranges (in brackets)of the demographic variables.**

All subjects who	n	Age (years)	Height (cm)	Weight (kg)	Broca Index
Entered	24	25.9 (19 – 45)	181.6 (169 – 198)	78.4 (65 – 106)	0.96 (0.85 – 1.10)
Completed	21	26.6 (19 – 45)	181.4 (169 – 198)	77.3 (65 – 106)	0.95 (0.85 – 1.10)

Data Analysis: R- and S-warfarin, roflumilast, and roflumilast N-oxide steady state concentration were analyzed using a non-compartmental approach. To compare pharmacokinetics between treatments, the logarithms of the applicable characteristics were analyzed using an analysis of variance (ANOVA) including sequence, subject (sequence), period and treatment effects. Based on these analyses, point estimates (LS-Means) and confirmatory two-sided 90% confidence intervals for the ratio "roflumilast + warfarin" / "placebo + warfarin" were calculated by re-transformation of the logarithmic data using the intra-individual standard deviation of the ANOVA.

Results: The concentration-time profiles and statistical analysis of roflumilast, roflumilast N-oxide, and warfarin are shown in the following figures and tables.

Figure 7: Combined graph of individual S-warfarin plasma concentrations for the warfarin + placebo treatment group

BY217/CP – 029
Plasma S – warfarin concentrations
Warfarin + Placebo
n = 21
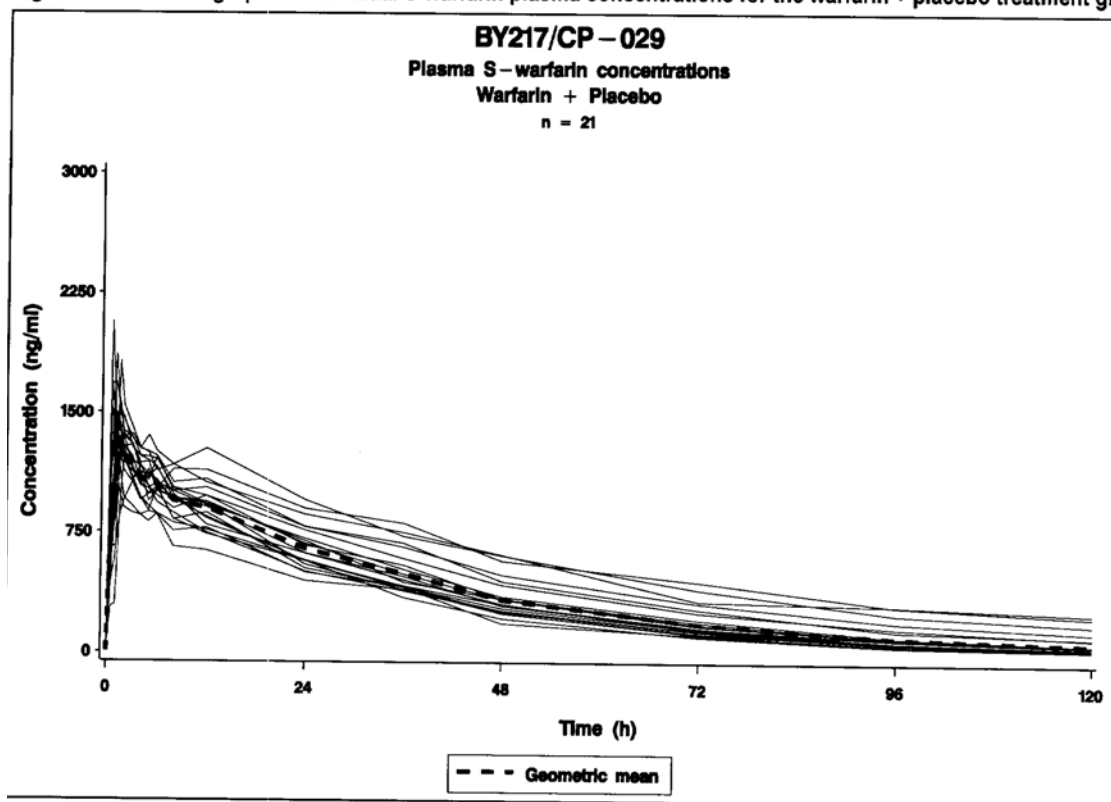
Figure 8: Combined graph of individual S-warfarin plasma concentrations for the warfarin + roflumilast treatment group

BY217/CP – 029
Plasma S – warfarin concentrations
Warfarin + Roflumilast
n = 21

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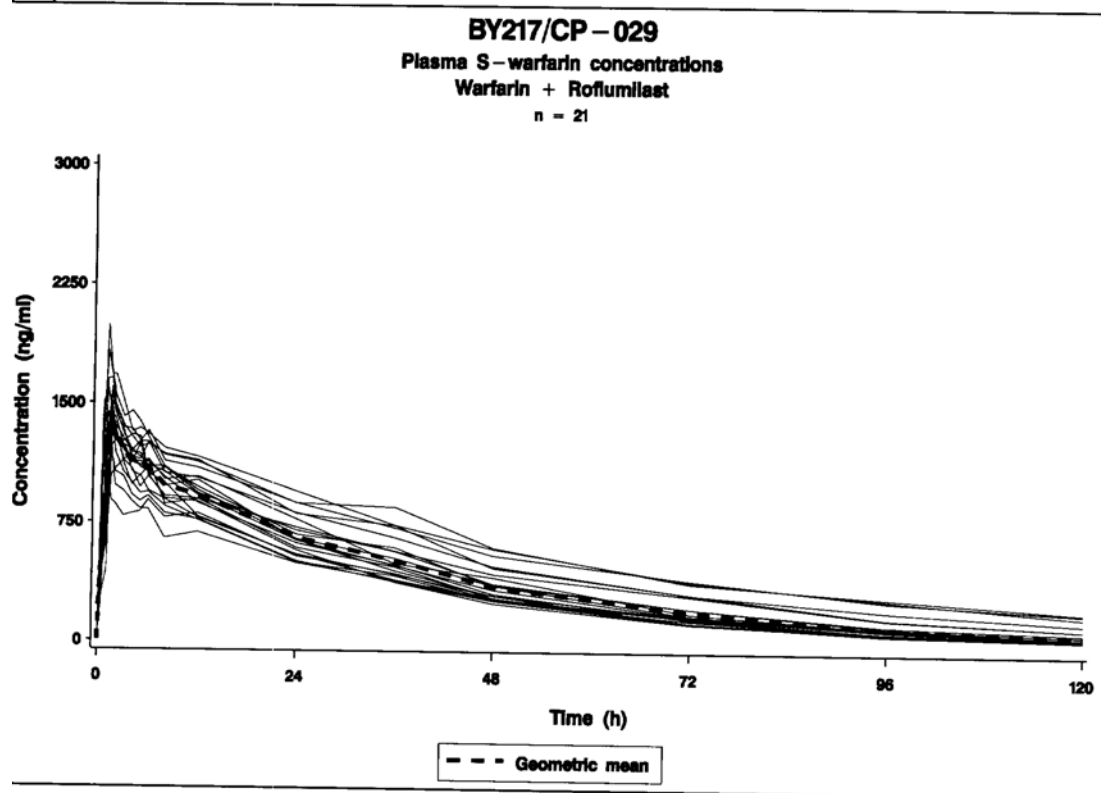
Table 3: Summary of pharmacokinetic characteristics of R-warfarin and S-warfarin after a single dose of 25 mg warfarin sodium of Day 8 [geometric mean, (68% range); t_{max}: median (min/max)].

Pharmacokinetic variable	Unit	R-warfarin		S-warfarin	
		Warfarin + Placebo	Warfarin + Roflumilast	Warfarin + Placebo	Warfarin + Roflumilast
AUC(0-t_{last})	(μg*h/l)	66138.6 (50799.5, 93222.2)	68224.0 (58442.5, 79642.7)	45679.0 (35736.2, 58388.1)	47200.9 (37483.2, 59438.0)
AUC(0-∞)	(μg*h/l)	78897.2 (63982.6, 97288.4)	80812.6 (66481.0, 98233.7)	49339.1 (36808.5, 66135.4)	50859.6 (38884.0, 66523.6)
C_{max}	(μg/l)	1439.9 (1254.2, 1653.0)	1457.7 (1290.0, 1647.1)	1450.1 (1227.8, 1712.7)	1453.0 (1259.2, 1676.7)
t_{max}	(h)	1.5 (0.5, 6.0)	1.5 (0.5, 12.0)	1.5 (0.5, 3.0)	1.5 (0.5, 4.0)
$t_{\frac{1}{2}}$	(h)	43.4 (37.1, 50.7)	43.0 (37.0, 50.0)	29.9 (24.4, 36.6)	30.0 (24.7, 36.3)

A summary of the statistical evaluation is given in Table 4, ... the effect ...

Table 4: Point estimate and 90%-confidence limits for the Test/Reference ratios of R- and S-warfarin AUC(0-t_{last}), AUC(0-∞) and C_{max} values.

Pharmacokinetic variable	Unit	R-warfarin		S-warfarin	
		Point estimate	90% confidence interval	Point estimate	90% confidence interval
AUC(0-t_{last})	(μg*h/l)	1.031	101.4% - 104.9%	1.033	101.5% - 105.1%
AUC(0-∞)	(μg*h/l)	1.024	99.9% - 105.0%	1.030	100.9% - 105.1%
C_{max}	(μg/l)	1.012	97.1% - 105.5%	1.001	94.9% - 105.6%

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Figure 9: Combined graph of individual roflumilast plasma concentrations on Day 7

BY217/CP – 029
Plasma roflumilast concentrations
Day 7
n = 21
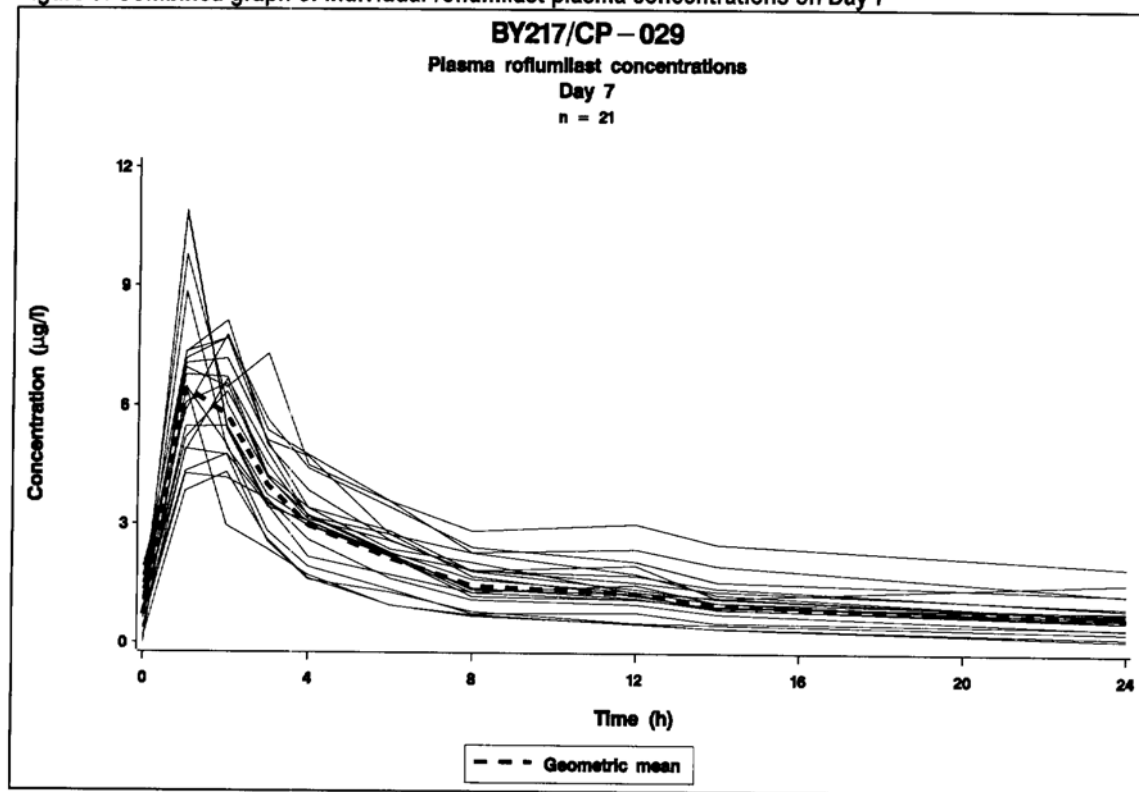
Figure 10:   Combined graph of individual roflumilast plasma concentrations on Day 8

BY217/CP – 029
Plasma roflumilast concentrations
Day 8
n = 21

210
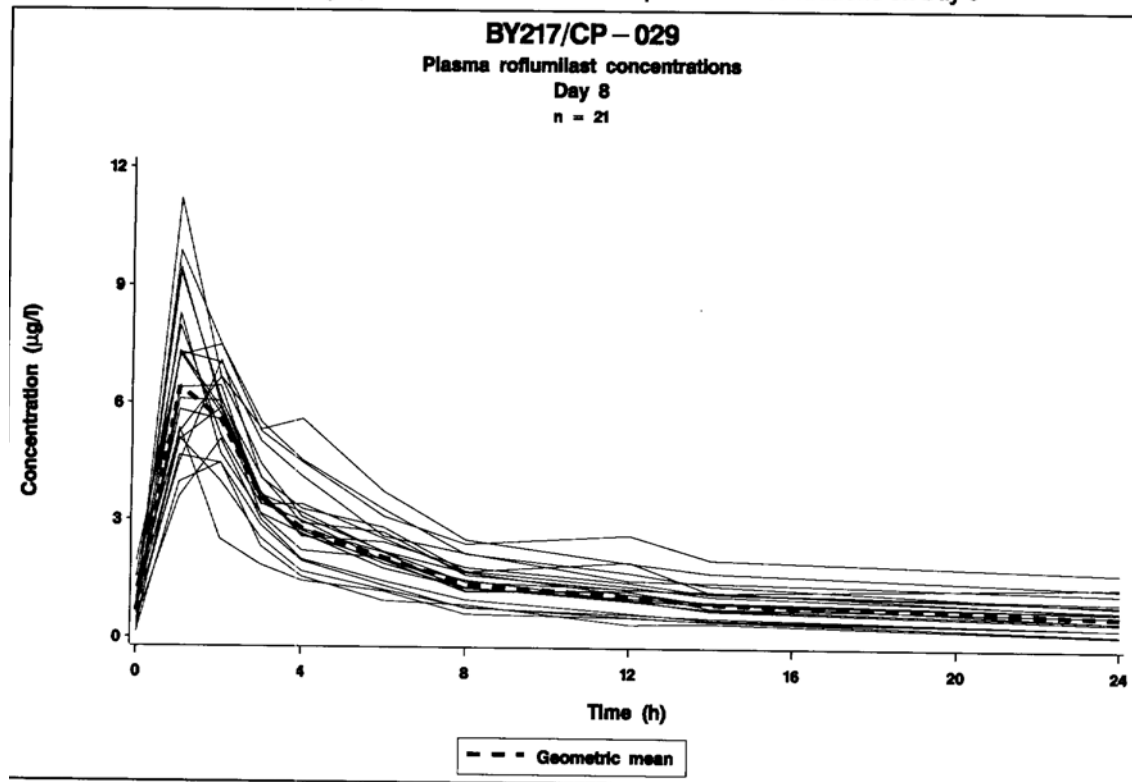
Figure 11:   Combined graph of individual roflumilast-N-oxide plasma concentrations on Day 7

BY217/CP – 029
Plasma roflumilast – N – oxide concentrations
Day 7
n = 21

– – – Geometric mean
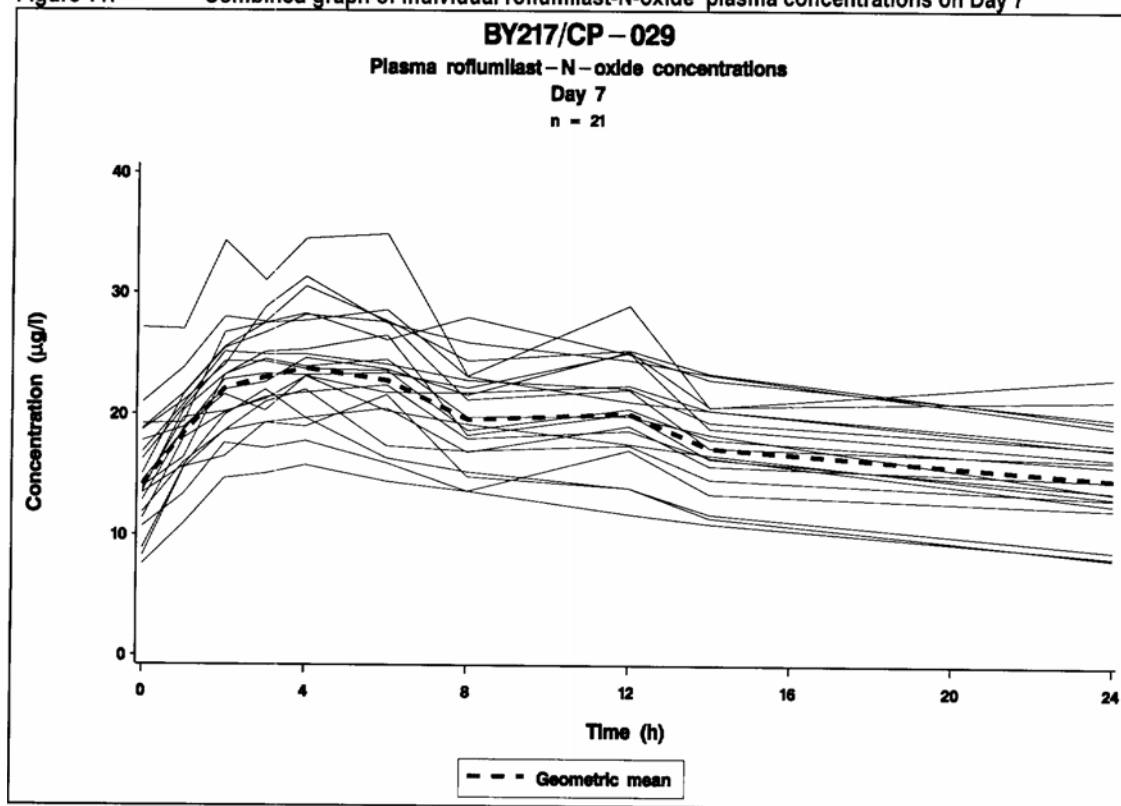
Figure 12:   Combined graph of individual roflumilast-N-oxide plasma concentrations on Day 8
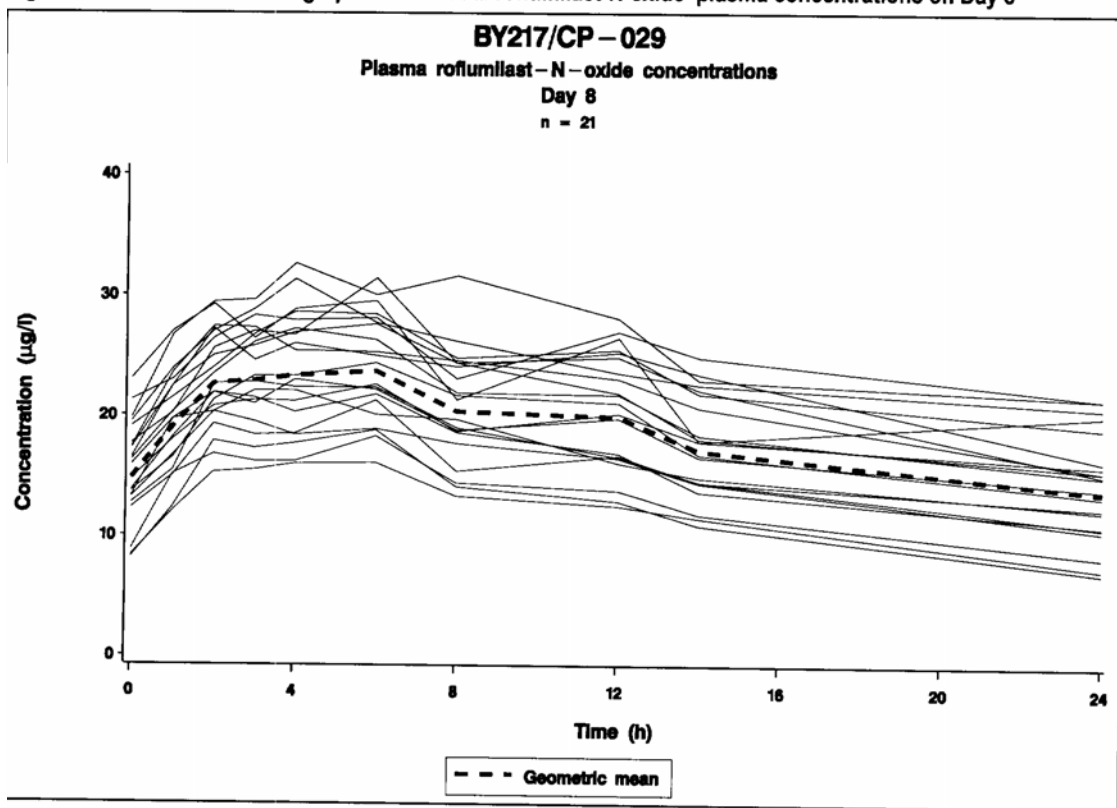
BY217/CP – 029
Plasma roflumilast – N – oxide concentrations
Day 8
n = 21

– – – Geometric mean

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Table 5: Summary of pharmacokinetic characteristics of roflumilast and its metabolite roflumilast-N-oxide in healthy male volunteers following the 7th (Reference) and the 8th (Test) of multiple once-daily oral doses of 500 μg roflumilast [geometric mean, (68% range); t_{max}: median (min/max)].

Pharmacokinetic variable	Unit	Roflumilast		Roflumilast-N-oxide	
		Roflumilast (Day 7)	Roflumilast + Warfarin (Day 8)	Roflumilast (Day 7)	Roflumilast + Warfarin (Day 8)
AUC(0-24h)	(μg*h/l)	42.9 (30.6, 60.0)	40.6 (28.8, 57.1)	449.9 (363.1, 557.4)	447.9 (354.5, 565.8)
C_{max}	(μg/l)	6.86 (5.25, 8.97)	6.84 (5.30, 8.81)	24.36 (20.20, 29.38)	24.46 (20.14, 29.71)
t_{max}	(h)	2.00 (1.00, 3.00)	1.00 (1.00, 2.00)	4.00 (2.00, 12.00)	4.00 (2.00, 6.00)
$t_{\frac{1}{2}}$	(h)	13.03 (8.82, 19.26)	16.03 (9.93, 25.89)	29.45 (21.91, 39.59)	24.89 (16.88, 36.70)

Table 6: Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast and roflumilast-N-oxide AUC(0-24h) values following the 7th (Reference) and the 8th (Test) of multiple once-daily oral doses of 500 μg roflumilast.

Pharmacokinetic variable	Unit	Roflumilast		Roflumilast-N-oxide	
		Point estimate	90% confidence interval	Point estimate	90% confidence interval
AUC(0-24h)	(μg*h/l)	0.95	0.92 – 0.97	1.00	0.97 - 1.02
C_{max}	(μg/l)	1.00	0.91 – 1.09	1.00	0.96 – 1.05

Conclusions: No pharmacokinetic interaction of roflumilast with racemic warfarin was observed in the healthy volunteers in this study. No significant influence on the pharmacokinetic parameters was found for roflumilast and its metabolite roflumilast N-oxide by concomitant warfarin treatment.

CP-070

Study Title: Cardiovascular pharmacodynamic and pharmacokinetic drug-drug interaction study between single oral doses of 500 μg roflumilast and 100 mg sildenafil in healthy male volunteers.

Objectives: The aim of the study was to assess the cardiovascular pharmacodynamic (blood pressure [BP] and pulse rate, electrocardiogram [ECG] and impedance cardiography [ZCG]) interaction between single oral doses of 500 μg roflumilast and 100 mg sildenafil relative to placebo.
Further objectives were to assess the pharmacokinetic (PK) interaction between single oral doses of 500 μg roflumilast and 100 mg sildenafil relative to placebo. In addition, safety and tolerability of single and combined oral doses of 500 μg roflumilast and 100 mg sildenafil relative to placebo in healthy male volunteers were assessed.

Study Design: The study was conducted according to a single-center, single-dose, double-blind, placebo- and active-controlled double-dummy, within-subject, 4-period change-over design with randomly assigned, period-balanced treatment sequences. The study consisted of a screening examination including laboratory tests, drug screening, and alcohol blood test (within 21 to 2 days before Day 1), 4 study periods of 7 days each with a washout interval between periods of at least 7 days (with administration of study medication on Day 1 of each period), and a post-study examination performed within 6 to 14 days after the last intake of study medication.

Healthy male subjects were randomly assigned to a treatment sequence and received the following treatments:

• Treatment A: 500 μg roflumilast and 100 mg sildenafil once daily (s.i.d.);
• Treatment B: 500 μg roflumilast and placebo s.i.d.;
• Treatment C: placebo and 100 mg sildenafil s.i.d.;
• Treatment D: placebo and placebo s.i.d.

Supine BP and pulse rate were measured on baseline (Day -1) and treatment (Day 1) days at pre-dose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h after dosing as well as on screening and post-study examination. In addition, BP and pulse rate after 1 min relaxed upright standing were taken on baseline (Day -1) and treatment (Day 1) days at pre-dose, 1.0, 2.0, 4.0, 6.0 and 8.0 h after dosing, on screening and post-study examination. Eight-hour profiles of supine ZCG were performed on Day −1 and Day 1 of each treatment. Signals were recorded at the following 12 time points: pre-dose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h after morning administration on the profile days and on screening and post-study examination. Supine ECG on baseline (Day −1) and treatment (Day 1) days was recorded at pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h after dosing and on screening and poststudy examination. The assessment of the ZCG and ECG profiles was performed by an external center (ACPS – Applied Clinical Pharmacology Services).

Blood samplings for PK measurements were performed on Test Day 1 at pre-dose, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0 and 96.0 h after dosing. The plasma concentrations of roflumilast, roflumilast N-oxide, sildenafil and N-desmethyl sildenafil were determined using high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS). The lower limits of quantification were 0.1 μg/L for roflumilast and roflumilast N-oxide and 1 μg/L for sildenafil and N-desmethyl sildenafil.

Study Population: A total of 12 healthy Caucasian male subjects were evaluated.

T-Table 10:   Demographic characteristics of the study population

Characteristic	Safety set (N = 12)
Age [years]	
mean ± SD	29 ± 6
median (min, max)	27 (22, 40)
Age group, n (%)	
18 to ≤25 years	4 (33.3%)
25 to ≤35 years	6 (50.0%)
>35 to ≤45 years	2 (16.7%)
Height [cm]	
mean ± SD	182 ± 8
median (min, max)	180 (174, 202)
Weight [kg]	
mean ± SD	81 ± 12
median (min, max)	79 (65, 114)
Body Mass Index [kg/m^2]	
mean ± SD	24 ± 2
median (min, max)	25 (19, 28)
Smoking status, n (%)	
Non-smokers	10 (83.3%)
Current Smokers	2 (16.7%)
Gender, n (%)	
Male	12 (100%)
Race, n (%)	
White	12 (100%)

N = number of subjects in analysis set, n = number of subjects in respective category, SD = standard deviation

Data source: Table 15.1.2.1 and Table 15.1.2.3

Data Analysis: All pharmacodynamic values entering the analyses were adjusted for time of day and for Day -1. All analyses were carried out calculating different summary measures that summarized the values of one subject and one treatment over clock-time of treatment day. The most prominent summary measure was the excess area under the curve (eAUC). Furthermore, minimum and maximum and AUC were calculated.

Estimation of PK parameter estimates were based on the actual time and calculated by a non-compartmental analysis (NCA) using WinNonlin. The primary PK variables were analyzed using an analysis of variance (ANOVA). Point estimates expressed as percentage (%) of the reference and their 90% confidence interval (CI) were computed for the test/reference ratio. The secondary pharmacodynamic and PK variables were analyzed descriptively, including summary statistics (e.g. geometric mean,
arithmetic mean, standard deviation, minimum, median, maximum).

Results: The assay performance of all the analytes are shown in the following two tables.

T-Table 4: **Analysis of roflumilast and roflumilast N-oxide in human plasma: Description of methods and assay performance**

Method Description

Matrix	Plasma
Type of method	Validated high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) detection [Ref. 6]
Validation report	73/2001 and 188/2007
Department or CRO	Department of Bioanalytics
Deviations from validated method	None
Sample volume	200 µL
Internal standards	BYK199199 (D$_5$-roflumilast)
	BYK199244 (D$_5$-roflumilast N-oxide)

Study Assay Performance

Analyte	Calibration Range		Quality Control (QC) Samples	
	Lower Limit (LLOQ)	Upper Limit (ULOQ)	Inter-day Precision (%CV)	Inter-day Accuracy (%)
Roflumilast	0.1 µg/L	50 µg/L	5.06 to 7.07	97.7 to 102.4
Roflumilast N-oxide	0.1 µg/L	50 µg/L	3.94 to 5.89	96.5 to 104.8

CV = coefficient of variation, LLOQ = lower limit of quantification, ULOQ = upper limit of quantification.
Data source: Section 15.2.7.1 (Analytical Report Plasma Concentrations)

T-Table 5: Analysis of sildenafil and N-desmethyl sildenafil in human plasma: Description of methods and assay performance

Method Description

Matrix	Plasma
Type of method	Validated high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) detection
Validation report	None
Department or CRO	(b) (4)
Deviations from validated method	Not provided
Sample volume	Not provided
Internal standards	D_8-sildenafil
	D_8-N-desmethyl sildenafil

Study Assay Performance

Analyte	Calibration Range		Quality Control (QC) Samples	
	Lower Limit (LLOQ)	Upper Limit (ULOQ)	Inter-day Precision (%CV)	Inter-day Accuracy (%)
Sildenafil	1 µg/L	500 µg/L	1.7 to 7.3	98.0 to 101.3
N-Desmethyl Sildenafil	1 µg/L	500 µg/L	3.3 to 8.5	100 to 101.3

CV = coefficient of variation, LLOQ = lower limit of quantification, ULOQ = upper limit of quantification.
Data source: Section 15.2.7.2 (Analytical Report Plasma Concentrations)

Pharmacodynamic assessment

Drug effects on heart rate and blood pressure are shown in the following table.

contrast	RS-PL			R-PL			S-PL		
summary value	MAX	MIN	AV	MAX	MIN	AV	MAX	MIN	AV
HR (ECG-derived)	(+)	0	(+)	(−)	(−)	(−)	0	−	(−)
HR (ZCG-derived)	(+)	0	0	(−)	0	(−)	0	(−)	(−)
SBP (oscillometric)	0	0	0	(+)	0	0	(−)	−	−
DBP (oscillometric)	0	(−)	(−)	(+)	0	0	0	−	(−)
MBP (oscillometric)	0	(−)	(−)	(+)	0	0	(−)	−	(−)

contrast	RS-R			RS-S		
summary value	MAX	MIN	AV	MAX	MIN	AV
HR (ECG-derived)	+	+	+	(+)	+	+
HR (ZCG-derived)	+	0	(+)	+	(+)	+
SBP (oscillometric)	(−)	(−)	(−)	(+)	(+)	(+)
DBP (oscillometric)	(−)	(−)	(−)	0	(+)	0
MBP (oscillometric)	(−)	(−)	(−)	(+)	(+)	0

0: no difference; +: statistically significant increase; −: statistically significant decrease; (+): trend towards and increase; (−): trend towards a decrease

Drug effects on ZCG/STI-criteria are shown in the following table.

contrast	RS-PL			R-PL			S-PL		
summary value	MAX	MIN	AV	MAX	MIN	AV	MAX	MIN	AV
PEP	−	(−)	(−)	0	(+)	0	0	0	0
VET	0	(−)	(−)	0	0	0	0	0	0
QS2	−	−	−	0	0	0	0	0	0
dZ/dt$_{max}$	+	(+)	(+)	0	0	0	(+)	0	0
CO	+	(+)	(+)	0	(−)	(−)	0	0	0
TPR (oscillometric BP)	0	0	0	+*	(+)*	+*	0	0	0

*: confounded by an unusually high mean BL on D-1

contrast	RS-R			RS-S		
summary value	MAX	MIN	AV	MAX	MIN	AV
PEP	−	−	−	−	(−)	−
VET	0	(−)	(−)	(−)	(−)	−
QS2	(−)	−	−	−	−	−
dZ/dt$_{max}$	+	(+)	(+)	(+)	(+)	(+)
CO	+	+	+	+	(+)	+
TPR (oscillometric BP)	(−)	(−)	(−)	0	0	0

0: no difference; +: statistically significant increase; −: statistically significant decrease; (+): trend towards and increase; (−): trend towards a decrease

Drug effects on ECG-criteria are shown in the following table.

contrast	RS-PL			R-PL			S-PL		
summary value	MAX	MIN	AV	MAX	MIN	AV	MAX	MIN	AV
PR	0	0	0	(−)	−	−	0	0	0
QRS	0	0	0	(−)	0	0	0	0	0
QT	0	0	0	0	(+)	0	(+)	(+)	(+)
QTc(F)	(+)	0	0	0	0	0	(+)	(−)	(+)
QTc(B)	(+)	0	(+)	0	(−)	0	(+)	(−)	0
QTc(Fra)	(+)	0	(+)	0	0	0	(+)	(−)	0

contrast	RS-R			RS-S		
summary value	MAX	MIN	AV	MAX	MIN	AV
PR	(+)	(+)	(+)	0	(−)	(−)
QRS	(+)	0	0	0	0	0
QT	0	(−)	(−)	(−)	(−)	(−)
QTc(F)	(+)	0	(+)	0	(+)	0
QTc(B)	(+)	(+)	(+)	0	(+)	(+)
QTc(Fra)	(+)	(+)	(+)	0	(+)	(+)

0: no difference; +: statistically significant increase; -: statistically significant decrease; (+): trend towards and increase; (−): trend towards a decrease

Roflumilast:

Roflumilast mono-therapy had little – if any – cardiovascular effect, the observed trend of smaller time-averaged changes in HR and smaller time-averaged changes in CO were noteworthy but of little relevance since they were quite small. Roflumilast treatment tended to shorten the electrocardiographic PR-interval, but had no effect on the QT and QTc-intervals.

Sildenafil:

Sildenafil mono-therapy tended to lower the time-averaged BP changes from baseline, without reflectory tachycardia; instead, there was a trend towards smaller minimum and average HR changes from baseline relative to placebo. Sildenafil was associated with a larger maximum change and a smaller minimum change in QTc than roflumilast, with little effect on the average time-matched QTc-change from baseline.

Roflumilast & sildenafil combination treatment:

The combination of 500 μg roflumilast & 100 mg sildenafil showed its own distinct cardiovascular HR, BP, ZCG/STI and QT/QTc response pattern, which is not explained by mere additivity of the effects of the mono-therapies (500 μg roflumilast or 100 mg sildenafil). Although there were no relevant differences in the summary measures of the time-matched

changes from baseline for the uncorrected QT of the combination treatment relative to placebo, the maximum and average change from baseline of the HR-corrected QT-intervals tended to be larger for the combination treatment, also relative to the mono-therapies roflumilast and sildenafil.

Pharmacokinetic assessment

Concentration time profiles and statistical analysis for roflumilast, sildenafil and their metabolites are shown below.

T-Figure 1: Roflumilast: Plasma concentration-time profiles (geometric mean, 68%-range) following a single dose of 500 μg roflumilast alone and with a single dose of 100 mg sildenafil (linear plot)
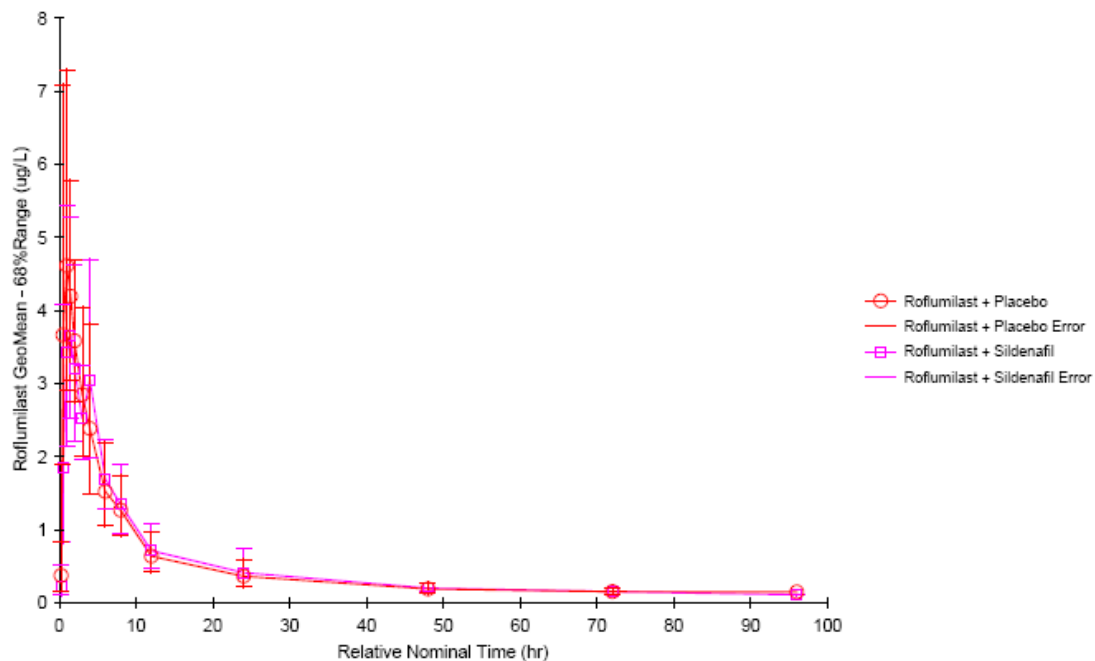
T-Table 13: Roflumilast: Plasma concentration-time profiles (geometric mean, 68%-range, N=12) following a single dose of 500 µg roflumilast alone and with a single dose of 100 mg sildenafil

	Roflumilast			Roflumilast & Sildenafil		
	Geometric Mean	68% Range		Geometric Mean	68% Range	
AUC_{inf} [h·µg/L]	42.3	30.2	59.4	42.2	30.5	58.3
AUC_{last} [h·µg/L]	37.8	27.1	52.7	38.2	27.5	52.9
C_{max} [µg/L]	6.08	4.68	7.91	4.65	3.48	6.21
C_{avg} [µg/L]	1.76	1.26	2.47	1.76	1.27	2.43
$t_{1/2}$ [h]	17.4	8.54	35.6	15.4	8.09	29.4
t_{max}^a [h]	1.03	0.517	4.02	2.03	0.533	4.02
CL/F [L/h]	11.8	8.42	16.6	11.8	8.57	16.4

[a] t_{max} displayed as median and min, max.
Data source: Section 15.2.1.6

T-Table 14: Roflumilast: AUC_{inf}, AUC_{last} and C_{max} ratios (90% CI) following a single dose of 500 µg roflumilast alone (Reference) and with a single dose of 100 mg sildenafil (Test)

	Ref	Test	Ref LSM	Test LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
$Ln(AUC_{inf})$ [h·µg/L]	roflumilast	w/sildenafil	3.75	3.74	99.8	91.6	109
$Ln(AUC_{last})$ [h·µg/L]	roflumilast	w/sildenafil	3.63	3.64	101	94.8	108
$Ln(C_{max})$ [µg/L]	roflumilast	w/sildenafil	1.81	1.54	76.4	66.2	88.3

Ratio = Ratio (Test/Reference) of treatment mean values, expressed as a percentage of Reference mean (100 x Test/Reference). 90% CI = 90% confidence interval estimate, expressed as a percentage of Reference mean (100 x Test/Reference).
Data source: Section 15.2.1.7

For roflumilast, the ratios of AUCinf and AUClast indicated a similar systemic exposure after the application of roflumilast & sildenafil when compared with roflumilast alone (with their 90% CIs entirely included in the equivalence range of 80 to 125%). Cmax ratios indicate a 24% lower peak concentration after the application of roflumilast & sildenafil when compared with roflumilast alone.

For roflumilast N-oxide, the geometric mean (68%-range) plasma concentration-time profiles following a single dose of 500 µg roflumilast alone and with a single dose of 100 mg sildenafil are displayed in T-Figure 2 (linear plot).

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T-Figure 2: Roflumilast N-oxide: Plasma concentration-time profiles (geometric mean, 68%-range) following a single dose of 500 µg roflumilast alone and with a single dose of 100 mg sildenafil (linear plot)
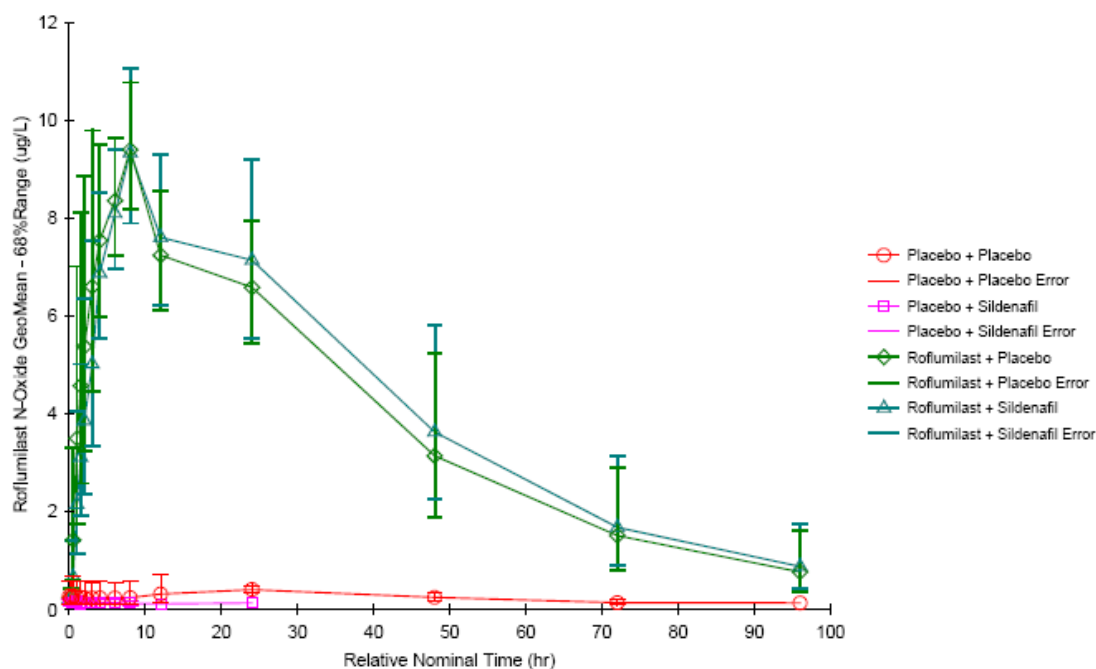
The mean roflumilast N-oxide PK parameter estimates following a single dose of 500 µg roflumilast alone and with a single dose of 100 mg sildenafil are presented in T-Table 15.

T-Table 15: Roflumilast N-oxide: Plasma concentration-time profiles (geometric mean, 68%-range, N=12) following a single dose of 500 µg roflumilast alone and with a single dose of 100 mg sildenafil

	Roflumilast			Roflumilast & Sildenafil		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
AUC_{inf} [h·µg/L]	417	311	559	440	313	618
AUC_{last} [h·µg/L]	380	301	480	401	302	533
C_{max} [µg/L]	9.39	8.19	10.8	9.37	7.92	11.1
C_{avg} [µg/L]	17.4	13.0	23.3	18.3	13.0	25.7
$t_{1/2}$ [h]	24.9	18.1	34.3	23.5	17.6	31.5
t_{max}^{a} [h]	8.03	8.00	8.03	8.03	6.00	8.05

[a] t_{max} displayed as median and min, max.
Data source: Section 15.2.2.6

For roflumilast N-oxide, AUCinf, AUClast and Cmax ratios (90% CI) following a single dose of 500 µg roflumilast alone (Reference) and with a single dose of 100 mg sildenafil (Test) are displayed in T-Table 16.

Roflumilast N-oxide: AUC_{inf}, AUC_{last} and C_{max} ratios (90% CI) following a single dose of 500 μg roflumilast alone (Reference) and with a single dose of 100 mg sildenafil (Test)

	Ref	Test	Ref LSM	Test LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Ln(AUC_{inf}) [h·μg/L]	roflumilast	w/sildenafil	6.03	6.08	105	100	111
Ln(AUC_{last}) [h·μg/L]	roflumilast	w/sildenafil	5.94	5.99	106	99.9	112
Ln(C_{max}) [μg/L]	roflumilast	w/sildenafil	2.24	2.23	99.8	94.8	105

Ratio = Ratio (Test/Reference) of treatment mean values, expressed as a percentage of Reference mean (100 x Test/Reference). 90% CI = 90% confidence interval estimate, expressed as a percentage of Reference mean (100 x Test/Reference).
Data source: Section 15.2.2.7

For sildenafil, the geometric mean (68%-range) plasma concentration-time profiles following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast are displayed in T-Figure 3 (linear plot).

T-Figure 3: Sildenafil: Plasma concentration-time profiles (geometric mean, 68%-range) following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast (linear plot)
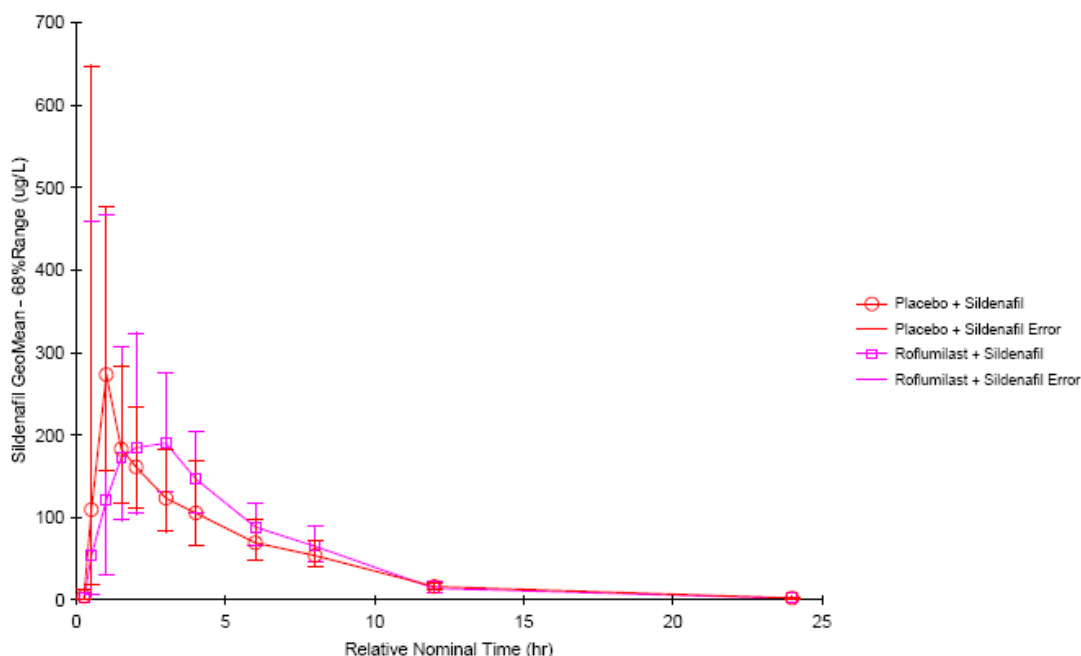
The mean sildenafil PK parameter estimates following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast are presented in T-Table 17.

T-Table 17: Sildenafil: Plasma concentration-time profiles (geometric mean, 68%-range, N=12) following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast

	Sildenafil			Sildenafil & Roflumilast		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
AUC_{inf} [h·µg/L]	1240	968	1590	1340	967	1860
AUC_{last} [h·µg/L]	1220	946	1580	1330	950	1850
C_{max} [µg/L]	337	210	541	294	186	466
C_{avg} [µg/L]	51.7	40.3	66.3	55.9	40.3	77.6
$t_{1/2}$ [h]	3.64	2.93	4.52	2.90	2.43	3.45
t_{max}[a] [h]	1.02	0.517	3.03	2.52	0.50	4.03
CL/F [L/h]	80.6	62.8	103	74.5	53.7	103

[a] t_{max} displayed as median and min, max.
Data source: Section 15.2.3.6

For sildenafil, AUCinf, AUClast and Cmax ratios (90% CI) following a single dose of 100 mg sildenafil alone (Reference) and with a single dose of 500 µg roflumilast (Test) are displayed in T-Table 18.

T-Table 18: Sildenafil: AUC_{inf}, AUC_{last} and C_{max} ratios (90% CI) following a single dose of 100 mg sildenafil alone (Reference) and with a single dose of 500 µg roflumilast (Test)

Dependent	Ref	Test	Ref LSM	Test LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
$Ln(AUC_{inf})$ [h·µg/L]	sildenafil	w/roflumilast	7.12	7.20	108	99.1	118
$Ln(AUC_{last})$ [h·µg/L]	sildenafil	w/roflumilast	7.11	7.19	108	99.0	119
$Ln(C_{max})$ [µg/L]	sildenafil	w/roflumilast	5.82	5.68	87.4	71.9	106

Ratio = Ratio (Test/ Reference) of treatment mean values, expressed as a percentage of Reference mean (100 x Test/Reference). 90% CI = 90% confidence interval estimate, expressed as a percentage of Reference mean (100 x Test/Reference).
Data source: Section 15.2.3.7

T-Figure 4: N-desmethyl sildenafil: Plasma concentration-time profiles (geometric mean, 68%-range) following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast (linear plot)
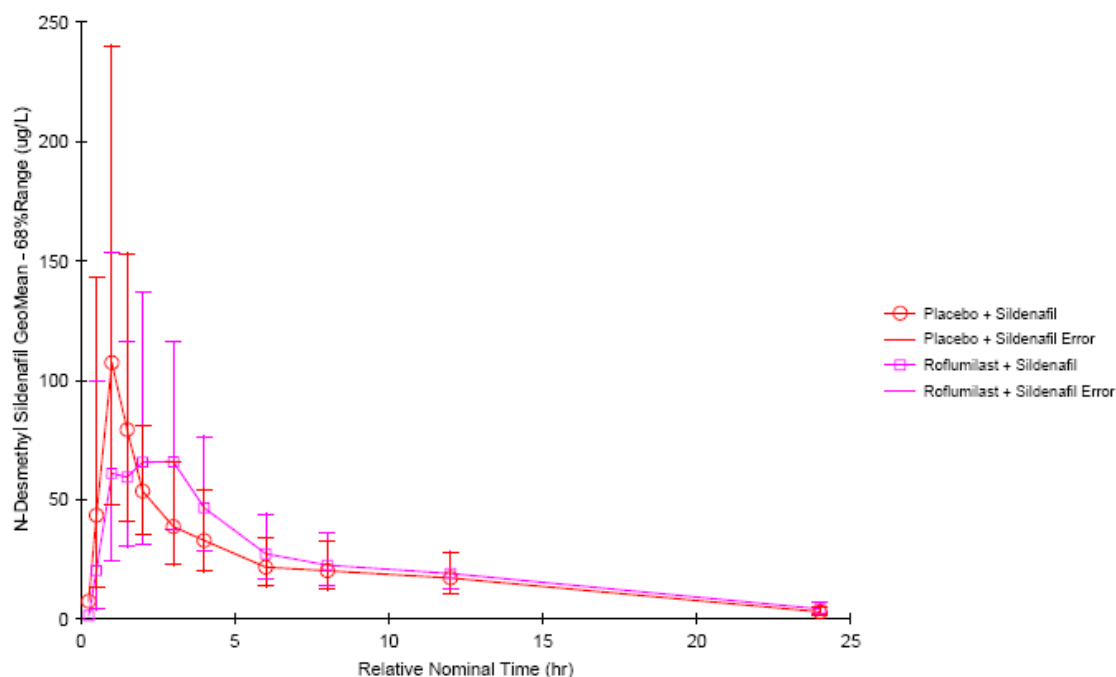
The mean N-desmethyl sildenafil PK parameter estimates following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast are presented in T-Table 19.

T-Table 19: N-desmethyl sildenafil: Plasma concentration-time profiles (geometric mean, 68%-range, N=12) following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast

	Sildenafil			Sildenafil & Roflumilast		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
AUC_{inf} [h·μg/L]	562	377	837	618	399	959
AUC_{last} [h·μg/L]	535	359	799	554	320	961
C_{max} [μg/L]	135	78.6	231	101	57.2	177
C_{avg} [mg/L]	23.4	15.7	34.9	25.8	16.6	39.9
$t_{1/2}$ [h]	5.77	4.83	6.91	5.78	4.60	7.25
t_{max}[a] [h]	1.03	0.517	4.02	2.03	1.02	3.02

[a]t_{max} displayed as median and min, max.

Data source: Section 15.2.4.6

For N-desmethyl sildenafil, AUCinf, AUClast and Cmax ratios (90% CI) following a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast (Test) are displayed in T-Table 20.

T-Table 20: N-desmethyl sildenafil: AUC_{inf}, AUC_{last} and C_{max} ratios (90% CI) following a single dose of 100 mg sildenafil alone (Reference) and with a single dose of 500 µg roflumilast (Test)

|	Ref	Test	Ref LSM	Test LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
$Ln(AUC_{inf})$ [h·µg/L]	sildenafil	w/roflumilast	6.33	6.43	110	101	120
$Ln(AUC_{last})$ [h·µg/L]	sildenafil	w/roflumilast	6.28	6.32	104	89.7	119
$Ln(C_{max})$ [µg/L]	sildenafil	w/roflumilast	4.90	4.61	74.7	60.8	91.8

Ratio = Ratio (Test/Reference) of treatment mean values, expressed as a percentage of Reference mean (100 x Test/Reference). 90% CI = 90% confidence interval estimate, expressed as a percentage of Reference mean (100 x Test/Reference).
Data source: Section 15.2.4.7

The mean free (unbound) plasma concentrations of roflumilast and roflumilast N-oxide at 1.5 h and 12 h after a single dose of 500 µg roflumilast alone and with a single dose of 100 mg sildenafil are presented in T-Table 21.

T-Table 21: Free roflumilast and roflumilast N-oxide: Free plasma concentrations (geometric mean, 68%-range) at 1.5 h and 12 h after a single dose of 500 µg roflumilast alone and with a single dose of 100 mg sildenafil

	Roflumilast			Roflumilast & Sildenafil		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
Free Roflumilast [µg/L]						
at 1.5 h	0.0174	0.0120	0.0252	0.0124	0.0104	0.0147
at 12 h	Missing	Missing	Missing	Missing	Missing	Missing
Free Roflumilast N-Oxide [µg/L]						
at 1.5 h	0.0777	0.0409	0.148	0.0505	0.0295	0.0865
at 12 h	0.133	0.112	0.158	0.136	0.116	0.160

Missing = refers to values below the lower limit of quantification
Data source: Section 15.2.5.2

For roflumilast, the mean free plasma concentrations were similar at 1.5 h after the application of roflumilast & sildenafil when compared with roflumilast alone. At 12 h after the application of study medication, all free plasma concentrations were below the lower limit of quantification.
For roflumilast N-oxide, free plasma concentrations nearly doubled when mean values at 1.5 h were compared with those at 12 h after the application of study medication. However, mean values at these time points were similar after roflumilast & sildenafil and roflumilast alone.

Mean free (unbound) plasma concentrations of sildenafil and N-desmethyl sildenafil at 1 h and 8 h after a single dose of 100 mg sildenafil alone and with a single dose of 500 µg roflumilast are presented in T-Table 22.

T-Table 22: Free sildenafil and N-desmethyl sildenafil: Free plasma concentrations (geometric mean, 68%-range) at 1 h and 8 h after a single dose of 100 mg sildenafil alone and with a single dose of 500 μg roflumilast

	Sildenafil			Sildenafil & Roflumilast		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
Free Sildenafil [μg/L]						
at 1 h	13.4	7.48	23.8	3.70	0.796	17.2
at 8 h	1.46	0.753	2.82	1.33	0.832	2.12
Free N-Desmethyl Sildenafil [μg/L]						
at 1 h	8.63	3.70	20.1	2.96	1.37	6.39
at 8 h	0.579	0.204	1.64	0.763	0.497	1.17

Parameters are defined in T-Table 7.
Data source: Section 15.2.6.2

For sildenafil, the mean free plasma concentration at 1 h after the application of roflumilast & sildenafil was lower when compared with sildenafil alone. At 8 h after the application of study medication, the mean free plasma concentrations were comparable.

Similarly, the mean free plasma concentration of N-desmethyl sildenafil at 1 h after the application of roflumilast & sildenafil was lower when compared with sildenafil alone.
At 8 h after the application of study medication, the mean free plasma concentrations were comparable.

Conclusions: Pharmacokinetic Conclusions
Roflumilast and roflumilast N-oxide
Similar systemic exposures were seen for roflumilast and roflumilast N-oxide after the application of roflumilast alone and together with sildenafil. Co-administration of sildenafil and roflumilast resulted in a 24% lower peak concentration for roflumilast but not for roflumilast N-oxide.
Sildenafil and N-desmethyl sildenafil
Similar systemic exposures were seen for sildenafil and N-desmethyl sildenafil after the application of sildenafil alone and together with roflumilast. A reduction in peak concentration (13% lower for sildenafil and 25% lower for N-desmethyl sildenafil) was
observed after the application of roflumilast & sildenafil in comparison with sildenafil alone.

Pharmacodynamic Conclusions
Roflumilast:
Roflumilast mono-therapy had little – if any – cardiovascular effect, the observed trend of smaller time-averaged changes in HR and smaller time-averaged changes in CO were noteworthy but of little relevance since they were quite small. Roflumilast treatment tended to shorten the electrocardiographic PR-interval, but had no effect on the QT and QTc-intervals.
Sildenafil:
Sildenafil mono-therapy tended to lower the time-averaged BP changes from baseline, without reflectory tachycardia; instead, there was a trend towards smaller minimum and

average HR changes from baseline relative to placebo. Sildenafil was associated with a larger maximum change and a smaller minimum change in QTc than roflumilast, with little effect on the average time-matched QTc-change from baseline.

Roflumilast & sildenafil combination treatment:

The combination of 500 μg roflumilast & 100 mg sildenafil showed its own distinct cardiovascular HR, BP, ZCG/STI and QT/QTc response pattern, which is not explained by mere additivity of the effects of the mono-therapies (500 μg roflumilast or 100 mg sildenafil). Although there were no relevant differences in the summary measures of the time-matched changes from baseline for the uncorrected QT of the combination treatment relative to placebo, the maximum and average change from baseline of the HR-corrected QT-intervals tended to be larger for the combination treatment, also relative to the mono-therapies roflumilast and sildenafil.

CP-049

Study Title: A study of the effects of steady state enoxacin on the single dose pharmacokinetics of roflumilast and roflumilast N-oxide.

Objectives: Primary objective:
 ˙To evaluate the effects of steady state enoxacin on the single dose pharmacokinetics of roflumilast and roflumilast N-oxide.
Secondary objectives:
 ˙To evaluate the safety and tolerability of roflumilast and co-administration of roflumilast and enoxacin.
 ˙To evaluate the effects of steady state enoxacin on the total phosphodiesterases type 4 inhibitory capacity (tPDE4i).
 ˙To evaluate the individual metabolic activities of CYP1A2 and CYP3A4 of all participating study subjects at baseline and their potential alteration by steady-state enoxacin treatment as assessed by caffeine and midazolam phenotyping, respectively.

Study Design: The study was conducted as a phase I, open-label, non-randomized, fixed sequence, two-period, single-center, drug-drug interaction study in healthy male and female subjects. The study consisted of:
 ˙One screening visit within three weeks prior to baseline (Study Days -21 to -3).
 ˙Two treatment periods of eight days (Period 1, Study Days -2 to 6) and 14 days (Period 2, Study Days 7 to 20).
 ˙A post-study examination on Study Day 21 or later.

T-Figure 1: Summarized study design

M=Midazolam, C=Caffeine, R=Roflumilast
S= Screening, T= Termination
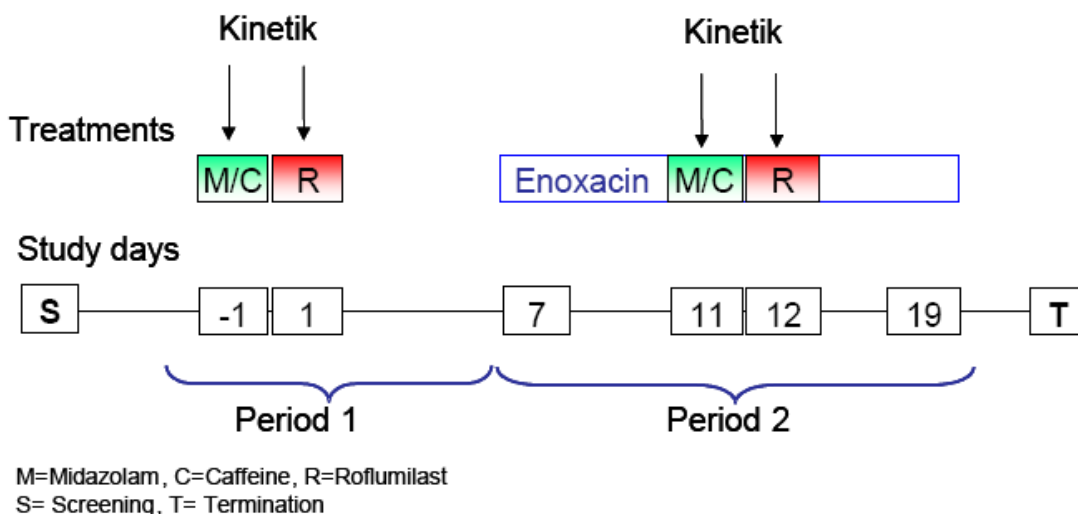
Study Population: A total of 19 healthy Caucasian male subjects were evaluated.

T-Table 9: Demographic and anthropometric data: Summary statistics – valid cases set (BY217/CP-049)

	Age [yr]	Height [cm]	Body Weight [kg]	BMI [kg/m^2]
N	19	19	19	19
Mean	33	173	71.7	23.99
SD	8	10.9	10.8	2.42
Median	32	174	70.0	24.30
Min	21	152	52	18.60
Max	45	193	91	27.40

Data source: Table 15.1.1.1

Data Analysis: Pharmacokinetic parameters including log-transformed Cmax and AUC values of roflumilast and roflumilast N-oxide were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals (CI) for Test (roflumilast with enoxacin) as a percentage of Reference (roflumilast alone) were generated.

Results: The concentration-time profiles and statistical analysis are shown in the following figures and tables.

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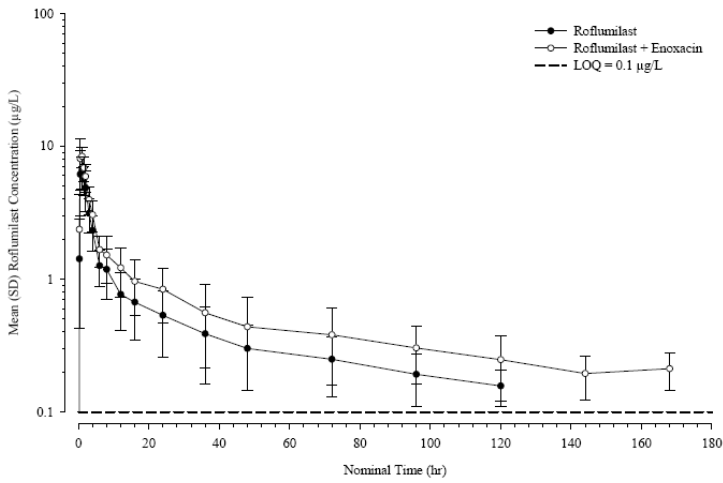
T-Figure 3:Roflumilast: Plasma concentration-time profiles (n=19, mean, SD) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049) (semilog plot)
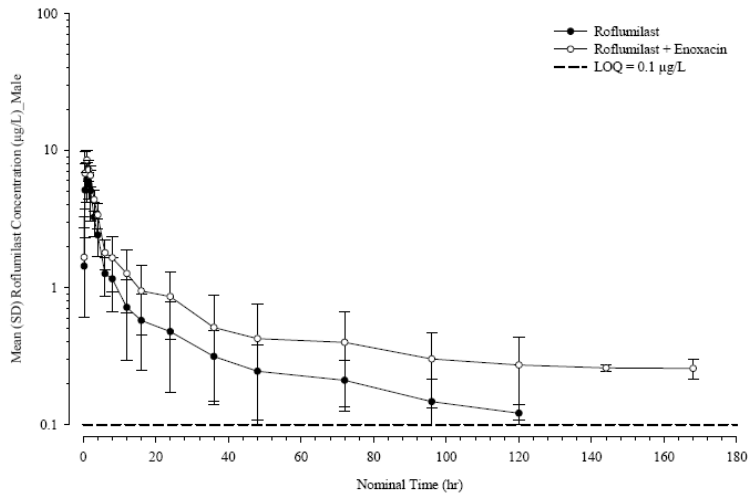
T-Figure 4:Roflumilast (male): Plasma concentration-time profiles (n=10, mean, SD) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049) (semilog plot)

229
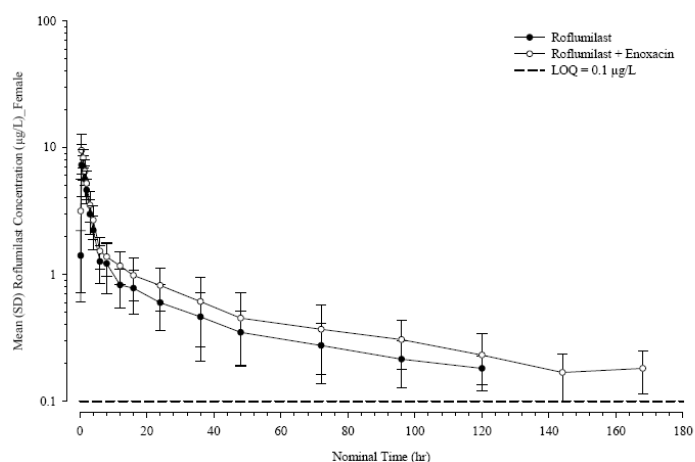
T-Figure 5: Roflumilast (female): Plasma concentration-time profiles (n=9, mean, SD) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049) (semilog plot)

T-Table 11: Roflumilast: Mean pharmacokinetic parameter estimates (n=19, geometric mean, 68%-range) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049)

	Roflumilast			Roflumilast & Enoxacin		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
AUC_{inf}	50.6	31.3	81.6	78.8	47.6	130
AUC_{tlast}	45.5	28.1	73.7	71.9	43.8	118
C_{max}	7.69	5.94	9.95	9.26	7.44	11.5
$t_{1/2}$	22.8	14.6	35.5	28.6	14.8	55.2
t_{max} *	1.00	0.50	2.00	0.50	0.50	1.52
CL/F	9.89	6.13	16.0	6.35	3.84	10.5

*t_{max} displayed as median and min, max
Source data: Section 15.2.1.4
Parameters are defined in T-Table 8.

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T-Table 12: Roflumilast by gender: Mean pharmacokinetic parameter estimates (geometric mean, 68%-range) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049)

	Roflumilast			Roflumilast & Enoxacin		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
Male (n=10)						
AUC_{inf}	43.8	26.7	71.7	74.5	42.9	130
AUC_{tlast}	40.2	24.4	66.4	68.5	40.1	117
C_{max}	7.25	5.78	9.09	8.61	6.88	10.8
$t_{1/2}$	19.3	12.5	29.9	22.7	10.9	47.5
t_{max} *	1.00	0.50	2.00	1.00	0.50	1.52
CL/F	11.4	6.97	18.7	6.71	3.86	11.7
Female (n=9)						
AUC_{inf}	59.3	38.6	91.3	83.8	52.5	134
AUC_{tlast}	52.2	33.4	81.7	75.7	47.3	121
C_{max}	8.22	6.17	11.0	10.0	8.28	12.1
$t_{1/2}$	27.4	18.4	40.7	36.9	23.1	59.0
t_{max} *	1.00	0.50	1.50	0.50	0.50	1.00
CL/F	8.43	5.48	13.0	5.97	3.74	9.52

*t_{max} displayed as median and min, max
Source data: Section 15.2.1.5
Parameters are defined in T-Table 8.

For roflumilast, pharmacokinetic parameter estimates stratified by gender followed the same trend as seen for the entire study population. However, mean values of systemic exposure, peak concentration and terminal elimination half-life after roflumilast alone and roflumilast & enoxacin were lower in male subjects when compared with those in female subjects. Mean values of apparent oral clearance in male subjects after roflumilast alone and roflumilast & enoxacin were higher when compared with those in female subjects.

For roflumilast, AUCinf, AUCtlast, Cmax and CL/F mean ratios (90% CI) following a single dose of 500 µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) are displayed in T-Table 13.

T-Table 13: Roflumilast: AUC_{inf}, AUC_{tlast}, C_{max} and CL/F mean ratios (90% CI, n=19) following a single dose of 500µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) (BY217/CP-049)

	Ref	Test	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
AUC_{inf}	roflumilast	w/ enoxacin	50.56	78.80	**155.84**	119.08	203.94
AUC_{tlast}	roflumilast	w/ enoxacin	45.53	71.85	**157.83**	120.78	206.25
C_{max}	roflumilast	w/ enoxacin	7.69	9.26	**120.37**	105.59	137.21
CL/F	roflumilast	w/ enoxacin	9.89	6.35	**64.17**	49.03	83.98

Source data: Section 15.2.1.8
Parameters are defined in T-Table 8
Ratio: Ratio (Test/ Reference) of treatment mean values, expressed as a percentage of Reference mean (100 × Test/ Reference).

For roflumilast, mean ratios of AUCinf and AUCtlast indicated a 56% and 58% higher systemic exposure after roflumilast & enoxacin when compared with those after roflumilast alone. The mean ratio of Cmax indicated a 20% higher peak concentration after roflumilast & enoxacin when compared with that after roflumilast alone. The mean ratios of CL/F indicated a 36% lower

apparent oral clearance after roflumilast & enoxacin when compared with that after roflumilast alone.

For **male** and **female** subjects, AUCinf, AUCtlast, Cmax and CL/F mean ratios (90% CI) of roflumilast following a single dose of 500 µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) are displayed in T-Table 14.

T-Table 14: Roflumilast by gender: AUC_{inf}, AUC_{tlast}, C_{max} and CL/F mean ratios (90% CI) following a single dose of 500 µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) (BY217/CP-049)

	Ref	Test	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Male (n=10)							
AUC_{inf}	roflumilast	w/ enoxacin	43.78	74.54	**170.27**	113.40	255.65
AUC_{tlast}	roflumilast	w/ enoxacin	40.23	68.53	**170.34**	113.88	254.78
C_{max}	roflumilast	w/ enoxacin	7.25	8.61	**118.88**	99.77	141.65
CL/F	roflumilast	w/ enoxacin	11.42	6.71	**58.73**	39.12	88.18
Female (n=9)							
AUC_{inf}	roflumilast	w/ enoxacin	59.34	83.82	**141.24**	97.55	204.49
AUC_{tlast}	roflumilast	w/ enoxacin	52.23	75.74	**145.01**	99.41	211.53
C_{max}	roflumilast	w/ enoxacin	8.22	10.03	**122.04**	99.82	149.21
CL/F	roflumilast	w/ enoxacin	8.43	5.97	**70.80**	48.90	102.51

Source data: Section 15.2.1.9
Parameters are defined in T-Table 8
Ratio: Ratio (Test/ Reference) of treatment mean values, expressed as a percentage of Reference mean (100 × Test/ Reference).

For roflumilast, pharmacokinetic parameter estimates stratified by gender followed the same trend as seen for the entire study population. However, mean ratios of AUCinf and AUCtlast between roflumilast alone and roflumilast & enoxacin were higher in male subjects when compared with those in female subjects. Mean ratios of Cmax and CL/F between roflumilast alone and roflumilast & enoxacin were lower in male subjects when compared with those in female subjects.

For roflumilast N-oxide, plasma concentration-time profiles (mean, SD) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin are displayed in T-Figure 6 (linear plot) and T-Figure 7 (semilog plot), and stratified by gender for male subjects in T-Figure 8 (semilog plot) and for female subjects in T-Figure 9 (semilog plot).
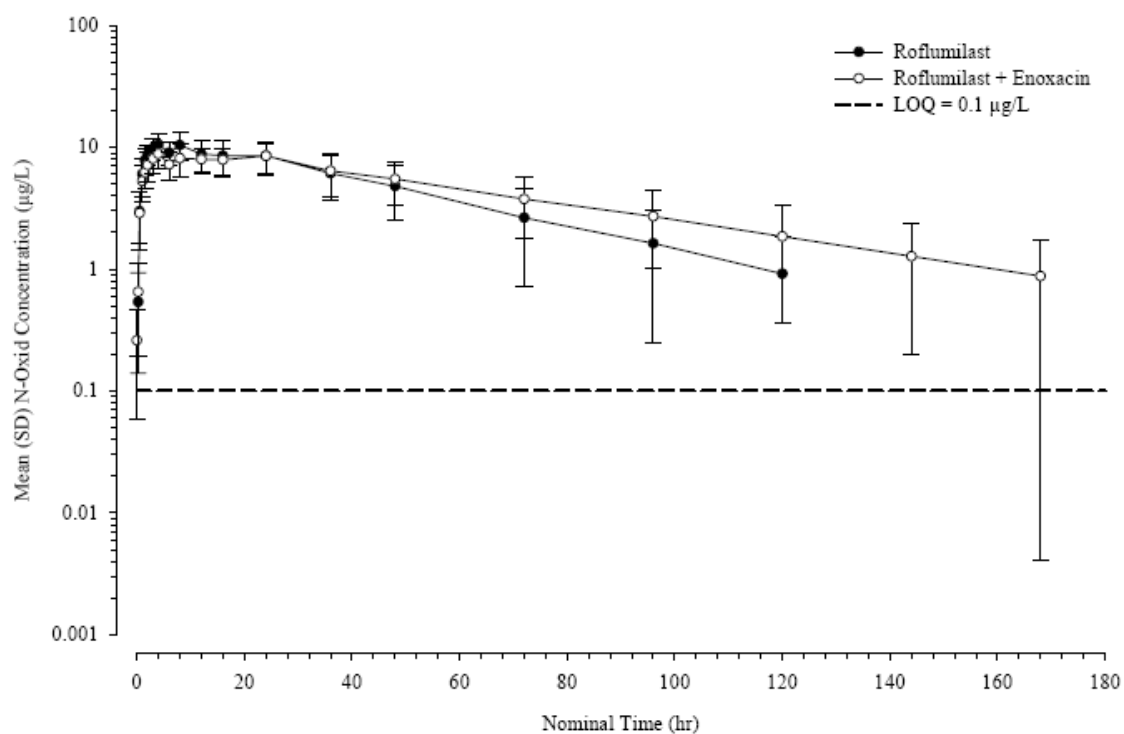
T-Figure 7:Roflumilast N-oxide: Plasma concentration-time profiles (n=19, mean, SD) following a single dose of 500µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049) (semilog plot)
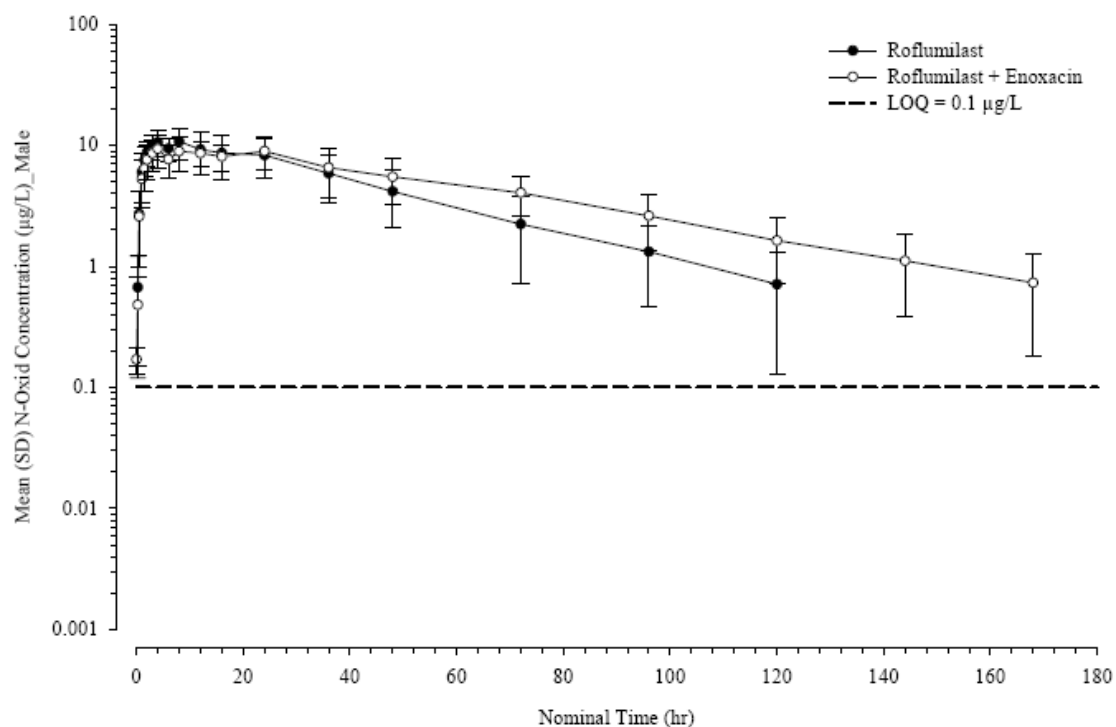
T-Figure 8:Roflumilast N-oxide (male): Plasma concentration-time profiles (n=10, mean, SD) following a single dose of 500µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049) (semilog plot)
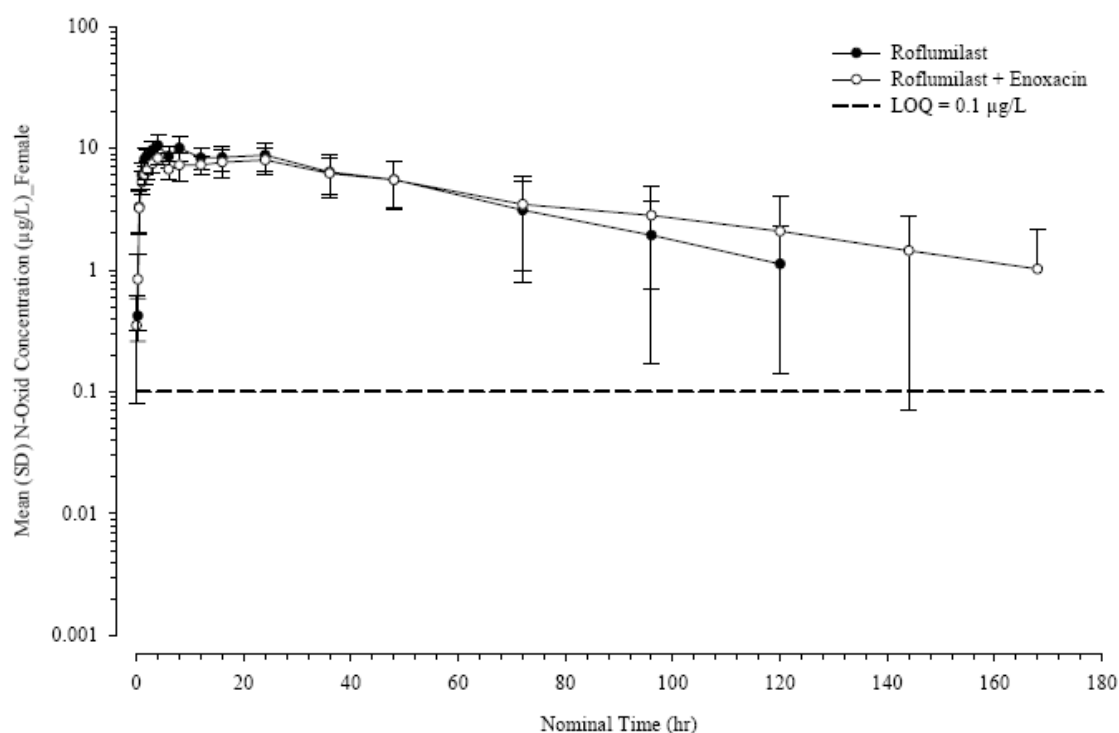
T-Figure 9: Roflumilast N-oxide (female): Plasma concentration-time profiles (n=9, mean, SD) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049) (semilog plot)

T-Table 15: Roflumilast N-oxide: Mean pharmacokinetic parameter estimates (n=19, geometric mean, 68%-range) following a single dose of 500µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049)

	Roflumilast			Roflumilast & Enoxacin		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
AUC_{inf}	529	349	801	648	422	995
AUC_{tlast}	498	342	724	597	408	874
C_{max}	10.9	8.65	13.7	9.37	7.44	11.8
$t_{1/2}$	24.7	17.5	34.8	37.5	23.4	60.1
t_{max} *	4.00	2.00	24.2	8.00	4.00	24.0

*t_{max} displayed as median and min, max
Source data: Section 15.2.2.4
Parameters are defined in T-Table 8

For roflumilast N-oxide, mean pharmacokinetic parameter estimates after roflumilast alone and roflumilast & enoxacin were comparable. Mean values of systemic exposure, terminal elimination half-life and time to peak concentration after roflumilast alone were lower when compared with those after roflumilast & enoxacin. Mean values of peak concentration after roflumilast alone were higher when compared with those after roflumilast & enoxacin.

For **male** and **female** subjects, mean roflumilast N-oxide pharmacokinetic parameter estimates following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin are presented in T-Table 16.

T-Table 16: Roflumilast N-oxide by gender: Mean pharmacokinetic parameter estimates (geometric mean, 68%-range) following a single dose of 500 µg roflumilast alone and with steady state 2 x 400 mg enoxacin (BY217/CP-049)

	Roflumilast			Roflumilast & Enoxacin		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
Male (n=10)						
AUC_{inf}	489	325	736	636	421	960
AUC_{tlast}	466	318	684	597	402	886
C_{max}	11.0	8.32	14.4	9.87	7.56	12.9
$t_{1/2}$	22.7	15.4	33.5	33.0	20.4	53.4
t_{max} *	8.00	4.00	24.2	8.00	4.00	24.0
Female (n=9)						
AUC_{inf}	577	376	885	662	414	1060
AUC_{tlast}	536	369	779	597	405	882
C_{max}	10.8	8.98	13.1	8.84	7.38	10.6
$t_{1/2}$	27.2	20.7	35.6	43.2	27.8	67.3
t_{max} *	4.00	2.00	8.02	4.00	4.00	24.0

*t_{max} displayed as median and min, max
Source data: Section 15.2.2.5
Parameters are defined in T-Table 8

For roflumilast N-oxide, pharmacokinetic parameter estimates stratified by gender followed the same trend as seen for the entire study population. However, mean values of systemic exposure and terminal elimination half-life after roflumilast alone and roflumilast & enoxacin were lower in male subjects when compared with those in female subjects. Mean values of peak concentration and time to peak concentration in male subjects after roflumilast alone and roflumilast & enoxacin were higher when compared with those in female subjects.

For roflumilast N-oxide, AUCinf, AUCtlast and Cmax mean ratios (90% CI) following a single dose of 500 µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) are displayed in T-Table 17.

T-Table 17: Roflumilast N-oxide: AUC_{inf}, AUC_{tlast} and C_{max} mean ratios (90% CI, n=19,) following a single dose of 500 µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) (BY217/CP-049)

	Ref	Test	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
AUC_{inf}	roflumilast	w/ enoxacin	528.84	648.19	122.57	97.29	154.42
AUC_{tlast}	roflumilast	w/ enoxacin	498.04	596.97	119.86	97.43	147.46
C_{max}	roflumilast	w/ enoxacin	10.90	9.37	85.95	75.72	97.56

Source data: Section 15.2.2.8 Parameters are defined in T-Table 8
Ratio: Ratio (Test/ Reference) of treatment mean values, expressed as a percentage of Reference mean (100 × Test/ Reference).

For **male** and **female** subjects, AUCinf, AUCtlast and Cmax mean ratios (90% CI) of roflumilast N-oxide following a single dose of 500 µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) are displayed in T-Table 18.

T-Table 18: Roflumilast N-oxide by gender: AUC_{inf}, AUC_{tlast} and C_{max} mean ratios (90% CI) following a single dose of 500 µg roflumilast alone (Reference) and with steady state 2 x 400 mg enoxacin (Test) (BY217/CP-049)

	Ref	Test	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Male (n=10)							
AUC_{inf}	roflumilast	w/ enoxacin	489.15	635.72	**129.96**	94.51	178.72
AUC_{tlast}	roflumilast	w/ enoxacin	466.01	596.68	**128.04**	94.66	173.19
C_{max}	roflumilast	w/ enoxacin	10.97	9.87	**90.05**	72.96	111.14
Female (n=9)							
AUC_{inf}	roflumilast	w/ enoxacin	576.73	662.34	**114.84**	79.34	166.23
AUC_{tlast}	roflumilast	w/ enoxacin	536.22	597.30	**111.39**	81.38	152.47
C_{max}	roflumilast	w/ enoxacin	10.83	8.84	**81.62**	70.15	94.95

Source data: Section 15.2.2.9
Parameters are defined in T-Table 8
Ratio: Ratio (Test/ Reference) of treatment mean values, expressed as a percentage of Reference mean (100 × Test/ Reference).

For roflumilast N-oxide, pharmacokinetic parameter estimates stratified by gender followed the same trend as seen for the entire study population. However, mean ratios of AUCinf, AUCtlast and Cmax between roflumilast alone and roflumilast & enoxacin were higher in male subjects when compared with those in female subjects.

For **enoxacin trough concentrations**, an 18% (CI 90%: 1% to 38%) higher mean value on Day 12 was seen when compared with that on Day 11.

Conclusions: For **roflumilast**, a 56% (CI 90%: 19% to 104%) higher mean systemic exposure (AUCinf), a 20% (CI 90%: 6% to 37%) higher mean peak concentration and a 36% (CI 90%: -51% to -16%) lower mean apparent oral clearance was seen after roflumilast & enoxacin when compared with roflumilast alone. For **roflumilast N-oxide**, a 23% (CI 90%: -3% to 54%) higher mean systemic exposure (AUCinf) and a 14% (CI 90%: -24% to -2%) lower mean peak concentration was seen after roflumilast & enoxacin when compared with roflumilast alone.

CP-041

Study Title: Effects of cimetidine repeated oral dose 400 mg twice-daily co-administration on the pharmacokinetics of roflumilast and roflumilast-N-oxide

Objectives: Primary objective:
˙ To characterize the effects of repeated dose cimetidine 400 mg bid co-administration on the 500 µg single-dose pharmacokinetics of roflumilast and roflumilast N-oxide in healthy male and female adults.
Secondary objectives:
˙ To assess further pharmacokinetic parameters.
˙ To assess safety and tolerability throughout all treatment periods.

Study Design: This study was conducted according to an open, single-center, non-randomized, three period, one fixed sequence design. It consisted of a screening examination, Period 1 (6 days) with single-dose roflumilast (500 mcg per os [po] on Day 1), Period 2 (7 days) with repeated twice daily (every 12 hours [h] = bid) doses of cimetidine (400 mg po on Days 6 to 12), Period 3 (5 days) with continued dosing of 400 mg cimetidine bid on Day 13 to Day 16 and roflumilast 500 µg po single dose co-administration on Day 13, and an end-of-study examination (on Day 18 or later).
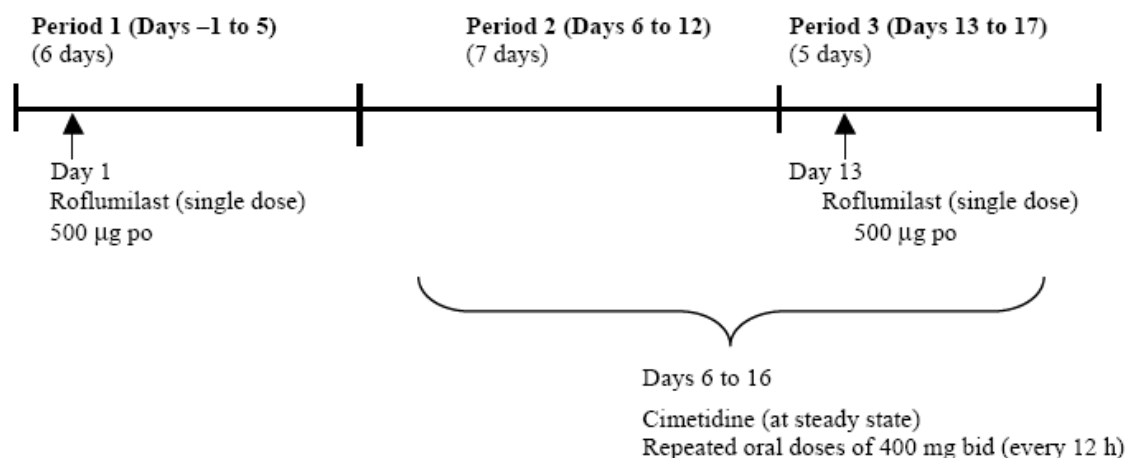
Pharmacokinetic sampling for determination of roflumilast and its N-oxide metabolite plasma concentration-time profiles was done at the following times post-dose on Day 1 and Day 13, respectively: pre-dose, and 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 16 h, 24 h, 36 h, 48 h, 72 h, and 96 h post-administration.

Study Population: In total, 16 healthy subjects (8 males, 8 females) were included in this study performed in a single center.

T-Table 7: Demographic characteristics of the study population

Characteristic	Full analysis set (N = 16)
Age [years]	
mean ± SD	25 ± 5
median (min, max)	25 (20, 39)
Height [cm]	
mean ± SD	176 ± 11
median (min, max)	174 (163, 202)
Weight [kg]	
mean ± SD	73 ± 16
median (min, max)	69 (53, 110)
Body Mass Index [kg/m^2]	
mean ± SD	23 ± 3
median (min, max)	23 (20, 28)
Smoking, n (%)	
Non-smokers	13 (81.3%)
Current Smokers	0 (0.0%)
Ex-smokers	3 (18.8%)
Gender, n (%)	
Female	8 (50%)
Male	8 (50%)

N = number of subjects in analysis set, n = number of subjects in respective category, SD = standard deviation

Data source: Table 15.1.1.1, Table 15.1.1.3 and Listing 16.2.1.1

Data Analysis: To compare the primary pharmacokinetic parameter estimates of roflumilast (AUClast, Cmax, and CL/F) and roflumilast N-oxide (AUClast, Cmax) between Period 1 (Reference) and Period 3 (Test), an analysis of variance (ANOVA) was performed where appropriate using the 90% confidence interval (CI). Geometric means were calculated as the antilogs of least-squares mean (LSM) log-transformed values (analogous to the geometric mean).

Results: Plasma concentration time profiles of roflumilast, roflumilast N-oxide, and cimedine and statistical analysis are shown in the following figures and tables.

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T-Figure 3: Roflumilast mean plasma concentration-time profiles in healthy adults following single oral dose of 500 µg roflumilast administered alone in Period 1 and together with twice-daily 400 mg cimetidine at steady state in Period 3 (semilogarithmic plot)
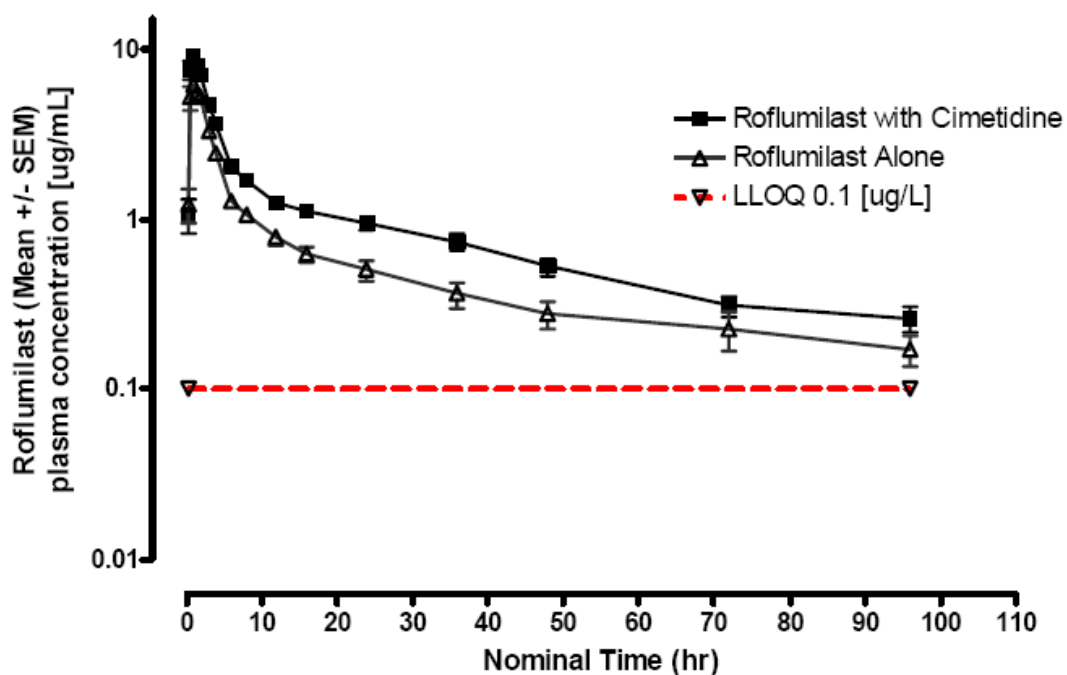
LLOQ = lower limit of quantitation. Single oral dose of 500 µg roflumilast alone in Period 1 = Reference; single oral dose of 500 µg roflumilast together with twice-daily 400 mg cimetidine at steady state in Period 3 = Test. SEM = standard error of the mean.

Data source: Values in Section 15.2.1.2. Means (SEM) are displayed; N = 16.

T-Figure 4: Roflumilast individual and mean (SD) AUC_{last} values in treatment Periods 1 and 3 (16 healthy adults)
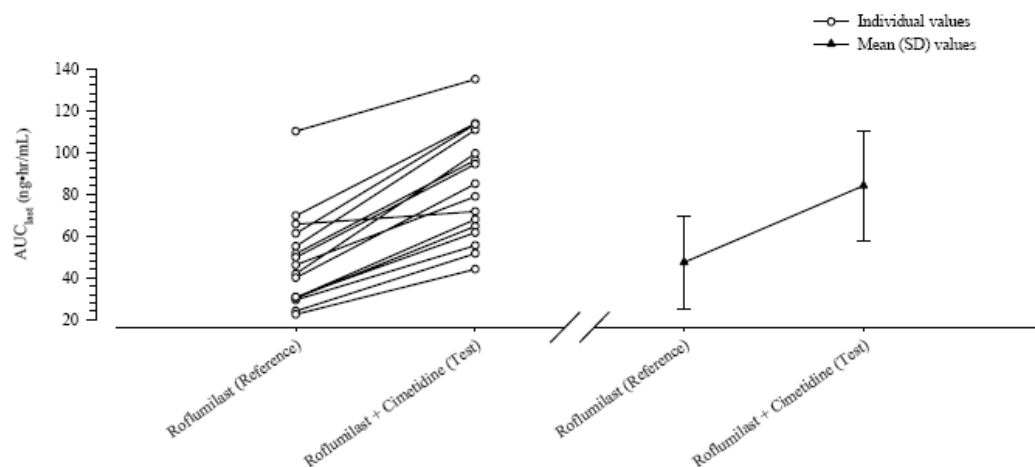
AUC_{last} = AUC from time zero to last observed concentration; Roflumilast (Reference) = single oral dose of 500 µg roflumilast in Period 1; Roflumilast + Cimetidine (Test) = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3; SD = standard deviation.
Data source: Values in Section 15.2.1.3.

T-Figure 5: Roflumilast individual and mean (SD) CL/F values in treatment Periods 1 and 3 (16 healthy adults)
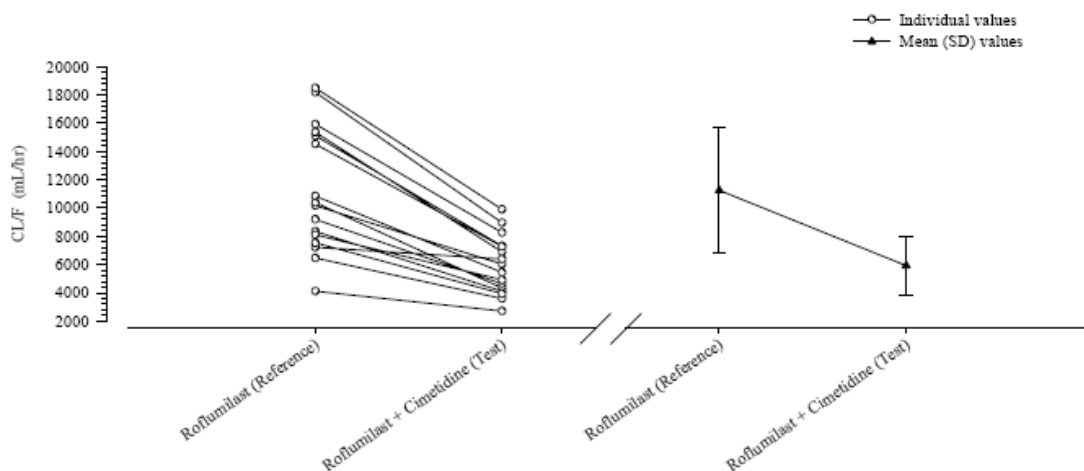
CL/F = apparent clearance; Roflumilast (Reference) = single oral dose of 500 µg roflumilast in Period 1; Roflumilast + Cimetidine (Test) = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3; SD = standard deviation.

Data source: Values in Section 15.2.1.3.

T-Figure 6: Roflumilast individual and mean (SD) C_{max} values in treatment Periods 1 and 3 (16 healthy adults)
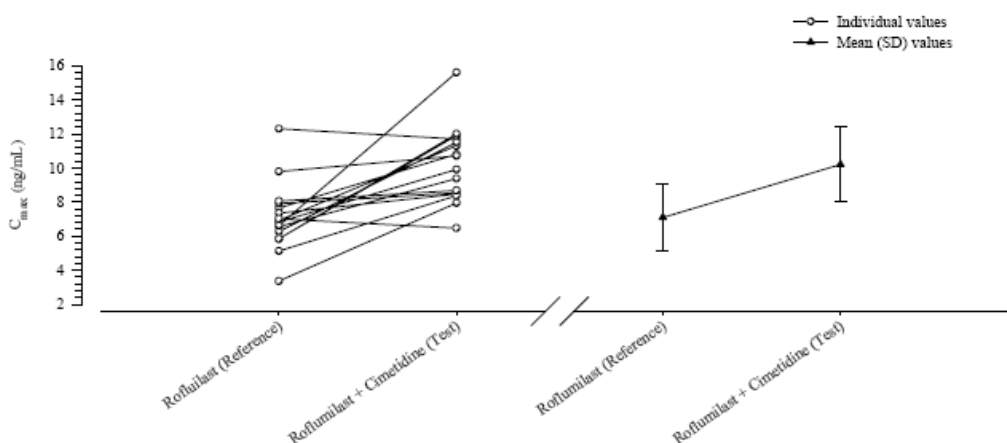
C_{max} = maximum drug concentration in plasma; Roflumilast (Reference) = single oral dose of 500 µg roflumilast in Period 1; Roflumilast + Cimetidine (Test) = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3; SD = standard deviation.
Data source: Values in Section 15.2.1.3.

T-Table 9: Descriptive statistics of primary and secondary pharmacokinetic parameter estimates for roflumilast in healthy adults following single oral dose of 500 µg roflumilast administered alone in Period 1 and together with twice-daily 400 mg cimetidine at steady state in Period 3

Pharmacokinetic variable for roflumilast	N	Roflumilast alone (Period 1)[a]		Roflumilast with cimetidine (Period 3)[b]	
		Mean (SD)	Geometric Mean (68%-range)	Mean (SD)	Geometric Mean (68%-range)
C_{max} (µg/L)	16	7.09 (1.98)	6.84 (5.16, 9.06)	10.20 (2.20)	9.99 (8.07, 12.36)
CL/F (L/h)	16	11.23 (4.40)	10.38 (6.81, 15.83)	5.92 (2.06)	5.58 (3.89, 8.01)
AUC_{last} (µg•h/L)	16	47.44 (22.26)	43.35 (28.20, 66.67)	83.96 (26.19)	80.06 (57.95, 110.61)
$t_{1/2}$ (h)	16	23.57 (10.72)	22.00 (15.34, 31.55)	30.16 (8.80)	29.08 (22.09, 38.30)
t_{max}[*] (h)	16		1.00 (0.50, 2.00)		1.00 (0.50, 2.00)

* median (min, max)

Pharmacokinetic parameter estimates are defined in T-Table 5.

N = number of subjects; SD = standard deviation.

[a]Treatment in Period 1 = single oral dose of 500 µg roflumilast alone (Reference)

[b]Treatment in Period 3 = single oral dose of 500 µg roflumilast together with twice-daily oral doses of 400 mg cimetidine at steady state (Test)

Data source: Section 15.2.1.3.

Ratio percentage of roflumilast parameter estimates (ANOVA), geometric means and their respective 90% confidence intervals in healthy adults following single oral dose of 500 µg roflumilast administered alone (Reference) and together with twice-daily 400 mg cimetidine at steady state (Test)

Analyte	Dependent	N	Ref Geom. mean	Test Geom. mean	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast	C_{max} (µg/L)	16	6.84	9.99	146.12	125.78	169.75
	AUC_{last} (h•µg/L)	16	43.35	80.06	184.66	146.95	232.04
	$t_{1/2}$ (h)	16	22.00	29.08	132.20	114.78	152.28
	CL/F (L/h)	16	10.38	5.58	53.72	42.45	67.99

ANOVA = analysis of variance; CI 90 = 90% confidence interval; Ref = single oral dose of 500 µg roflumilast in Period 1; Test = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3. Ratio = (Test/Ref) x 100.

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T-Figure 8: Roflumilast N-oxide mean plasma concentration-time profiles in healthy adults following single oral dose of 500 µg roflumilast administered alone in Period 1 and together with twice-daily 400 mg cimetidine at steady state in Period 3 (semilogarithmic plot)
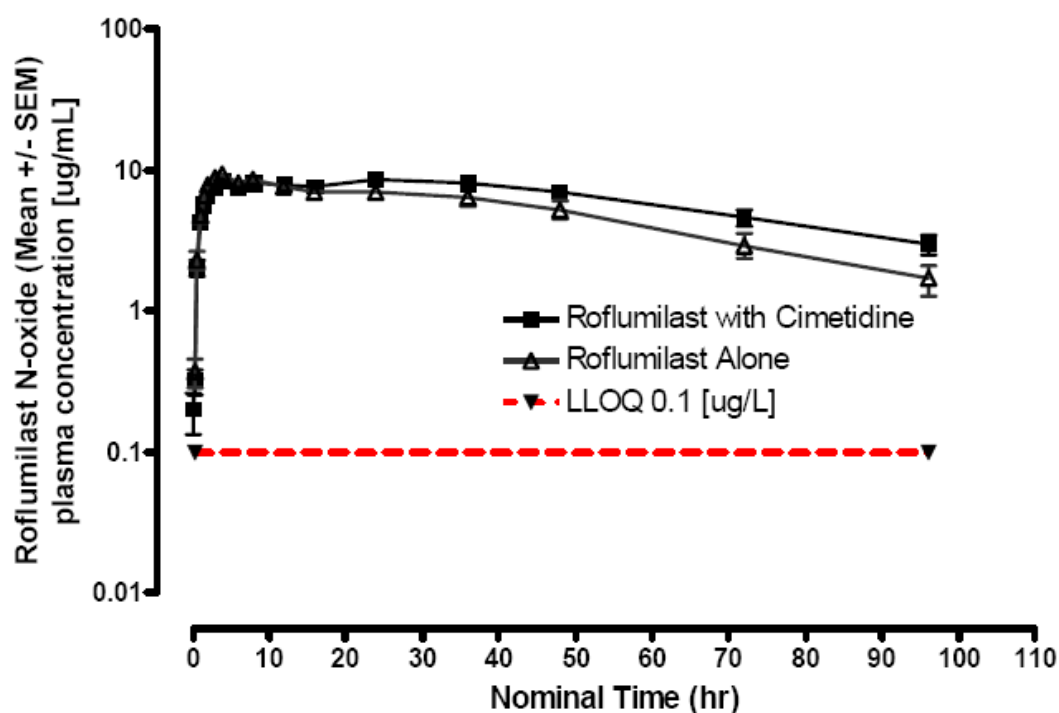
LLOQ = lower limit of quantitation. Single oral dose of 500 µg roflumilast alone in Period 1 = Reference; single oral dose of 500 µg roflumilast together with twice-daily 400 mg cimetidine at steady state in Period 3 = Test. SEM = standard error of the mean.

Data source: Values in Section 15.2.3.2. Means (SEM) are displayed; N = 16.

Ratio percentage of roflumilast N-oxide parameter estimates (ANOVA), geometric means and their respective 90% confidence intervals in healthy adults following single oral dose of 500 µg roflumilast administered alone (Reference) and together with twice-daily 400 mg cimetidine at steady state (Test)

Analyte	Dependent	N	Ref Geom. mean	Test Geom. mean	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast N-oxide	C_{max} (µg/L)	16	9.48	9.13	96.29	82.60	112.25
	AUC_{last} (h·µg/L)	16	448.43	570.69	127.27	103.60	156.34
	$t_{1/2}$ (h)	16	26.53	37.79	142.44	128.44	157.97

ANOVA = analysis of variance; CI 90 = 90% confidence interval; Ref = single oral dose of 500 µg roflumilast in Period 1; Test = single oral dose of 500 µg roflumilast plus twice-daily oral doses of 400 mg cimetidine at steady state in Period 3. Ratio = (Test/Ref) x 100.

Conclusions: The pharmacokinetic parameter estimates AUClast, Cmax, CL/F and half-life indicate that multiple administration of cimetidine 400 mg bid alters the single-dose pharmacokinetics of roflumilast (500 µg); it also increases the exposure (AUClast) and half-life of roflumilast N-oxide.

CP-068

Study Title: A Study of the Effect of Erythromycin on the Pharmacokinetics of Roflumilast and Roflumilast-N-Oxide

Objectives: To evaluate the effect of erythromycin on the pharmacokinetics of roflumilast;
. To evaluate the effect of erythromycin on the pharmacokinetics of roflumilast-N-oxide; and
. To investigate the safety and tolerability of coadministration of roflumilast and erythromycin.

Study Design: This was an open-label, nonrandomized, 1-sequence, 2-period, 2-treatment crossover study in 16 healthy volunteers.

Table S1. Study Treatment (Protocol A5821014)

Study Day 1	Study Days 9-14	Study Day 15	Study Days 16-21
Roflumilast 500 µg PO	Erythromycin 500 mg TID w/meals	Roflumilast 500 µg PO Erythromycin 500 mg TID w/meals	Erythromycin 500 mg TID w/meals

Study Population: Sixteen healthy volunteers (8 males and 8 females) entered the study. Fifteen subjects completed the study. One subject was withdrawn due to an adverse event following 1 dose of 500 µg roflumilast.

Data Analysis: Pharmacokinetic parameters including log-transformed maximum observed plasma concentration (Cmax,) area under the plasma concentration-time profile (AUC), and oral clearance (CL/F) values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (roflumilast with erythromycin) as a percentage of reference (roflumilast alone) were generated. Lack of an effect of erythromycin on roflumilast would be concluded if the 90% confidence intervals for both Cmax and AUC, based on log-transformed data, were entirely contained within the interval of 80% to 125%.

Results: Plasma concentration time profiles of roflumilast, roflumilast N-oxide, and cimedine and statistical analysis are shown in the following figures and tables.

Figure S1. Mean Roflumilast (Left Panels) and Roflumilast-N-Oxide (Right Panels) Plasma Concentration-Time Profiles Following Single Oral 500-μg Roflumilast Doses Alone (Filled Symbols) and With Steady-State Erythromycin (Open Symbols) (Study A5821014)
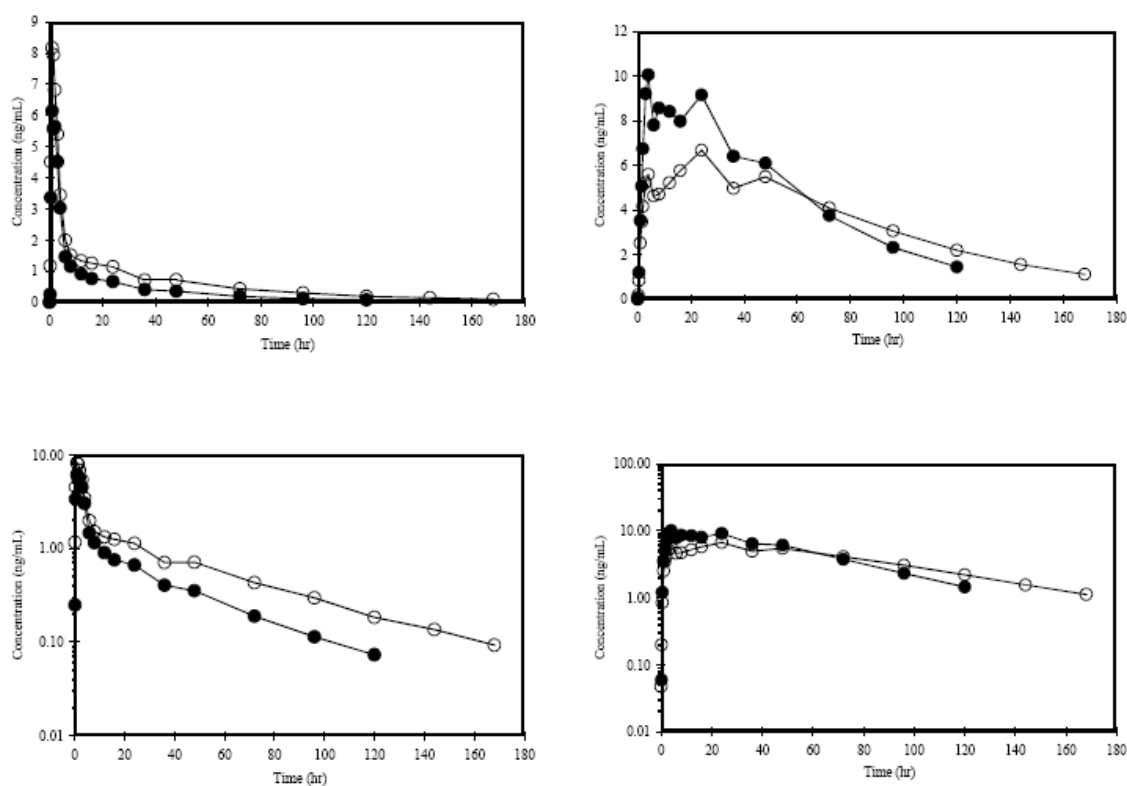
Left panel – roflumilast   Right panel – roflumilast-N-oxide
Upper and lower panel are linear and semi-logarithmic plots, respectively.

Table S3. Summary of Roflumilast Pharmacokinetic Parameter Values Following Single Oral 500-μg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Erythromycin 500 mg TID (Protocol A5821014)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Erythromycin (Test)	Roflumilast Alone (Reference)		
N	15	16		
Cmax, ng/mL	9.79	6.97	140	125 to 158
$AUC_{(0-tlqc)}$, ng·hr/mL	97.6	57.2	171	152 to 191
$AUC_{(0-\infty)}$, ng·hr/mL	104	61.0	170	150 to 192
CL/F (L/hr)	4.83	8.20	58.9	52.1 to 66.5
tmax	1.62	1.59		Not Applicable
t½	38.0	28.0		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Table S4. Summary of Roflumilast-N-Oxide Pharmacokinetic Parameter Values Following Single Oral 500-μg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Erythromycin 500 mg TID (Protocol A5821014)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Erythromycin (Test)	Roflumilast Alone (Reference)		
N	15	16		
Cmax, ng/mL	6.90	10.4	66.4	61.02 to 72.30
$AUC_{(0-tlqc)}$, ng·hr/mL	589	574	103	94.33 to 111.77
$AUC_{(0-\infty)}$, ng·hr/mL	669	646	104	91.63 to 117.04
tmax	24.5	8.69		Not Applicable
t½	48.0	32.4		Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

In the presence of steady-state erythromycin, mean roflumilast AUC values were approximately 70% higher than those observed when roflumilast was administered alone and mean CL/F decreased by 41%. Mean roflumilast time to maximum observed plasma concentration (tmax) did not change, but Cmax increased by 40% with erythromycin co-administration. Mean roflumilast terminal half-life (t½) was about 10 hours (36%) longer with erythromycin.

In the presence of steady-state erythromycin, mean roflumilast-N-oxide AUC values were similar to those observed when roflumilast was administered alone. The 90% confidence intervals for the treatment ratios of AUC(0-∞) and AUC(0-tlqc) values, based on log-transformed data, were both within the 80% to 125% range. However, with erythromycin co-administration mean roflumilast-N-oxide Cmax was about 34% lower, and mean tmax nearly tripled, occurring almost 16 hours later. Mean roflumilast-N-oxide t½ increased by about 48% with erythromycin.

Conclusions: Based on AUC values, steady-state erythromycin administration (500 mg TID) increases roflumilast exposure approximately 70% but has no effect on roflumilast-N-oxide exposure. Cmax values of roflumilast increased with steady-state erythromycin administration (40%) while Cmax values of roflumilast-N-oxide decreased about 34%.

CP-066 Study Protocol No.: Pfizer A5821012

Study Title:	A Study of the Effect of Ketoconazole on the Pharmacokinetics of Roflumilast and Roflumilast-N-Oxide
Phase:	1
Principal Investigator:	Robert Noveck, MD, PhD
Study Population:	Healthy Volunteers
Study Period:	05-May-2004 to 21-Jun-2004
Report No.:	398/2004

OBJECTIVE(S)

- To evaluate the effect of ketoconazole on the pharmacokinetics of roflumilast;

- To evaluate the effect of ketoconazole on the pharmacokinetics of roflumilast-N-oxide; and

- To investigate the safety and tolerability of roflumilast and co-administration of roflumilast and ketoconazole.

STUDY DESIGN

This was an open-label, nonrandomized, 1-sequence, 2-period, 2-treatment study in 16 healthy volunteers. Study treatments were as follows:

Study Day 1	Study Days 8-10	Study Day 11	Study Days 12-20
Roflumilast 500 µg PO	Ketoconazole 200 mg PO BID	Roflumilast 500 µg PO + Ketoconazole 200 mg PO BID	Ketoconazole 200 mg PO BID

STUDY TREATMENT

Subjects received a single dose of roflumilast 500 µg on Days 1 and 11. Ketoconazole 400 mg daily (200 mg BID) was taken from Study Days 8 to 20. On Study Day 11, roflumilast and the morning dose of ketoconazole were taken at the same time. Each roflumilast dose was administered with 8 oz of room-temperature water. For Study Days 1 and 11, subjects began fasting 8 hours prior to the roflumilast dose and continued fasting for 4 hours after dosing. Water could be consumed ad libitum during each overnight fast. Following each roflumilast dose, subjects were required to refrain from drinking water until the 2-hour blood draw was completed. Water could be consumed ad libitum following collection of the 2-hour blood sample. Identical lunches and dinners were served at approximately 4 and 10 hours, respectively, following the dose of roflumilast on Days 1 and 11.

PHARMACOKINETIC BLOOD SAMPLING

Five milliliters of venous blood were withdrawn in vacuum blood collection tubes containing lithium heparin at the following times: predose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours post the Day 1 roflumilast dose; and predose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post the Day 11 roflumilast dose. The 24-, 48-, 72-, 96-, 120-, 144-, 168-, 192-, and 216-hour blood draws were taken prior to the ketoconazole doses on Days 12-20. The vacutainer was mixed by gentle inversion and placed immediately into an ice/water bath. Plasma was to be separated from the whole blood within 30 minutes of collection. Each specimen was to be centrifuged at 1000 to 1200 X g for approximately 10 to 15 minutes in a refrigerated centrifuge. After centrifugation, the upper plasma layer was carefully transferred with a disposable pipette into a labeled screw-capped plastic storage tube. If red blood cells (RBCs) were inadvertently drawn into the plasma, the sample was to be re-centrifuged as soon as possible. Specimens were frozen in an upright position in a -20°C freezer within 60 minutes of sample collection.

ANALYTICAL METHODS

Sample analysis method for roflumilast and roflumilast-N-oxide in plasma is summarized in the following Table:

Method Description	
Matrix	Plasma (heparin)
Type of Method	LC/MS/MS
Validation Report	RR# 764-04632
Deviations From Validated Method	None
Sample Volume	500 µL
Internal Standard	D_5 Roflumilast for Roflumilast D_5 Roflumilast-N-Oxide for Roflumilast-N-Oxide

Study Assay Performance				
	Analytical Range		Quality Control Samples	
Analyte	Lower Limit (LLOQ)	Upper Limit (ULOQ)	Precision (%CV)	Accuracy (%RE)
Roflumilast	0.0400 ng/mL	60 ng/mL	≤8.76%	-2.00% to −1.20%
Roflumilast-N-Oxide	0.0400 ng/mL	60 ng/mL	≤5.89%	-0.60 % to 5.60%
Databook Number			95088	

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters including log-transformed Cmax, AUC, and CL/F values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (roflumilast with ketoconazole) as a percentage of reference (roflumilast alone) were generated. Lack of an effect of ketoconazole on roflumilast would be concluded if the 90% confidence intervals for both Cmax and AUC, based on log-transformed data, were entirely contained within the interval of 80% to 125%.

RESULTS
Roflumilast:

In the presence of steady-state ketoconazole, mean roflumilast AUC values were approximately double those observed when roflumilast was administered alone and mean CL/F decreased by 50%. Mean roflumilast Cmax increased by 23% and mean t½ increased by about 68% with ketoconazole co-administration. One subject had a quantifiable roflumilast concentration at predose on Day 11 but the value was less than 2% of the Day 11 Cmax for this subject and was not considered to be of concern.

Table 8.   Summary of Roflumilast Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Ketoconazole (Test) (Protocol A5821012)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Roflumilast With Ketoconazole (Test, N = 16)	Roflumilast Alone (Reference, N = 16)		
Cmax, ng/mL	6.94	5.63	123	106 to 143
AUC(0-tlqc), ng·hr/mL	83.7	41.6	201	175 to 232
AUC(0-∞), ng·hr/mL	88.2	44.3	199	171 to 231
CL/F (L/hr)	5.67	11.3	50.2	43.3 to 58.4
tmax	2.16	1.69	Not Applicable	
t½	39.7	23.7	Not Applicable	

Parameters are defined in Table 5.
Ratio   = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Figure 1.   Mean Roflumilast Plasma Concentration-Time Profiles Following Single Oral 500-µg Roflumilast Doses Alone (Filled Symbols) and With Steady-State Ketoconazole (Open Symbols) (Protocol A5821012)
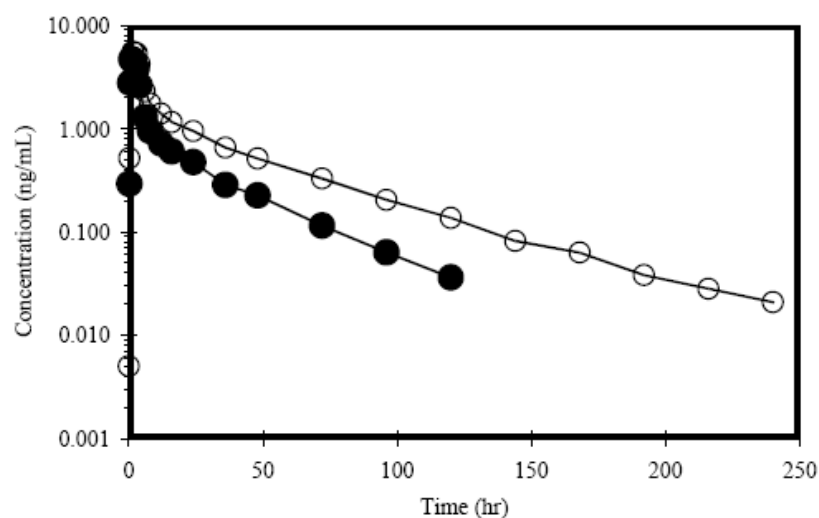
Roflumilast-N-Oxide:

In the presence of steady-state ketoconazole, mean roflumilast N-oxide AUC values were similar to those observed when roflumilast was administered alone. However, mean roflumilast N-oxide Cmax was about 37% lower than that observed without ketoconazole and mean tmax was more than double that observed without ketoconazole. Mean roflumilast N-oxide t½ increased by about 38% with ketoconazole.

Eleven of the 16 subjects had quantifiable concentrations of roflumilast N-oxide at predose on Day 11, and the predose concentrations exceeded 5% of Cmax for 2 subjects. Corrected Cmax and AUC values (both AUC(0-tlqc) and AUC(0-∞)) were determined for roflumilast N-oxide on Day 11.

Results for corrected Cmax and AUC were comparable to those for the uncorrected values.

Table 9. Summary of Roflumilast N-Oxide Pharmacokinetic Parameter Values Following Single Oral 500-µg Roflumilast Tablet Doses Alone (Reference) and With Steady-State Ketoconazole (Test) (Protocol A5821012)

| | Least-Squares Mean Parameter Values | | | |
| | Roflumilast With Ketoconazole (Test, N = 16) | Roflumilast Alone (Reference, N = 16) | | 90% Confidence Interval |
Parameter			Ratio	
Cmax, ng/mL	6.69	10.7	62.3	56.8 to 68.3
AUC(0-tlqc), ng*hr/mL	586	540	109	97.8 to 121
AUC(0-∞), ng*hr/mL	611	595	103	91.5 to 115
tmax	21.5	9.56		Not Applicable
t½	43.5	31.5		Not Applicable

Parameters are defined in Table 5.
Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Figure 3. Mean Roflumilast N-Oxide Plasma Concentration-Time Profiles Following Single Oral 500-µg Roflumilast Doses Alone (Filled Symbols) and With Steady-State Ketoconazole (Open Symbols) (Protocol A5821012)
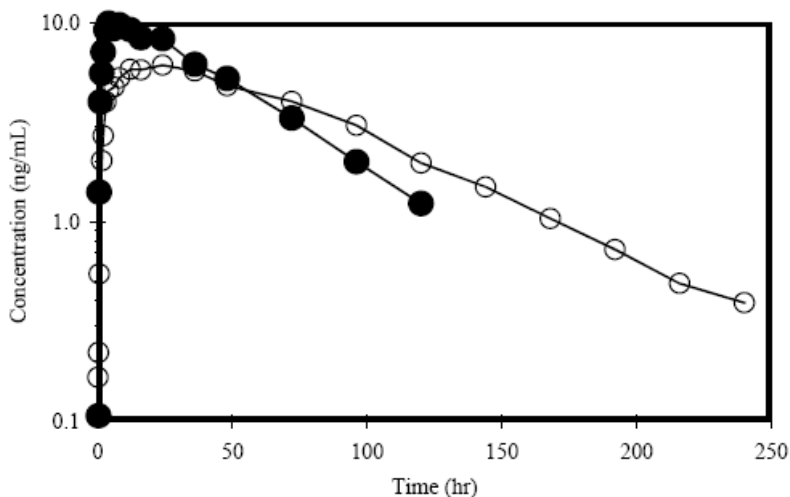
CONCLUSION(S)

Based on AUC values, steady-state ketoconazole administration (200 mg, BID) increased roflumilast exposure approximately 2-fold but had no effect on roflumilast-N-oxide exposure. Cmax values of roflumilast increased with steady-state ketoconazole administration (23%) while Cmax values for roflumilast-N-oxide decreased about 38%.

CP-061

Study Title: 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

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*
 . 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 coadministration
 . To evaluate whether a potential interaction would affect the safety and tolerability of single-dose MDZ and steady-state roflumilast

Study Design: This study was conducted according to an open, randomized, five period cross-over design with interspersed fixed treatment periods.
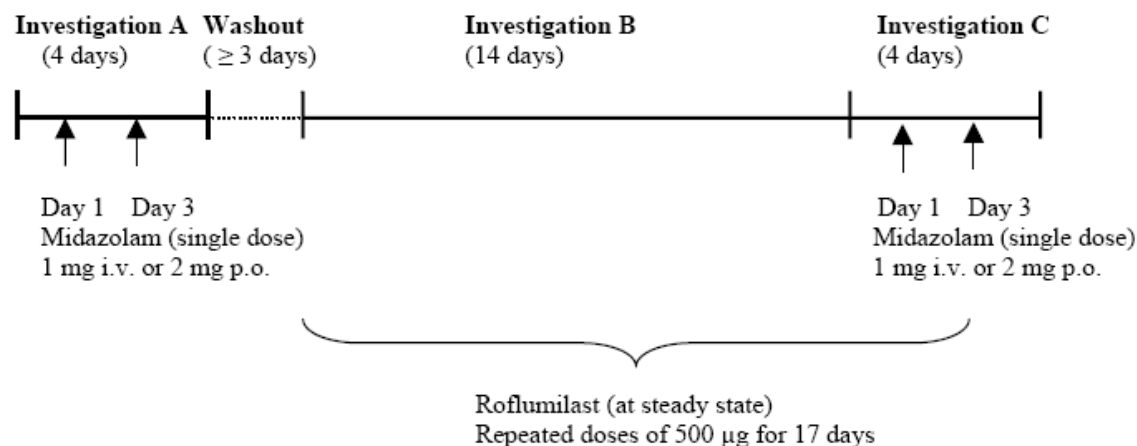
Blood samplings for pharmacokinetic purposes were performed on:
 . Study Days 1 and 3 of **Investigation A** at pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 h after study drug administration (MDZ 1 mg i.v. or 2 mg 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)

Study Population: Sixteen healthy volunteers (8 males and 8 females) entered the study. Fifteen subjects completed the study. One subject was withdrawn due to an adverse event following 1 dose of 500 µg roflumilast.

Data Analysis: Pharmacokinetic parameters including log-transformed maximum observed plasma concentration (Cmax,) area under the plasma concentration-time profile (AUC), and oral clearance (CL/F) values were analyzed with an analysis of variance (ANOVA) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (roflumilast with erythromycin) as a percentage of reference (roflumilast alone) were generated. Lack of an effect of erythromycin on roflumilast would be concluded if the 90% confidence intervals for both Cmax and AUC, based on log-transformed data, were entirely contained within the interval of 80% to 125%.

Results: 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.

Plasma concentration time profiles of roflumilast, roflumilast N-oxide, MDZ, 1-hydroxy MDZ, and 4-hydroxy MDZ and statistical analysis are shown in the following figures and tables.

Figure 3   Geom. mean MDZ plasma concentrations (semilog. scale) following single i.v. dose of 1 mg MDZ administered alone or in combination with 500 µg roflumilast at steady state.
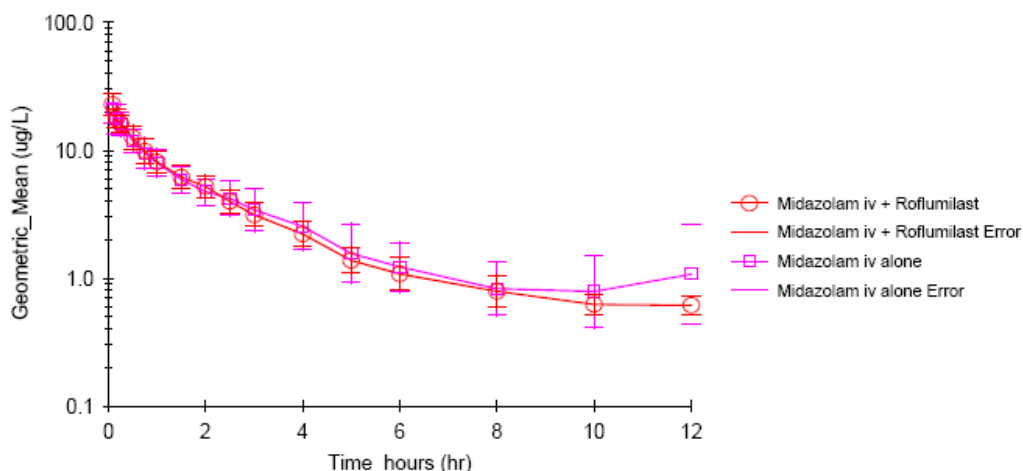
Data source: Section 15.2.1.1; geometric mean displayed with error bars (68% range)

Figure 5   Geom. mean MDZ plasma concentrations (semilog. scale) following single p.o. dose of 2 mg MDZ administered alone or in combination with 500 μg roflumilast at steady state.
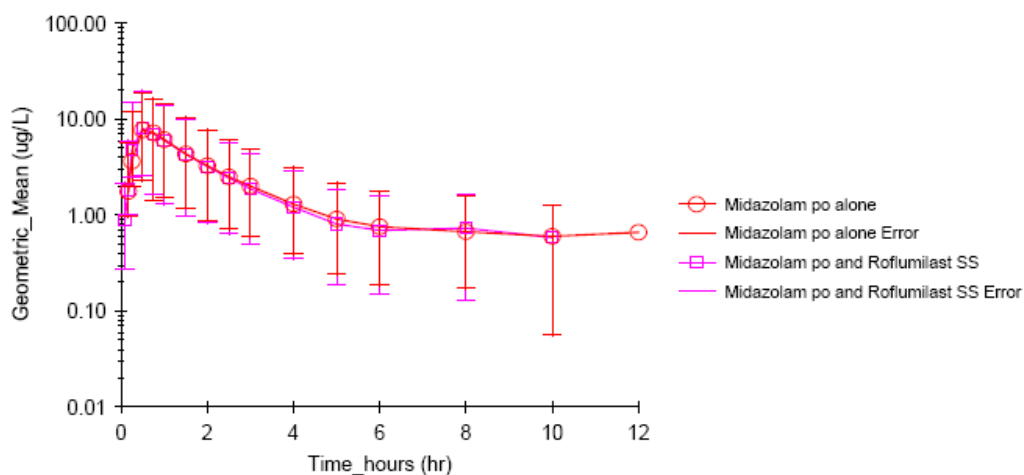
Data source: Section 15.2.1.2; geometric mean displayed with error bars (68% range)

Table 9:   Summary of pharmacokinetic parameter estimates of MDZ after single i.v. dose of 1 mg administered alone (MDZ Reference) and together with 500 μg roflumilast at steady state (MDZ $Test_{iv}$) [geometric mean, (68% range); t_{max}: median (min, max)].

MDZ i.v. (N=18)							
		AUC_{last} (hr*μg/L)	$AUC_{(0-\infty)}$ (hr*μg/L)	C_{max} (μg/L)	CL (L/hr)	$t_{1/2}$ (hr)	t_{max} (hr)
MDZ i.v. alone	Geometric Mean	33.615	36.342	22.035	27.516	2.437	0.083
	Upper 68%	45.9233	50.6518	27.8444	38.3505	3.5035	0.25
	Lower 68%	24.6056	26.0749	17.4377	19.7424	1.6951	0.083
MDZ i.v. + Roflu	Geometric Mean	32.866	35.247	22.934	28.372	2.419	0.083
	Upper 68%	39.5450	41.9879	27.6222	33.7980	3.4259	0.167
	Lower 68%	27.3151	29.5883	19.0415	23.8171	1.7081	0.083

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.1.1

Table 10: Summary of pharmacokinetic parameter estimates of MDZ after single p.o. dose of 2 mg administered alone (MDZ Reference) and together with 500 μg roflumilast at steady state (MDZ Test$_{po}$) [geometric mean, (68% range); t$_{max}$: median (min, max)].

MDZ p.o. (N=18)		AUC$_{last}$ (hr*μg/L)	AUC$_{(0-\infty)}$ (hr*μg/L)	C$_{max}$ (μg/L)	CL_F (L/hr)	t$_{1/2}$ (hr)	t$_{max}$ (hr)
MDZ p.o. alone	Geometric Mean	16.144	17.932	8.976	111.53	1.709	0.5
	Upper 68%	23.1165	25.1683	12.2137	156.5372	2.4324	1
	Lower 68%	11.2746	12.7762	6.5966	79.4632	1.2007	0.25
MDZ p.o. + Roflu	Geometric Mean	15.928	17.551	8.722	113.952	1.619	0.5
	Upper 68%	21.7819	23.8339	11.9037	154.7448	2.2206	1
	Lower 68%	11.6473	12.9243	6.3907	83.9127	1.1803	0.25

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.1.2

Table 11: Point estimate and 90%-confidence limits for the Test/Reference ratios of i.v. MDZ primary pharmacokinetic parameter estimates following single i.v. dose of 1 mg MDZ administered alone or together with 500 μg roflumilast at steady state.

Geometric mean ratio and 90% CI							
Ref (N = 18)	Test (N= 18)	Dependent	RefGeoLSM	TestGeoLSM	Ratio[%Ref]	CI_90_Lower	CI_90_Upper
MDZ i.v. alone	MDZ i.v. + Roflu	AUC$_{(0-\infty)}$	36.342	35.247	96.985	83.505	112.64
		AUC$_{last}$	33.615	32.866	97.771	84.627	112.956
		CL	27.516	28.372	103.109	88.778	119.754
		C$_{max}$	22.035	22.934	104.078	92.382	117.255

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.2.1

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Table 12: Point estimate and 90%-confidence limits for the Test/Reference ratios of p.o. MDZ primary pharmacokinetic parameter estimates following single p.o. dose of 2 mg MDZ administered alone or together with 500 μg roflumilast at steady state.

Geometric mean ratio and 90% CI							
Ref (N = 18)	Test (N= 18)	Dependent	RefGeoLSM	TestGeoLSM	Ratio[%Ref]	CI_90_Lower	CI_90_Upper
MDZ p.o. alone	MDZ p.o. + Roflu	$AUC_{(0-\infty)}$	17.932	17.551	97.874	81.592	117.406
		AUC_{last}	16.144	15.928	98.659	81.609	119.273
		CL/F	111.53	113.952	102.172	85.175	122.561
		C_{max}	8.976	8.722	97.164	81.618	115.67

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.2.2

Pharmacokinetic Parameter Estimates of 1-Hydroxy MDZ

Figure 7   Geom. mean 1-hydroxy MDZ plasma concentrations (semilog. scale) following single dose of 1 mg i.v. MDZ administered alone or in combination with 500 μg roflumilast at steady state.
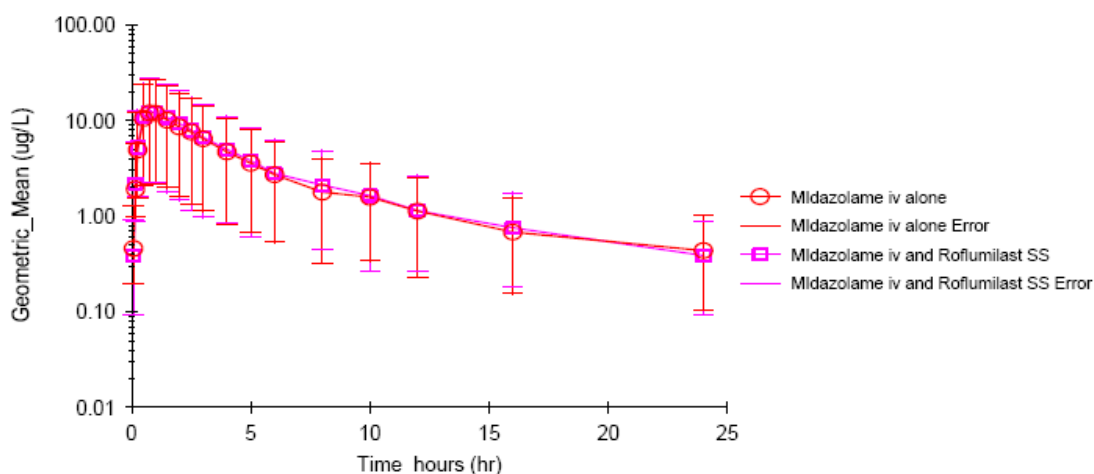
Data source: Section 15.2.1.3; geometric mean displayed with error bars (68% range)

Figure 9   Geom. mean 1-hydroxy MDZ plasma concentrations (semilog. scale) following single dose of 2 mg p.o. MDZ administered alone or in combination with 500 µg roflumilast at steady state.
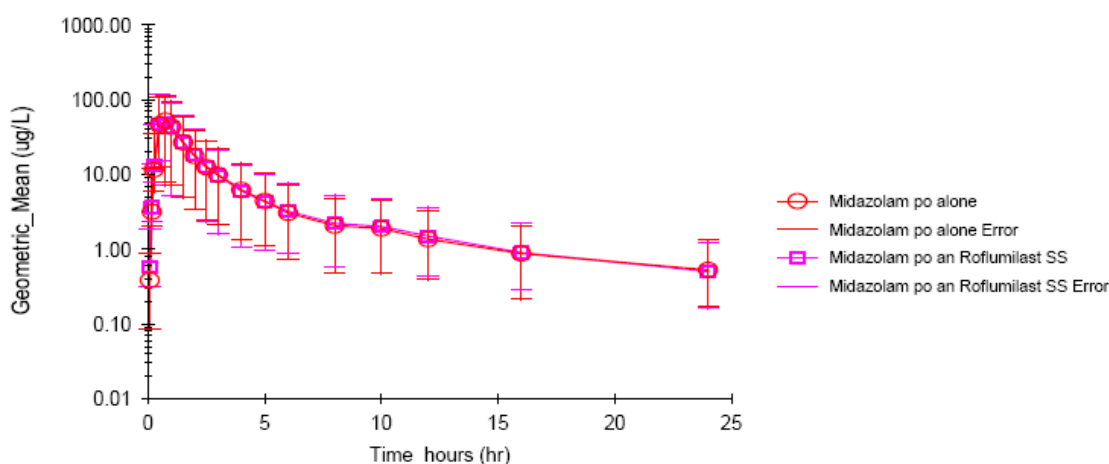
Data source: Section 15.2.1.4; geometric mean displayed with error bars (68% range)

Table 13:   Summary of pharmacokinetic parameter estimates of 1-hydroxy MDZ after single i.v. dose of 1 mg MDZ administered alone (MDZ Reference) and together with 500 µg roflumilast at steady state (MDZ $Test_{iv}$) [geometric mean, (68% range); t_{max}: median (min, max)].

1-hydroxy MDZ i.v. (N=18)						
		$AUC_{(0-\infty)}$ (hr*µg/L)	AUC %Extrap	C_{max} (µg/L)	$t_{\frac{1}{2}}$ (hr)	t_{max} (hr)
MDZ i.v. alone	Geometric Mean	63	7.464	12.289	7.414	0.75
	Upper 68%	75.8028	11.2199	15.0715	9.5665	1
	Lower 68%	52.3596	4.9654	10.0202	5.7458	0.75
MDZ i.v. + Roflu	Geometric Mean	65.315	6.169	12.614	6.914	0.75
	Upper 68%	77.2635	8.9570	15.3054	8.2784	1
	Lower 68%	55.2143	4.2488	10.3959	5.7745	0.75

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.1.3

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Table 14:   Summary of pharmacokinetic parameter estimates of 1-hydroxy MDZ after single p.o. dose of 2 mg MDZ administered alone (MDZ Reference) and together with 500 µg roflumilast at steady state (MDZ Test$_{po}$) [geometric mean, (68% range); t_{max}: median (min, max)].

1-hydroxy MDZ p.o. (N=18)						
		AUC_{last} (hr*µg/L)	$AUC_{(0-\infty)}$ (hr*µg/L)	C_{max} (µg/L)	$t_{\frac{1}{2}}$ (hr)	t_{max} (hr)
MDZ p.o. alone	Geometric Mean	53.258	59.504	17.646	7.295	2
	Upper 68%	64.9195	73.1889	22.0103	9.6041	2
	Lower 68%	43.6913	48.3779	14.1471	5.5411	2
MDZ p.o. + Roflu	Geometric Mean	54.13	59.055	18.007	6.143	2
	Upper 68%	65.3259	72.2021	22.2816	8.3504	2
	Lower 68%	44.8529	48.3018	14.5525	4.5191	2

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.1.4

Table 15:   Point estimate and 90%-confidence limits for the Test/Reference ratios of 1-hydroxy MDZ pharmacokinetic parameter estimates after single i.v. dose of 1 mg MDZ administered alone or together with 500 µg roflumilast at steady state.

Geometric mean ratio and 90% CI							
Ref (N = 18)	Test (N= 18)	Dependent	RefGeoLSM	TestGeoLSM	Ratio[%Ref]	CI_90_Lower	CI_90_Upper
MDZ i.v. alone	MDZ i.v. + Roflu	$AUC_{(0-\infty)}$	62.22	65.58	105.41	95.50	116.35
		AUC_{last}	58.00	61.13	105.39	95.56	116.23
		C_{max}	12.29	12.61	102.64	91.76	114.82

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.2.4

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Table 16: Point estimate and 90%-confidence limits for the Test/Reference ratios of 1-hydroxy MDZ pharmacokinetic parameter estimates after single p.o. dose of 2 mg MDZ administered alone or together with 500 µg roflumilast at steady state.

Geometric mean ratio and 90% CI							
Ref (N = 18)	Test (N= 18)	Dependent	RefGeoLSM	TestGeoLSM	Ratio[%Ref]	CI_90_Lower	CI_90_Upper
MDZ p.o. alone	MDZ p.o. + Roflu	$AUC_{(0-\infty)}$	59.50	59.06	99.25	88.46	111.35
		AUC_{last}	53.26	54.13	101.64	91.16	113.32
		C_{max}	17.65	18.01	102.05	90.29	115.34

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.2.5

Pharmacokinetic Parameter Estimates of 4-Hydroxy MDZ

Figure 11   Geom. mean 4-hydroxy MDZ plasma concentrations (semilog. scale) following single dose of 1 mg i.v. MDZ administered alone or in combination with 500 µg roflumilast at steady state.
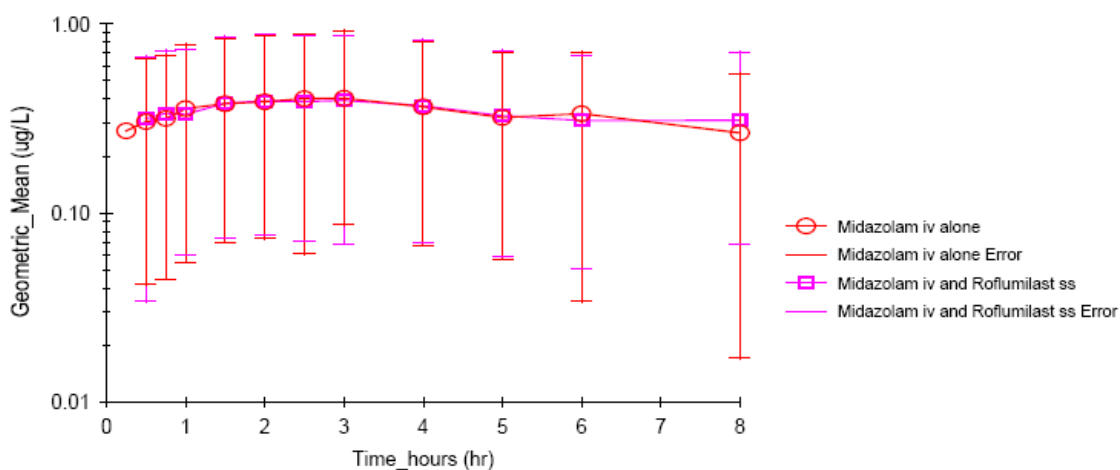
Data source: Section 15.2.1.5; geometric mean displayed with error bars (68% range)

Figure 13   Geom. mean 4-hydroxy MDZ plasma concentrations (semilog. scale) following single dose of 2 mg p.o. MDZ administered alone or in combination with 500 μg roflumilast at steady state.
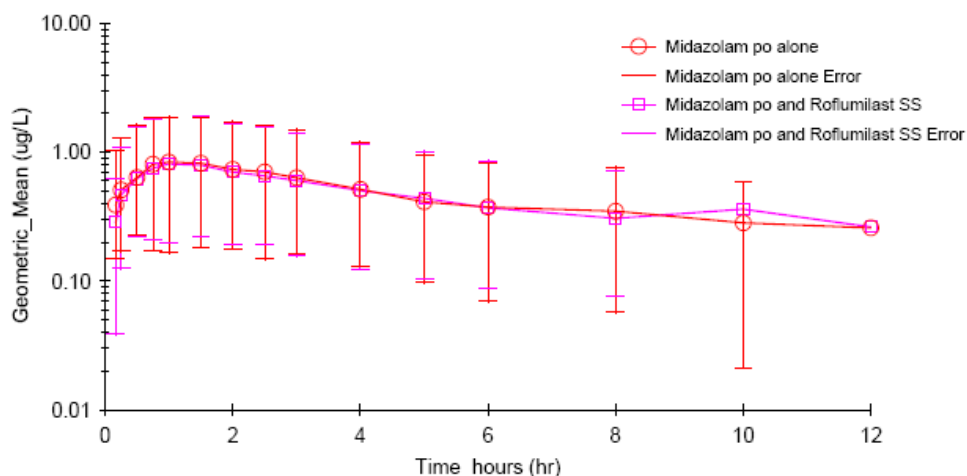
Data source: Section 15.2.1.6; geometric mean displayed with error bars (68% range)

Table 17:   Summary of pharmacokinetic parameter estimates of 4-hydroxy MDZ after single i.v. dose of 1 mg MDZ administered alone (MDZ Reference) and together with 500 μg roflumilast at steady state (MDZ Test$_{iv}$) [geometric mean, (68% range); t$_{max}$: median (min, max)].

4-hydroxy MDZ i.v. (N=18)					
		AUC$_{last}$ (hr*μg/L)	C$_{max}$ (μg/L)	t$_{\frac{1}{2}}$ (hr)	t$_{max}$ (hr)
MDZ i.v. alone	Geometric Mean	1.683	0.431	7.502	2.5
	Upper 68%	2.5820	0.5165	28.9674	3
	Lower 68%	1.0970	0.3596	1.9429	1.5
MDZ i.v. + Roflu	Geometric Mean	1.541	0.428	5.518	2.5
	Upper 68%	2.5094	0.5107	7.3508	4
	Lower 68%	0.9463	0.3587	4.1422	0.75

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.1.5

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Table 18: Summary of pharmacokinetic parameter estimates of 4-hydroxy MDZ after single p.o. dose of 2 mg MDZ administered alone (MDZ Reference) and together with 500 µg roflumilast at steady state (MDZ Test$_{po}$) [geometric mean, (68% range); t_{max}: median (min, max)].

4-hydroxy MDZ p.o. (N=18)		AUC$_{last}$ (hr*µg/L)	AUC$_{(0-\infty)}$ (hr*µg/L)	C$_{max}$ (µg/L)	t$_{½}$ (hr)	t$_{max}$ (hr)
MDZ p.o. alone	Geometric Mean	3.527	5.135	0.896	3.383	1
	Upper 68%	5.1575	7.0082	1.1266	4.1861	1.5
	Lower 68%	2.4120	3.7625	0.7126	2.7340	0.5
MDZ p.o. + Roflu	Geometric Mean	3.26	5.033	0.864	3.475	1
	Upper 68%	5.4561	6.7262	1.1570	4.9214	2
	Lower 68%	1.9479	3.7660	0.6452	2.4537	0.5

MDZ: midazolam; Roflu: roflumilast

Data source: Section 15.2.1.6

Roflumilast and its Metabolite Roflumilast N-Oxide

Figure 15   Geom. mean roflumilast plasma concentrations (semilog. scale) following multiple once-daily oral doses of 500 µg roflumilast administered alone or in combination with a single dose of MDZ (1 mg i.v. or 2 mg p.o.)
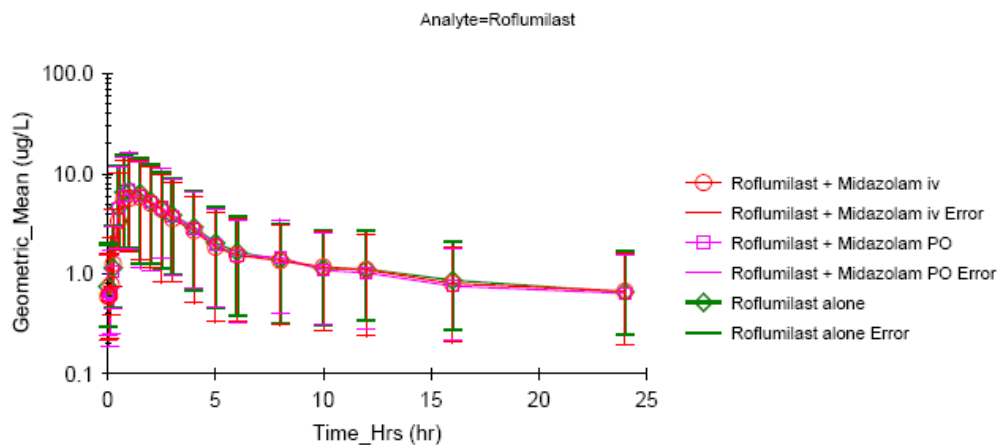
Data source: Section 15.2.1.7; geometric mean displayed with error bars (68% range)

Figure 17 Geom. mean roflumilast N-oxide plasma concentrations (linear scale) following multiple once-daily oral doses of 500 μg roflumilast administered alone or in combination with a single dose of MDZ (1 mg i.v. or 2 mg p.o.).
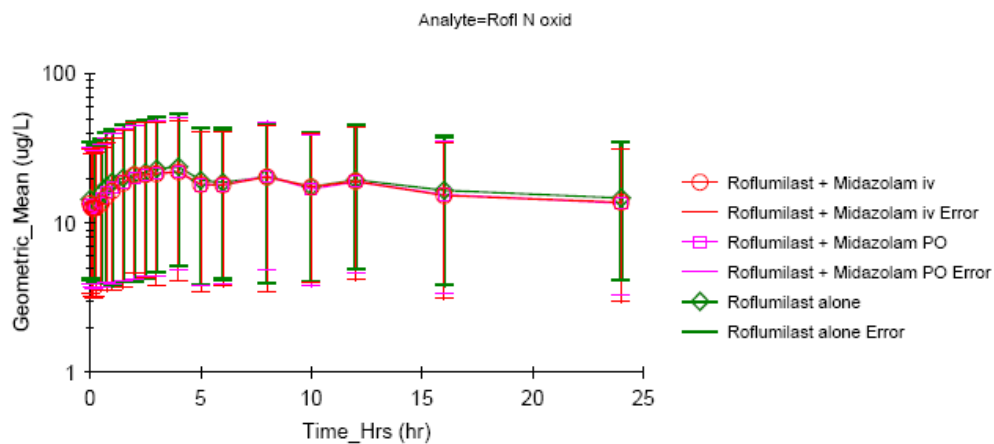
Data source: Section 15.2.1.8; geometric mean displayed with error bars (68% range)

Table 19: Summary of pharmacokinetic parameter estimates of 500 µg roflumilast at steady state without (Reference) and with concomitant MDZ (1 mg i.v. or 2 mg p.o.) treatment (Test) [geometric mean, (68% range); t_{max}: median (min, max)].

Analyte (N=18)			CLss_F (L/hr)	AUC_{last} (hr*µg/L)	C_{max} (µg/L)	$t_{1/2}$ (hr)	t_{max} (hr)
Roflumilast	Reference (Roflumilast alone)	Geometric Mean	12.117	41.263	7.941	16.949	1
		Upper 68%	15.404	52.456	9.671	26.999	2.5
		Lower 68%	9.532	32.459	6.520	10.640	0.5
	$Test_{po}$ (Roflumilast + MDZ p.o.)	Geometric Mean	12.638	39.564	7.783	15.269	1
		Upper 68%	15.643	48.971	9.893	21.431	2.5
		Lower 68%	10.210	31.964	6.123	10.879	0.5
	$Test_{iv}$ (Roflumilast + MDZ i.v.)	Geometric Mean	12.917	38.707	7.374	16.594	0.875
		Upper 68%	15.766	47.244	9.579	23.510	2.5
		Lower 68%	10.583	31.713	5.677	11.712	0.5

Reference: 500 µg roflumilast at steady state administered alone; $Test_{iv}$: 500 µg steady-state roflumilast with concomitant 1 mg i.v. MDZ; $Test_{po}$: 500 µg steady-state roflumilast with concomitant 2 mg p.o. MDZ

CLss_F: apparent oral clearance (CL/F) at steady state (ss)

Data source: Section 15.2.1.7

Table 20: Summary of roflumilast N-oxide pharmacokinetic parameter estimates following steady-state dosing of 500 μg roflumilast daily without (Reference) and with concomitant MDZ (1 mg i.v. or 2 mg p.o.) treatment (Test) [geometric mean, (68% range); tmax: median (min, max)].

Analyte (N=18)			AUC_{last} (hr*μg/L)	C_{max} (μg/L)	$t_{1/2}$ (hr)	t_{max} (hr)
Roflumilast N-oxide	Reference (Roflumilast alone)	Geometric Mean	436.016	24.598	46.594	4
		Upper 68%	560.640	31.414	121.240	12
		Lower 68%	339.095	19.261	17.907	2
	Test$_{po}$ (Roflumilast + MDZ p.o.)	Geometric Mean	414.193	23.162	34.734	4
		Upper 68%	529.658	29.968	53.657	8
		Lower 68%	323.899	17.902	22.484	1.5
	Test$_{iv}$ (Roflumilast + MDZ i.v.)	Geometric Mean	413.001	22.818	33.792	3.5
		Upper 68%	516.849	28.221	47.197	8
		Lower 68%	330.019	18.450	24.195	2

Reference: 500 μg roflumilast at steady state administered alone; Test$_{iv}$: 500 μg steady-state roflumilast with concomitant 1 mg i.v. MDZ; Test$_{po}$: 500 μg steady-state roflumilast with concomitant 2 mg p.o. MDZ

Note: Point estimate and 90%-confidence limits are not reported for CLss_F (apparent oral clearance at steady state) in the case of roflumilast N-oxide because this would be based on various unreliable assumptions (see Section 9.8)

Data source: Section 15.2.1.8

Table 21: Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast primary pharmacokinetic parameter estimates following repeated once-daily oral administration of 500 µg roflumilast together with MDZ (1 mg i.v. or 2 mg p.o.)

Analyte: Roflumilast, Reference: Roflumilast alone (N=18)						
Test	Dependent	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
p.o. (Roflumilast + MDZ p.o.)	AUC$_{last}$	41.263	39.564	95.881	84.879	108.310
i.v. (Roflumilast + MDZ i.v.)		41.263	38.707	93.806	83.041	105.965
p.o. (Roflumilast + MDZ p.o.)	CLss_F	12.117	12.638	104.296	92.328	117.815
i.v. (Roflumilast + MDZ i.v.)		12.117	12.917	106.603	94.371	120.422
p.o. (Roflumilast + MDZ p.o.)	C$_{max}$	7.941	7.783	98.016	85.988	111.727
i.v. (Roflumilast + MDZ i.v.)		7.941	7.374	92.859	81.463	105.848

Reference: 500 µg roflumilast at steady state administered alone; Test$_{iv}$: 500 µg steady-state roflumilast with concomitant 1 mg i.v. MDZ; Test$_{po}$: 500 µg steady-state roflumilast with concomitant 2 mg p.o. MDZ

CLss_F: apparent oral clearance (CL/F) at steady state (ss)

Data source: Section 15.2.2.3

Table 22: Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast N-oxide primary pharmacokinetic parameter estimates following repeated once-daily oral administration of 500 µg roflumilast together with MDZ (1 mg i.v. or 2 mg p.o.)

Analyte: Roflumilast N-oxide, Reference: Roflumilast alone (N=18)						
Test	**Dependent**	**Ref Geo LSM**	**Test Geo LSM**	**Ratio [%Ref]**	**CI 90 Lower**	**CI 90 Upper**
p.o. (Roflumilast + MDZ p.o.)	AUC_{last}	436.016	414.193	94.995	83.040	108.670
i.v. (Roflumilast + MDZ i.v.)		436.016	413.001	94.722	82.801	108.358
p.o. (Roflumilast + MDZ p.o.)	C_{max}	24.598	23.162	94.162	82.396	107.608
i.v. (Roflumilast + MDZ i.v.)		24.598	22.818	92.761	81.170	106.007

Reference: 500 µg roflumilast at steady state administered alone; $Test_{iv}$: 500 µg steady-state roflumilast with concomitant 1 mg i.v. MDZ; $Test_{po}$: 500 µg steady-state roflumilast with concomitant 2 mg p.o. MDZ

Note: Point estimate and 90%-confidence limits are not reported for CLss_F (apparent oral clearance at steady state) in the case of roflumilast N-oxide because this would be based on various unreliable assumptions (see Section 9.8)

Data source: Section 15.2.2.3

Conclusions: Based on CL (MDZ i.v.), CL/F (MDZ p.o.), AUC, and Cmax, steady-state roflumilast (500 µg once daily) does not alter the pharmacokinetics of single-dose MDZ following i.v. and p.o. administration. 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.

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

The pharmacokinetic parameter estimates AUC, Cmax, tmax, and t1/2 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 Cmax 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.

CP-064

Study Protocol No.:	**BY217/CP-064**
Study Title:	Effects of Rifampicin (600 mg Repeated Oral Dose) Co-administration on the Pharmacokinetics of Roflumilast (500 mcg Single Oral Dose) and Roflumilast-N-Oxide. A CYP3A4 Inducer Study in Healthy Male Subjects.
Phase:	1
Principal Investigator:	Manuela Koch, Physician
Study Population:	Healthy Male Subjects
Study Site:	AAI Applied Analytical Industries Deutschland, ALTANA Pharma AG, Konstanz, Germany
Study Period:	16-Sep-2004 to 16-Oct-2004
Report No.:	8/2005

OBJECTIVE(S)

The primary objective of this study was to investigate the effects of steady-state rifampicin (600 mg repeated oral dose) co-administration on the pharmacokinetics of roflumilast and roflumilast N-oxide after a single oral dose of 500 μg roflumilast. The secondary objectives were to assess safety and tolerability throughout all treatment periods.

Further, pharmacokinetics of ADCP and ADCP N-oxide were assessed after co-administration of roflumilast and rifampicin.

STUDY DESIGN

This study was conducted according to an open-label, three-period, fixed-sequence design. It consisted of a screening examination, Period 1 (1 day), a washout period (3 days), Period 2 (7 days), Period 3 (4 days), and a post-study examination. The study design did not involve any washout phase between Period 2 and Period 3. A schematic depiction of the study design is shown below:
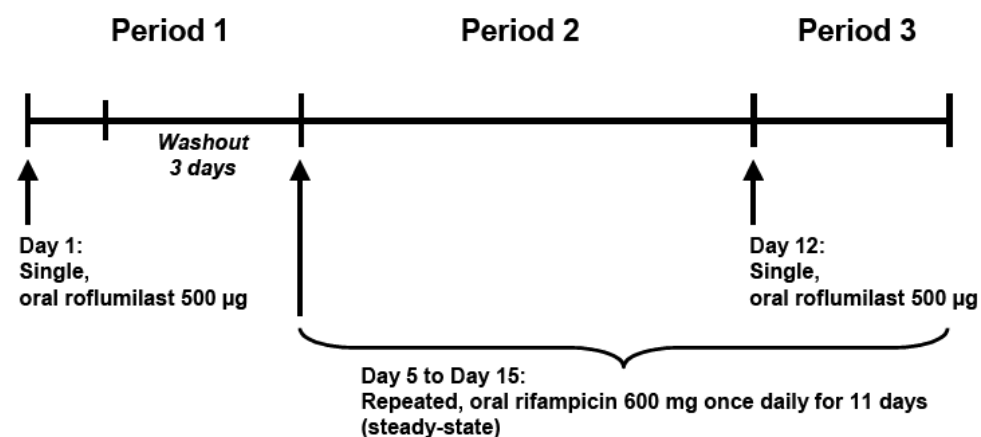
STUDY TREATMENT

Period 1: Administration of a single, oral dose of roflumilast 500 μg once daily in the morning of study Day 1

Period 2: Repeated administration of oral rifampicin 600 mg once daily in the morning of study Day 5 to Day 11

Period 3: Continued (repeated) once-daily, oral administration of rifampicin 600 mg in the morning of Day 12 to Day 15 <u>and</u> co-administration of a single oral dose of roflumilast 500 μg in the morning of study Day 12.

PHARMACOKINETIC BLOOD SAMPLING

Blood samples for measuring plasma concentrations of roflumilast and roflumilast N-oxide over time for pharmacokinetic analyses were taken at:

Period 1: pre-dose, and 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 30 h, 48 h, 54 h, 72 h and 96 h after administration. Period 1 is regarded as the pre-induction phase and will be referred to accordingly hereafter.

Period 3: pre-dose, and 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 30 h, 48 h, 54 h, 72 h and 96 h after administration. Period 3 is regarded as the induced phase and will be referred to accordingly hereafter.

Blood samples collected in Period 3 and used to assess roflumilast and roflumilast N-oxide in plasma were also used to measure plasma concentrations of ADCP and ADCP N-oxide.

Blood samples to determine plasma concentrations of rifampicin and to check for adequate exposure were collected pre-dose on Day 5, Day 10, and Day 11 during Period 2. On Day 12 (Period 3), blood samples were taken pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, and 3 h after administration.

ANALYTICAL METHODS
The plasma concentrations of roflumilast, roflumilast N-oxide, ADCP, and ADCP N-oxide were determined using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay. The plasma concentrations of rifampicin were determined by using a validated liquid chromatography method with ultraviolet detection.

ANALYSIS OF PHARMACOKINETIC PARAMETERS
Pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide following oral administration were obtained by standard non-compartmental analysis using the program WinNonlin Professional, Version 4.1. Calculations of pharmacokinetic parameter estimates for ADCP, ADCP N-oxide, and rifampicin were not performed, as this was not the objective of this study.

RESULTS
Roflumilast:
Following the induction of CYP3A4 with rifampicin, the extent ($AUC_{0-\infty}$) and rate (Cmax) of systemic exposure of roflumilast decreased by about 79% and 68%, respectively, when compared with the respective values of roflumilast under non-induced conditions.

T-Table 8: Pharmacokinetic parameter estimates of roflumilast in Period 1 (N = 16) and Period 3 (N = 15) following oral administration of a single dose of roflumilast 500 μg.

Per[a]	Pharmacokinetic parameter estimate [b]	Mean	SD	Min	Median	Max	Geom. Mean	Upper limit 68% range	Lower limit 68% range
	$AUC_{(0-\infty)}$ (h*μg/L)	42.93	22.05	21.26	32.49	92.43	38.49	61.53	24.08
	AUC_{last} (h*μg/L)	39.25	20.24	18.25	29.64	84.25	35.06	56.66	21.70
	CL/F (L/h)	14.26	5.82	5.41	15.44	23.52	12.99	20.77	8.13
1	C_{max} (μg/L)	7.287	2.78	3.82	6.13	13.20	6.86	9.70	4.85
	$C_{max}/AUC_{(0-\infty)}$ (1/h)	0.20	0.09	0.08	0.17	0.40	0.18	0.28	0.11
	$t_{1/2}$ (h)	17.72	9.02	5.84	14.66	34.18	15.68	26.30	9.35
	t_{max} (h)	1.03	0.59	0.50	1.00	3.00	0.92	1.47	0.58
	$AUC_{(0-\infty)}$ (h*μg/L)	8.36	3.43	4.16	7.24	15.99	7.80	11.37	5.36
	AUC_{last} (h*μg/L)	6.93	2.75	3.55	6.07	13.28	6.50	9.36	4.51
	CL/F (L/h)	68.20	24.18	31.27	69.07	120.18	64.06	93.35	43.96
3	C_{max} (μg/L)	2.24	0.58	1.28	2.26	3.60	2.17	2.82	1.67
	$C_{max}/AUC_{(0-\infty)}$ (1/h)	0.29	0.08	0.13	0.31	0.42	0.28	0.38	0.21
	$t_{1/2}$ (h)	7.15	4.57	2.15	5.23	17.21	5.94	11.19	3.16
	t_{max} (h)	1.00	0.27	0.50	1.00	1.50	0.96	1.30	0.71

[a] Period 1: Roflumilast pre-induction; Period 3: Roflumilast after the induction with rifampicin; [b] For explanation of pharmacokinetic parameter estimates see T-Table 6. Data source: section 15.2.1

Percent ratios of Test/Reference[a] of roflumilast pharmacokinetic parameter estimates based on least-squares geometric mean and the respective lower and upper limits of the 90% confidence interval (ANOVA). Calculations were performed with observations from N = 15 subjects in Period 1 (Reference) and Period 3 (Test).

Pharmacokinetic parameter estimate	RefGeo LSMean	TestGeo LSMean	Difference	Ratio (% Ref)	CI 90 Lower	CI 90 Upper
$AUC_{(0-\infty)}$ (h*μg/L)	37.77	7.80	-1.577	20.66	15.81	27.01
AUC_{last} (h*μg/L)	34.29	6.50	-1.663	18.95	14.50	24.77
CL/F (L/h)	13.24	64.06	1.577	483.92	370.24	632.49
C_{max} (h)	6.78	2.17	-1.139	32.02	26.37	38.87

[a] Percent rations = (Period 3 'roflumilast+rifampicin'/Period 1 'roflumilast alone') x 100.

Figure 3: Geometric mean (and 68% range) of roflumilast plasma concentration *vs* time curves following administration of a single dose of roflumilast 500 μg in Period 1 and in Period 3 (semilog. scale).
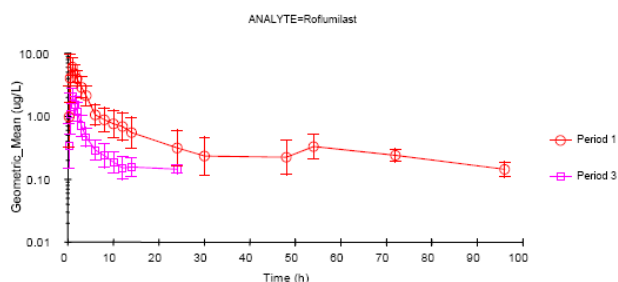
Roflumilast-N-Oxide:

roflumilast N-oxide showed only a decrease in $AUC_{(0-\infty)}$ of 56% whereas C_{max} was increased by 30%. The increase of C_{max} of roflumilast N-oxide in the induced phase is consistent with the observed increase in CL/F of roflumilast, i.e. the rate of conversion of roflumilast to its N-oxide metabolite was considerably higher when compared to the non-induced phase. Statistical comparison of the key inferential parameter CL/F in Period 1 and Period 3 confirmed this observation: CL/F of roflumilast was almost five-fold higher in Period 3 and which may explain the decrease in $AUC_{(0-\infty)}$ and C_{max} of roflumilast.

Notably, under CYP3A4 induction, the decrease of $AUC_{(0-\infty)}$ of roflumilast N-oxide (56%) was less pronounced when compared with the decrease of roflumilast $AUC_{(0-\infty)}$ (79%), which suggests that the relative contribution of CYP3A4 on the clearance of the N-oxide metabolite may be lower than for the parent compound roflumilast.

T_{max} of roflumilast N-oxide also reflected the increased formation rate. In the same subject population, median t_{max} values showed tendencies towards shorter t_{max} for roflumilast N-oxide after induction and longer t_{max} without induction. Elimination $t_{1/2}$ was also decreased about three-fold.

T-Table 9: Pharmacokinetic parameter estimates of roflumilast N-oxide in Period 1 (N = 16) and Period 3 (N = 15) following administration of a single dose of roflumilast 500 µg.

Per[a]	Pharmacokinetic parameter estimate [b]	Mean	SD	Min	Median	Max	Geom. Mean	Upper limit 68% range	Lower limit 68% range
1	$AUC_{(0-\infty)}$ (h*µg/L)	454.05	247.86	250.03	378.16	1287.00	414.06	622.19	275.55
	AUC_{last} (h*µg/L)	382.01	116.56	245.05	363.15	726.17	367.96	484.34	279.54
	C_{max} (µg/L)	9.64	1.86	5.64	10.20	13.30	9.45	11.69	7.64
	$C_{max}/AUC_{(0-\infty)}$ (1/h)	0.03	0.01	0.01	0.02	0.04	0.02	0.04	0.01
	$t_{1/2}$ (h)	26.82	15.96	13.91	21.73	78.15	23.99	37.54	15.34
	t_{max} (h)	8.06	6.72	3.00	5.00	30.00	6.49	12.20	3.45
3	$AUC_{(0-\infty)}$ (h*µg/L)	185.46	47.67	126.25	166.05	298.33	180.20	230.23	141.03
	AUC_{last} (h*µg/L)	182.21	47.04	124.57	164.16	293.41	177.00	226.25	138.48
	C_{max} (µg/L)	12.45	2.44	9.68	11.90	16.90	12.23	14.81	10.10
	$C_{max}/AUC_{(0-\infty)}$ (1/h)	0.07	0.01	0.05	0.07	0.09	0.07	0.08	0.06
	$t_{1/2}$ (h)	10.05	1.83	6.88	10.28	13.07	9.89	11.97	8.17
	t_{max} (h)	2.87	1.29	1.50	2.00	6.00	2.63	4.01	1.72

[a] Period 1: Roflumilast pre-induction; Period 3: Roflumilast after the induction with rifampicin; [b] For explanation of pharmacokinetic parameter estimates see T-Table 6. Data source: section 15.2.1

Percent ratios of Test/Reference[a] of roflumilast N-oxide pharmacokinetic parameter estimates based on least-squares geometric mean and the respective lower and upper limits of the 90% confidence interval (ANOVA). Calculations were performed with observations from N = 15 subjects in Period 1 (Reference) and Period 3 (Test).

Pharmacokinetic parameter estimate	RefGeo LSMean	TestGeo LSMean	Difference	Ratio (% Ref)	CI 90 Lower	CI 90 Upper
$AUC_{(0-\infty)}$ (h*µg/L)	407.15	180.19	-0.815	44.26	35.80	54.71
AUC_{last} (h*µg/L)	363.06	177.00	-0.718	48.75	41.41	57.40
C_{max} (h)	9.38	12.23	0.265	130.40	114.79	148.13

[a] Percent rations = (Period 3 'roflumilast+rifampicin'/Period 1 'roflumilast alone') x 100.

Figure 5: Geometric mean (and 68% range) of roflumilast N-oxide plasma concentration *vs* time curves following single administration of 500 µg of roflumilast in Period 1 and in Period 3 (semilog. scale).
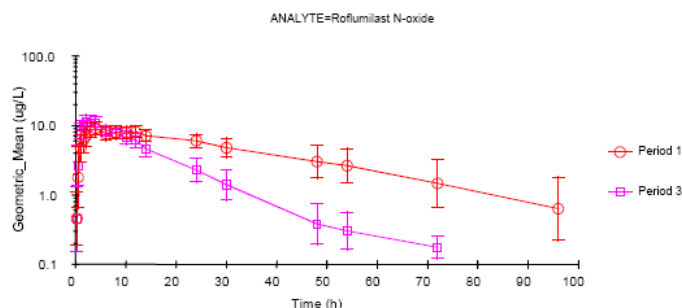
ADCP and ADCP-N-oxide:
Analysis of ADCP and ADCP-N-oxide in plasma samples showed that concentrations of both metabolites were below the limit of quantification.

CONCLUSION(S)
In this study, a substantial decrease in AUC (by 79%) and C_{max} (68%) of roflumilast was observed following the induction with rifampicin as compared to non-induced conditions. These findings were consistent with the observed increase in roflumilast CL/F, which was about five-fold higher following the induction with rifampicin. In contrast, roflumilast N-oxide showed a decrease in AUC by 56% and an increase in C_{max} by 30%.

Notably, ADCP and ADCP N-oxide were not affected by the induction of metabolizing enzymes investigated in this study.

CP-028

Study Title: Investigation of the pharmacokinetic drug-drug interaction between oral formoterol and oral roflumilast
-A randomized, open, 2-period- study-

Objectives: The aim of the study was the investigation of possible pharmacokinetic drug-drug interactions of oral formoterol and roflumilast.
Further objectives were safety and tolerability of the substances when given separately or in combination. In addition also in the light of safety possible pharmacodynamic interactions were investigated.

Study Design: This was an open, randomized, 2-period-crossover study in 24 healthy subjects. The study consisted of a screening examination, two study periods and a post study visit. The study periods were separated by a wash-out period of 2 –4 weeks. In one study period subjects received 40 µg oral formoterol (as formoterol fumarate) as a single dose (on Study Day 1). This period was called "Treatment Period I".

In the other study period the subjects received roflumilast 250 µg once daily for nine days (Study Days 1-9) and roflumilast 250 µg plus formoterol 40 µg (as fumarate) on the tenth study day (Study Day 10). This period was called "Treatment Period II".
The sequence of Treatment Periods was randomly assigned, i.e. subjects started with Treatment Period II and continued with Treatment Period I or vice versa.

Pharmacokinetic assessments:
Blood samplings for pharmacokinetic purposes (analysis of roflumilast and its N-oxide metabolite) were performed on Study Days 9 and 10 of Treatment Period II at pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h and 24 h.
Urine samples for pharmacokinetic purposes (analysis of formoterol) were performed on the Study Days 1-3 of Treatment Period I and on the Study Days 10-12 of Treatment Period II, and all urine of a subject of the following periods had to be sampled: predose, 0 – 2 h, 2 h – 4 h, 4 h – 8 h, 8 h – 12 h, 12 h – 24 h, 24 h – 36 h, 36 h – 48 h.

Study Population: The subject population consisted of 24 healthy Caucasian male and female subjects. Their mean and median age was 34 years (age range 19 – 45 years), their mean (median) height 174 cm (176 cm) and their mean and median weight 70.5 kg.

Data Analysis: For each primary variable and separately for roflumilast, its N-oxide metabolite, and formoterol, point estimate and 90%-confidence limits were given for the ratio of the population medians for Test and the respective Reference using a multiplicative model and a parametric analysis.

Results: Concentrations of roflumilast and roflumilast N-oxide in plasma were determined by using a validated liquid chromatographic method employing liquid-liquid extraction and MS/MS

detection. Roflumilast standard curves were valid up to 20 ng/ml and roflumilast N-oxide standard curves were valid up to 40 ng/ml. The lower limit of quantitation (LLOQ) was 0.10 ng/ml for both analytes. The intra-batch accuracy of roflumilast obtained from back calculated calibration standards was found to be within the range of –13.1% to +18.0%, while the accuracy of the calibration standards of roflumilast N-oxide ranged from –15.7% to +10.0%. The intra-batch accuracy of the roflumilast quality control samples ranged from –14.8% to +7.7% and from –14.7% to +4.7% in case of roflumilast N-oxide.

The inter-batch precision of the roflumilast quality control samples ranged from 4.6% to 6.7%, the inter-batch accuracy from –8.5% to –1.1%. In case of roflumilast N-oxide the interday precision ranged from 3.7% to 4.2%, the inter-day accuracy from –8.5% to –4.0%.Concentrations formoterol in urine were determined by using a validated liquid chromatographic method employing liquid-liquid extraction and MS/MS detection. Formoterol standard curves were valid up to 15 ng/ml. The lower limit of quantitation (LLOQ) was 0.20 ng/ml. The inter-batch accuracy of formoterol obtained from back calculated calibration standards was found to be within the range of –2.0% to +4.0%. The inter-batch precision was within the range of 0.0% to +4.1%. The inter-batch precision found for the QC samples was between 5.4 and 5.7 and the accuracy ranged from +1.0 to +6.7.

The plasma concentration time profiles of roflumilast, roflumilast N-oxide, and formoterol are shown the in following figures and tables.
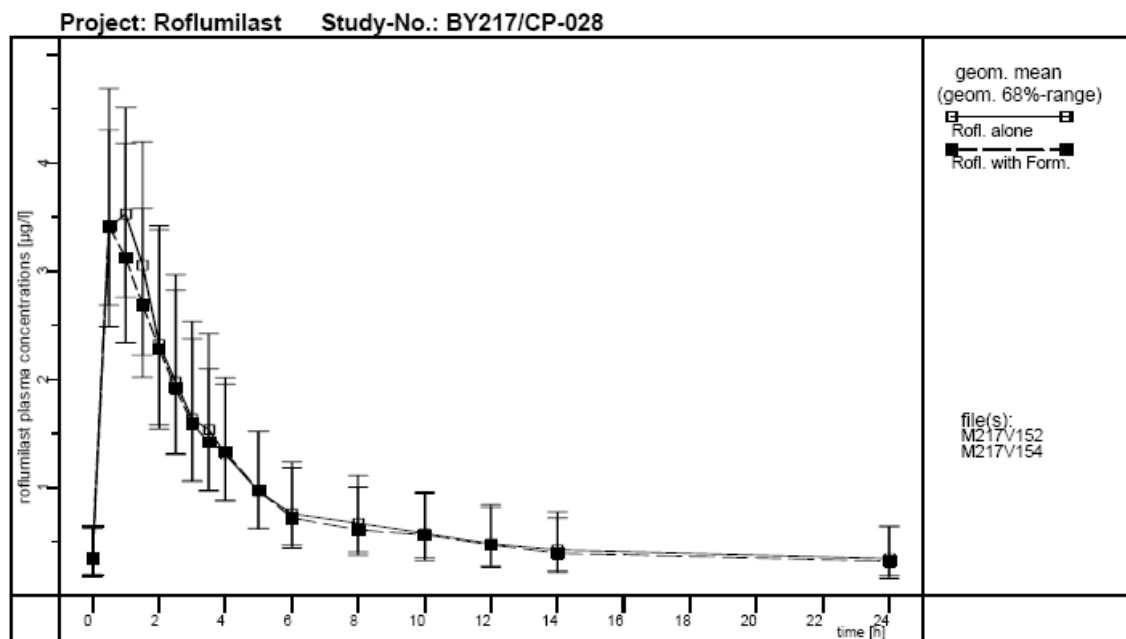
Figure 1: Comparison of geom. mean roflumilast plasma concentrations in healthy male or female subjects following multiple once-daily oral doses of 250 µg of roflumilast alone or in combination with one single oral dose of 40 µg of formoterol fumarate, linear scale

Project: Roflumilast   Study-No.: BY217/CP-028
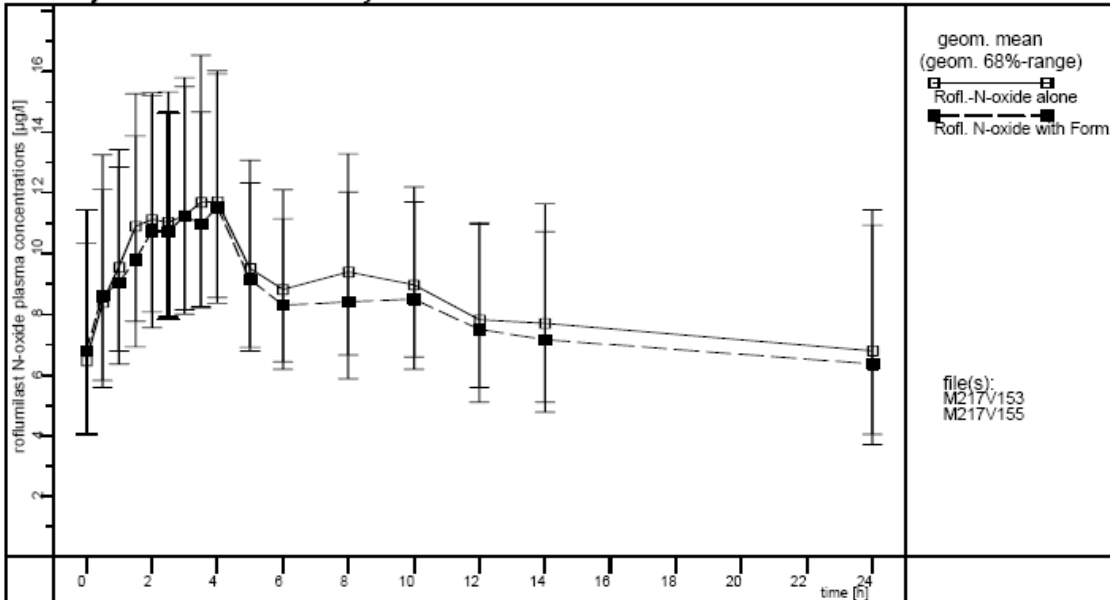
Figure 3: Comparison of geom. mean roflumilast N-oxide plasma concentrations in healthy male or female subjects following multiple once-daily oral doses of 250 µg of roflumilast alone or in combination with one single oral dose of 40 µg of formoterol fumarate, linear scale

Table 2: Summary of pharmacokinetic characteristics of roflumilast and its metabolite roflumilast N-oxide in healthy male and female volunteers following the 9th (Reference) and the 10th (Test) of multiple once-daily oral doses of 250 µg roflumilast [geometric mean, (68% range); t_{max}: median (min/max)].

Pharmacokinetic Characteristic	Roflumilast (R. alone) (Day 9)	Roflumilast (R. with Formoterol) (Day 10)	Roflumilast N-oxide (R. alone) (Day 9)	Roflumilast N-oxide (R. with Formoterol) (Day 10)
$AUC_{(0-24h)}$ [µg/lxh]	19.7 (13.0, 29.9)	18.9 (12.4, 28.7)	200.1[****] (139.2, 287.6)	194.8[****] (133.3, 284.6)
C_{max} [µg/l]	3.87 (3.06, 4.90)	3.74 (3.00, 4.67)	12.25 (8.75, 17.16)	11.79 (8.58, 16.21)
t_{max} [h]	0.75 (0.50, 1.50)	0.50 (0.50, 1.50)	3.50 (1.50, 14.00)	4.00 (2.00, 4.00)
$t_{1/2}$ [h]	15.43[*] (9.38, 25.40)	14.20[***] (8.30, 24.30)	25.96[**] (19.84, 33.95)	24.91[**] (16.26, 38.15)

* = n = 22 (terminal rate constant could not be estimated by log-linear regression in 2 subjects)

** = n = 11 (terminal rate constant could not be estimated by log-linear regression in 13 subjects)

*** = n = 19 (terminal rate constant could not be estimated by log-linear regression in 5 subjects)

**** = n = 23 (extrapolated part of the AUC did exceed 30% of the total AUC, consequently AUC value was not included in analysis in 1 subject)

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Table 3: Point estimates and 90%-confidence limits for the Test/Reference ratios of roflumilast and roflumilast N-oxide $AUC_{(0-24h)}$, $t_{1/2}$, C_{max} and t_{max} values following the 9th (Reference) and the 10th (Test) of multiple once-daily oral doses of 250 µg roflumilast.

Pharmacokinetic Characteristic	Roflumilast Point estimate	Roflumilast 90% confidence limit	Roflumilast N-oxide Point estimate	Roflumilast N-oxide 90% confidence limit
$AUC_{(0-24h)}$	0.96	0.93 – 0.99	0.94***)	0.92 – 0.97***)
C_{max}	0.97	0.91 – 1.03	0.96	0.92 – 1.00
$t_{1/2}$	0.90*)	0.76 – 1.08*)	0.92**)	0.73 – 1.16**)
t_{max}	0.00	-0.25 – 0.00	0.00	-0.25 – 0.50

* = n = 18 (terminal rate constant could not be estimated by log-linear regression in 6 subjects)

** = n = 8 (terminal rate constant could not be estimated by log-linear regression in 16 subjects)

*** = n = 22 (extrapolated part of the AUC did exceed 30% of the total AUC, consequently AUC value was not included in analysis in 2 subjects)

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Project: Formoterol   Study-No.: BY217/CP-028
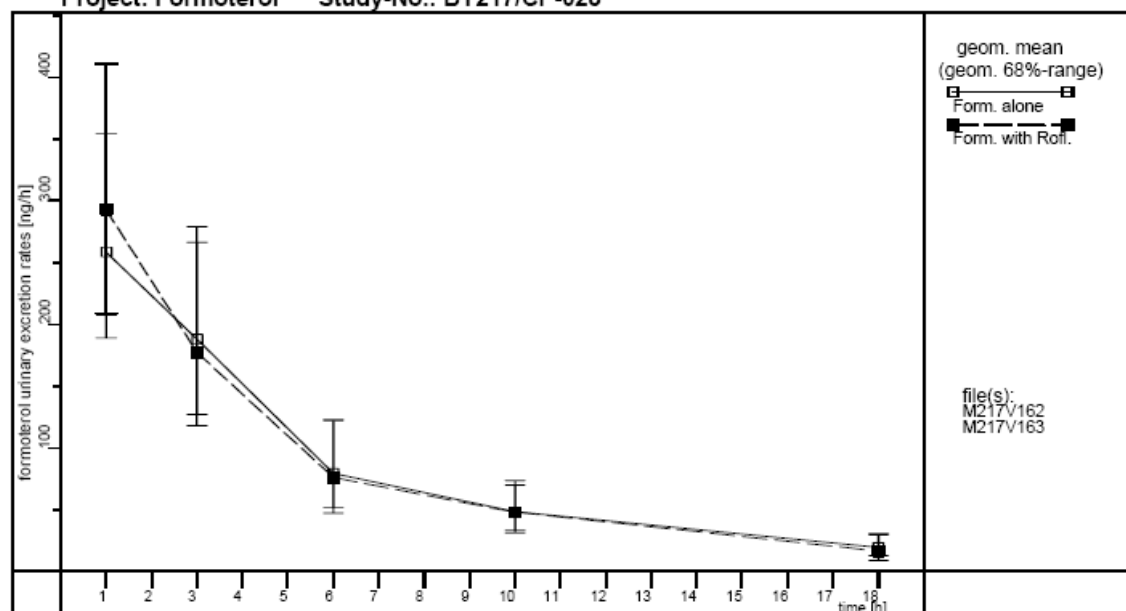
Figure 5: Comparison of mean urinary excretion rates of formoterol in healthy male or female subjects following one single oral dose of 40 µg of formoterol fumarate alone on Study Day 1 or in combination with multiple once daily oral doses of 250 µg of roflumilast on Study Day 10, linear scale

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Table 4: Summary of urinary pharmacokinetic characteristics of formoterol in healthy male and female volunteers following one single oral administration of formoterol on Study Day 1; Treatment Period I (Reference) and one single oral administration of formoterol under roflumilast steady state conditions on Study Day 10, Treatment Period II (Test) [geometric mean, (68% range)].

Pharmacokinetic Characteristic	Formoterol (F. alone) (Day 1)	Formoterol (F. with R.) (Day 10)
$A_{e(0-48h)}$ [µg]	1.69 (1.22, 2.33)	1.58 (1.18, 2.11)
$t^*_{1/2}$ [h]	5.31[*] (3.89, 7.24)	5.29[**] (3.89, 7.19)

* = n = 20 (terminal rate constant could not be estimated by log-linear regression in 4 subjects)

** = n = 21 (terminal rate constant could not be estimated by log-linear regression in 3 subjects)

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Table 5: Point estimates and 90%-confidence limits for the Test/Reference ratios of formoterol $A_{e(0-48h)}$ and $t^e_{1/2}$ values following one single oral administration of formoterol on Study Day 1; Treatment Period I (Reference) and one single oral administration of formoterol under roflumilast steady state conditions on Study Day 10, Treatment Period II. The number of subjects was N = 24.

Pharmacokinetic Characteristic	Formoterol Point estimate	Formoterol 90% confidence limit
$A_{e(0-48h)}$	0.94	0.87 – 1.01
$t^e_{1/2}$	1.00*)	0.85 – 1.17*)

* = n = 18 (terminal rate constant could not be estimated by log-linear regression in 6 subjects)

Conclusions: No drug – drug interaction was found for all three compounds subjected to this study, namely roflumilast, its major metabolite roflumilast N-oxide and formoterol.

CP-038

Study Title: Effects of repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinylestradiol on the pharmacokinetics of roflumilast and roflumilast N-oxide.

Objectives: Primary objectives:
• to assess the single dose PK (pharmacokinetics) of roflumilast and roflumilast N-oxide in female subjects with and without OCs (oral contraceptives).
Secondary objectives:
• to assess safety and tolerability;
• to assess further PK characteristics;
• to evaluate the OCs effects on tPDE4i (total phosphodiesterase-4 inhibitory activity).

Study Design: This was a Phase I, single center, open-label, non-randomized, fixed sequence, PK study after a single oral dose of 500 µg roflumilast in healthy adult female subjects. The eligibility of the subjects was evaluated during the screening visit (Day -28 to -2) and related

procedures prior to study enrolment. Eligible subjects entered into the study treatment period which consisted of two treatment periods that were ordered in a fixed sequence:

Treatment Period I (Day –1 to Day 6):

A single dose of roflumilast was administered on one of the first 3 days of the individual

female subject's menstrual cycle. The first day of the menstrual cycle was the day on which the menstruation (bleeding) began before 10.00 am. Study Day 1 was defined as the day of the roflumilast administration. Following the administration of roflumilast, blood samples for the analysis of roflumilast and its N-oxide metabolite were taken up to 120 h (Day 6) after roflumilast dosing.

Treatment Period II (Day 6 to Day 26):

In the subsequent Treatment Period II, a daily fixed combination of 0.075 mg gestodene and 0.03 mg ethinylestradiol (Minulet®) was administered over 3 weeks (21 days, Day 6 to 26 of the study). On Day 21, a single dose of roflumilast 500 µg was concomitantly administered.

Blood samples for the PK of roflumilast and its N-oxide metabolite were then taken over the subsequent 120 h (corresponding to Day 21 to 26 of the study).

The study was completed by an end of study examination which occurred on Day 27 or later.

At least 5.5 mL of blood/sample was taken, using lithium-heparinized monovettes, for the

sampling for roflumilast and roflumilast N-oxide. On Days 1 to 6 and Days 21 to 26 blood samples were taken at the following times: pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 h (36 samples) after roflumilast dosing on Day 1 and Day 21, respectively.

Study Population: Overall, 21 subjects were enrolled and 1 subject (Subject No.11) withdrew consent prior to treatment.

Data Analysis: PK parameters were analyzed with an ANOVA (analysis of variance) model consisting of subject and treatment; the subject effect was considered random. Model-based 90% confidence intervals for test (roflumilast with OCs) as a percentage of

reference (roflumilast alone) were generated.

Results:

T-Figure 3: Plasma concentration-time profiles for roflumilast, following a single dose of 500 µg roflumilast (semilogarithmic plot)
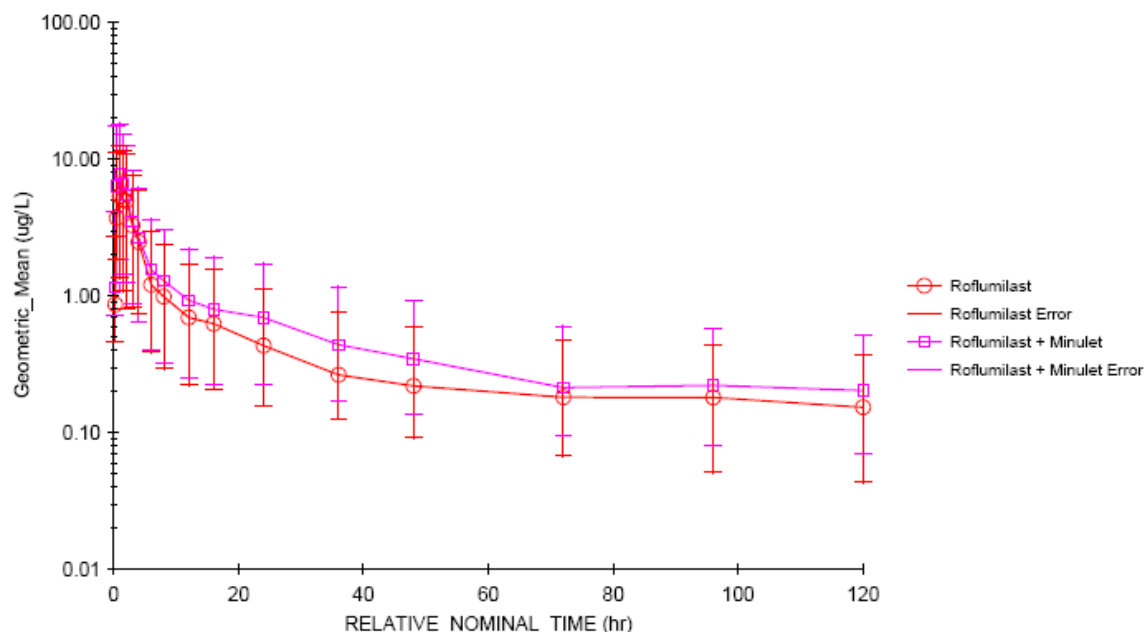
T-Table 8: Mean pharmacokinetic parameter estimates for roflumilast, following a single dose of 500 µg roflumilast

	Period I			Period II		
	Geometric Mean	68% Range		Geometric Mean	68% Range	
AUC_{tlast}	42.5	28.5	63.4	63.2	44.1	90.7
AUC_{inf}	46.7	30.9	70.7	70.6	48.1	104
C_{max}	6.13	4.79	7.84	8.45	6.54	10.9
$t_{1/2}$	19.7	12.4	31.2	29.3	20.0	42.9
t_{max} [a]	1.25	0.500	3.00	1.00	0.500	3.00
CL/F	10.7	7.07	16.2	7.08	4.83	10.4

[a] t_{max} displayed as median, minimum and maximum.

Note: For Period I roflumilast was administered without Minulet® and for Period II roflumilast was administered following 3 weeks use of Minulet®.

AUC_{inf} = area under the plasma concentration vs. time curve extrapolated to until infinity, AUC_{tlast} = area under the plasma concentration vs. time curve until the last measured plasma concentration above or equal to the lower limit of quantification, C_{max} = maximum plasma concentration, CL/F = apparent oral clearance, $t_{1/2}$ = elimination half-life, t_{max} = time to reach maximum plasma concentration. Parameters are defined in T-Table 4.

Data source: Section 15.2.1.4.

T-Table 9: AUC_{tlast}, AUC_{inf}, and C_{max} mean ratios (90% CI) for roflumilast, following a single dose of 500 µg roflumilast

	Period I Geometric LSM	Period II Geometric LSM	Ratio [%Period II]	CI 90 Lower	CI 90 Upper
AUC_{tlast}	42.5	63.2	149	122	182
AUC_{inf}	46.7	70.6	151	122	187
C_{max}	6.13	8.45	138	121	158

Ratio: Ratio (Period II/ Period I) of treatment mean values, expressed as a percentage of Period I mean (100 x Period II/ Period I).
Note: For Period I roflumilast was administered without Minulet® and for Period II roflumilast was administered following 3 weeks use of Minulet®.
AUC_{inf} = area under the plasma concentration vs. time curve extrapolated to until infinity, AUC_{tlast} = area under the plasma concentration vs. time curve until the last measured plasma concentration above or equal to the lower limit of quantification, C_{max} = maximum plasma concentration, LSM = Least square mean, CI = confidence interval.
Parameters are defined in T-Table 4.
Data source: Section 15.2.1.5.

For roflumilast, mean ratios of AUCtlast and AUCinf indicated a 49% and 51% higher systemic exposure during Period II when compared with Period I. The mean ratio of Cmax, indicated a 38% higher peak concentration during Period II when compared with Period I.

T-Figure 5:   Roflumilast N-Oxide: Plasma concentration-time profiles, following a single dose of 500 µg roflumilast (semilogarithmic plot)
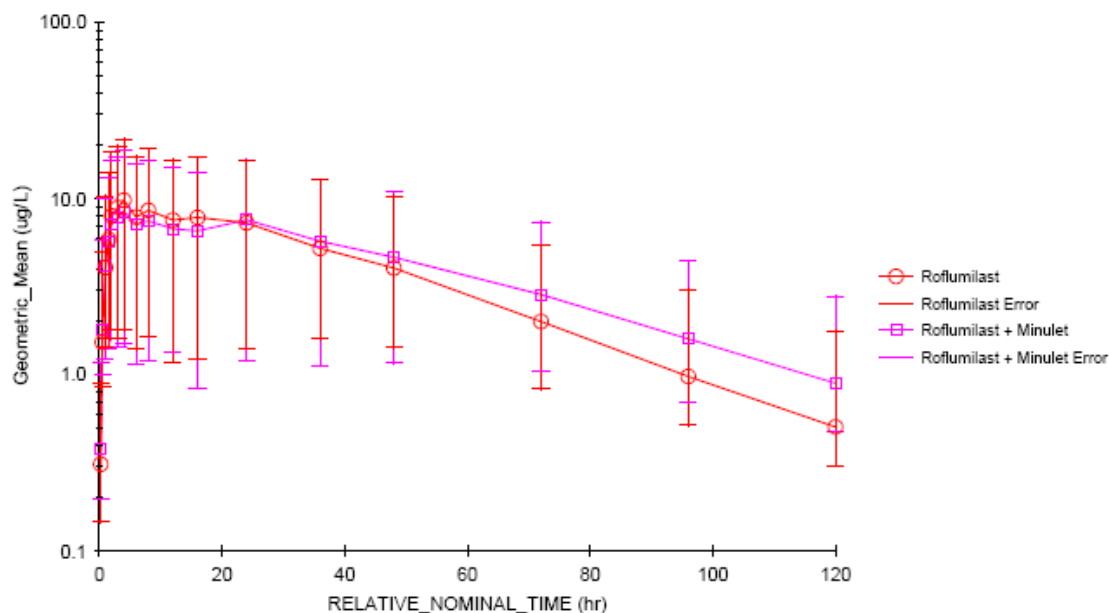
T-Table 10: Mean pharmacokinetic parameter estimates for roflumilast N-Oxide, following a single dose of 500 µg roflumilast

	Period I			Period II		
	Geometric Mean	68% Range		Geometric Mean	68% Range	
AUC_{tlast}	457	353	592	495	399	612
AUC_{inf}	487	356	667	555	411	749
C_{max}	10.4	9.00	12.1	9.14	7.67	10.9
$t_{1/2}$	25.2	18.1	35.1	30.7	20.6	45.6
t_{max} [a]	4.00	3.00	36.0	7.00	3.00	36.0

[a] t_{max} displayed as median, minimum and maximum.
Note: For Period I roflumilast was administered without Minulet® and for Period II roflumilast was administered following 3 weeks use of Minulet®.
AUC_{inf} = area under the plasma concentration vs. time curve extrapolated to until infinity, AUC_{tlast} = area under the plasma concentration vs. time curve until the last measured plasma concentration above or equal to the lower limit of quantification, C_{max} = maximum plasma concentration, $t_{1/2}$ = elimination half-life, t_{max} = time to reach maximum plasma concentration.
Parameters are defined in T-Table 4.
Data source: Section 15.2.2.4.

T-Table 11: AUC_{tlast}, AUC_{inf}, and C_{max} mean ratios (90% CI) for roflumilast N-oxide, following a single dose of 500 µg roflumilast

	Period I Geometric LSM	Period II Geometric LSM	Ratio [%Period II]	CI 90 Lower	CI 90 Upper
AUC_{tlast}	457	495	108	95.3	123
AUC_{inf}	487	555	114	96.6	134
C_{max}	10.4	9.14	87.6	80.4	95.5

Ratio: Ratio (Period II/ Period I) of treatment mean values, expressed as a percentage of Period I mean (100 x Period II/ Period I).
Note: For Period I roflumilast was administered without Minulet® and for Period II roflumilast was administered following 3 weeks use of Minulet®.
AUC_{inf} = area under the plasma concentration vs. time curve extrapolated to until infinity, AUC_{tlast} = area under the plasma concentration vs. time curve until the last measured plasma concentration above or equal to the lower limit of quantification, C_{max} = maximum plasma concentration, LSM = Least square mean, CI = confidence interval.
Parameters are defined in T-Table 4.
Data source: Section 15.2.2.5.

For roflumilast N-oxide, mean ratios of AUCtlast indicated a similar systemic exposure during both treatment periods. The mean ratio of AUCinf indicated a 14% higher systemic exposure during Period II when compared with Period I. The mean ratio of Cmax indicated a 12% lower peak concentration during Period II when compared with Period I.

Conclusions: For roflumilast, mean ratios of AUCtlast and AUCinf indicated a 49% and 51% higher systemic exposure after roflumilast and OC (ie Period II) when compared with roflumilast alone (Period I). The mean ratio of Cmax, indicated a 38% higher peak concentration after roflumilast and OC when compared with roflumilast alone. For roflumilast N-oxide, mean ratios of AUCtlast indicated a similar systemic exposure after roflumilast and OC when compared with roflumilast alone. The mean ratio of AUCinf indicated a 14% higher systemic exposure after roflumilast and OC when compared with roflumilast alone. The mean ratio of Cmax indicated a 12% lower peak concentration after roflumilast and OC when compared with roflumilast alone.

252/2008

Study Title: Total PDE4 Inhibitory Activity of Roflumilast and Roflumilast N-oxide.

Objectives: The objective of this report is to describe tPDE4i concept and to document tPDE4i values for those clinical pharmacology studies that are not documented elsewhere (e.g. in the clinical study report).

Study Design:

Total PDE4 inhibition values were calculated according to the following equation:

$$tPDE4i = \frac{\lfloor AUC_{rof} \times f_{rof} \rfloor}{\lfloor IC_{50,rof} \times \tau \rfloor} + \frac{\lfloor AUC_{rofNO} \times f_{rofNO} \rfloor}{\lfloor IC_{50,rofNO} \times \tau \rfloor}$$

with

- AUC_{rof} = AUC of roflumilast [µg×h/L; either AUC_{inf} following a single dose or $AUC_{0-\tau}$ following repeated doses at steady state]
- AUC_{rofNO} = AUC of roflumilast N-oxide [µg×h/L; either AUC_{0-inf} following a single dose or $AUC_{0-\tau}$ following repeated doses at steady state]
- f_{rof} = unbound fraction [%] of roflumilast in plasma
- f_{rofNO} = unbound fraction [%] of roflumilast N-oxide in plasma
- $IC_{50,rof}$ = roflumilast concentration [µg/L] resulting in 50% PDE4 inhibition *in vitro*
- $IC_{50,rofNO}$ = roflumilast N-oxide concentration [µg/L] resulting in 50% PDE4 inhibition *in vitro*
- τ = dosing interval (24 h for once-daily dosing).

Table 2   Constant values in tPDE4i equation

	f	IC_{50} [µg/L]	τ [h]
Roflumilast (p)	0.011	0.3	24
Roflumilast N-oxide (m)	0.034	0.8	24

Log-transformed tPDE4i values were analyzed by study applying an analysis of variance (ANOVA). For fixed-sequence crossover studies, the ANOVA model included subject and treatment effects, with the subject effect considered random. For randomized-sequence crossover studies, the ANOVA model included treatment, period, and sequence as fixed effects, and subject within sequence as random effect. For parallel studies, the ANOVA model included only a group effect. ANOVA results were used to determine 90% confidence intervals for the ratios (test/reference) of treatment or group mean tPDE4i values for each study.

Data Analysis: Log-transformed tPDE4i values were analyzed by study applying an analysis of variance (ANOVA). For fixed-sequence crossover studies, the ANOVA model included subject and treatment effects, with the subject effect considered random. For randomized-sequence crossover studies, the ANOVA model included treatment, period, and sequence as fixed effects, and subject within sequence as random effect. For parallel studies, the ANOVA model included only a group effect. ANOVA results were used to determine 90% confidence intervals for the ratios (test/reference) of treatment or group mean tPDE4i values for each study.

Results:

Table 4   tPDE4i values: Geometric least squares means, ratios and 90% confidence intervals

Study	Treatment or Group Test	Reference	N	Geo LSMeans[a] Test	Ref	Ratio[b]	(90% CI[c])
FHP010	Fed	Fasted	12	0.685	0.670	102	(88.83, 117.67)
FHP014	Roflumilast & salbutamol	Roflumilast	12	0.746	0.756	98.6	(90.69, 107.34)
FHP017	Roflumilast & budesonide	Roflumilast	12	0.686	0.740	92.6	(86.75, 98.99)
FHP020	Renally impaired	Healthy	11	0.812	0.887	91.5	(76.24, 109.93)
FHP021	Smoker	Non-smoker	12	0.875	0.903	96.9	(71.56, 131.33)
FHP026	Roflumilast & theophylline	Roflumilast	24	0.825	0.761	108	(99.34, 118.19)
FHP027[d]	Roflumilast & digoxin	Roflumilast	15	0.894	0.918	97.3	(81.52, 116.22)
CP-029	Roflumilast & warfarin	Roflumilast	21	0.857	0.865	99.1	(96.56, 101.77)
CP-041	Roflumilast & cimetidine	Roflumilast	16	1.44	0.975	147	(113.95, 191.43)
CP-044	Roflumilast & Maalox®	Roflumilast	28	1.14	1.18	96.6	(90.10, 103.69)
	Roflumilast & Maalox® after 2 h	Roflumilast	28	1.21	1.18	102	(95.45, 109.82)
CP-047	Roflumilast & erythromycin	Roflumilast	18	0.650	0.719	90.4	(88.24, 92.54)
CP-050	Female	Male	30	1.46	1.02	143	(126.36, 161.84)
CP-050	Middle-aged	Young	19	1.13	1.15	98.1	(82.26, 116.92)
	Elderly	Young	19	1.37	1.15	119	(99.94, 142.06)
CP-055	Roflumilast & ketoconazole	Roflumilast	24	1.10	1.21	90.6	(89.10, 92.04)
CP-059	Roflumilast & formoterol	Roflumilast	12	0.790	0.794	99.4	(78.87, 125.46)
CP-060	Roflumilast & montelukast	Roflumilast	24	0.782	0.793	98.6	(87.78, 110.96)
CP-061	Roflumilast & midazolam i.v.	Roflumilast	18	0.791	0.836	94.6	(82.66, 108.30)
	Roflumilast & midazolam p.o.	Roflumilast	18	0.784	0.836	93.7	(81.93, 107.34)
CP-062[e]	Child-Pugh A	Healthy	8	0.748	0.593	126	(93.41, 170.53)
	Child-Pugh B	Healthy	8	0.867	0.593	146	(108.27, 197.64)
CP-064	Roflumilast & rifampicin	Roflumilast	15	0.335	0.793	42.3	(37.55, 47.60)

Study	Treatment or Group Test	Reference	N	Geo LSMeans[a] Test	Ref	Ratio[b]	(90% CI[c])
CP-066	Roflumilast & ketoconazole	Roflumilast	16	1.22	1.12	109	(97.49, 121.92)
CP-067	Roflumilast & fluvoxamine	Roflumilast	14	2.33	1.47	159	(138.07, 182.62)
CP-068	Roflumilast & erythromycin	Roflumilast	15	1.35	1.24	109	(96.30, 122.80)
CP-070	Roflumilast & sildenafil	Roflumilast	12	0.844	0.805	104	(99.90, 110.02)

[a] Treatment or group mean PDE4i values=back-transformed least-squares mean from the ANOVA of natural log-transformed values; [b] Ratio of treatment or group means, expressed as a percentage (100% × test/reference); [c] 90% confidence interval for the ratio (test/reference) of treatment or group mean values, expressed as a percentage of the reference mean; [d] Subject ___ (b) (6) excluded; [e] Patients and subjects of study CP-062 received only 250 μg OD for 14 days.

CYP 3A4 inhibitors and inducers: Co-administration of ketoconazole, a strong inhibitor of CYP 3A4 or erythromycin, a moderate inhibitor of CYP 3A4 had no significant effect on mean tPDE4i values of roflumilast. The 90% confidence intervals for treatment ratios, based on logtransformed data, were within the conventional bioequivalence range of 80% to 125%. Coadministration of rifampicin, a potent inducer of CYP enzymes, decreased the mean tPDE4i value by 58%.

CYP 1A2 inhibitors and inducers: Co-administration of fluvoxamine, a potent inhibitor of CYP 1A2, increased the mean tPDE4i value of roflumilast by 59%. Co-administration of theophylline, a substrate of CYP 1A2, had no significant effect on the mean tPDE4i value. Coadministration of cigarette smoke, an inducer of CYP 1A2, decreased the mean tPDE4i value by 4%.

Commonly used co-medications in COPD patients: Co-administration of salbutamol, budesonide, digoxin, warfarin, Maalox®, montelukast and sildenafil had no significant effect on mean tPDE4i values of roflumilast. Co-administration of cimetidine, a weak inhibitor of CYP1A2 and 3A4, increased the mean tPDE4i value by 47%. Co-administration of formoterol decreased the mean tPDE4i value by 1%.

Age and gender: The mean tPDE4i value of healthy middle-aged subjects was similar to that of young healthy subjects. The 90% confidence intervals for the ratio of mean tPDE4i values, based on log-transformed data, were within the conventional bioequivalence range of 80% to 125%. However, the mean tPDE4i value of healthy elderly was 19% higher when compared with healthy young subjects. The mean tPDE4i value of female healthy subjects was 43% higher when compared with healthy male subjects. For results of the population kinetic assessment, please refer to report 175/2008.

Renal and hepatic impairment: The mean tPDE4i value of patients with severe renal impairment was 9% lower when compared with matched healthy control subjects. The mean tPDE4i value of patients with mild (Child Pugh A) and moderate (Child Pugh B) liver impairment was 26% and 46% higher, respectively, when compared with matched healthy control subjects. However, liver impaired patients and healthy subjects received only roflumilast 250 µg OD for 14 days.

Smokers vs nonsmokers: Although concentration-time values of roflumilast N-oxide were documented for subjects 16 and 22 (both non-smokers) in report 213/2000, AUCinf values of roflumilast N-oxide were not calculated due to an extrapolated part of AUC of more than 50%. Therefore, these roflumilast N-oxide values were excluded from the statistical evaluation. However, on visual inspection of these individual roflumilast N-oxide profiles it was evident that they had high peak concentrations with a regularly descending part, suitable for a reliable evaluation of AUC.

JP702

Study Title: A clinical pharmacological (Phase I) study of APTA-2217 in healthy elderly male volunteers (single oral dose)

Objectives: To evaluate the pharmacokinetics and safety of APTA-2217 after single oral administration of 250 mcg or 500 mcg under the fasting condition in healthy elderly male volunteers.

Study Design: 1) Screening examination
After obtaining the written informed consent from subjects, screening examinations were performed to confirm the eligibility to participate in the study.
2) Administration period
Of the subjects who were eligible, based on the results of screening examination, 12 subjects and at least 1 substitute were selected for each Group A and B. The randomized investigational drug was administered to subjects in Group A during Period 1 and those in Group B during Period 2 (9 subjects for the study medication and 3 subjects for placebo), and specified observations and tests were performed. Subjects were hospitalized for 10 days and 9 nights in each study period; the minimum-dosing interval between study periods 1 and 2 was at least 14 days.
3) Post-study examination
Specified observations and tests were to be performed on Day 15 ± 2 days after administration (the post-study examination in Period 1 was actually performed on Day 15 + 3 days).

	Period 1	Period 2
Group A (12 subjects) (+ at least one substitute)	250 mcg: 9 subjects Placebo: 3 subjects	Not applicable
Group B (12 subjects) (+ at least one substitute)	Not applicable	500 mcg: 9 subjects Placebo: 3 subjects
Subjects were hospitalized from 2 days before administration to Day 8 for 10 days (10 days and 9 nights) in each period.		

Study Population: Overall, 12 subjects were enrolled and completed the study for analysis.

Data Analysis: The pharmacokinetic parameters of roflumilast and roflumilast N-oxide were calculated for each subject by non-compartment model analysis. The geometric mean and 68% range for each parameter (median, and min to max for Tmax) were calculated by each dose.

Results:

	Roflumilast		Roflumilast N-oxide	
Dose	250 mcg	500 mcg	250 mcg	500 mcg
$AUC_{(0-inf.)}$ [mcg·h/L]	33.4 (23.9, 46.8)	60.4 (49.2, 74.1)	376.4 (277.9, 509.7)	709.3 (599.2, 839.7)
C_{max} [mcg/L]	4.708 (3.278, 6.763)	6.177 (4.478, 8.522)	6.188 (5.121, 7.477)	12.393 (10.801, 14.220)
T_{max} [h]	0.50 (0.50, 3.00)	0.50 (0.50, 3.00)	4.00 (3.00, 24.00)	4.00 (4.00, 24.00)
$t_{1/2}$ [h]	33.19 (19.16, 57.49)	29.34 (24.05, 35.80)	32.90 (23.60, 45.88)	32.19 (27.21, 38.08)
CLt or CLmet [L/h]	7.48 (5.35, 10.46)	8.27 (6.74, 10.15)	0.69 (0.51, 0.93)	0.73 (0.62, 0.87)
Vd/F [L]	357.95 (238.69, 536.80)	350.23 (281.49, 435.75)	32.78 (26.35, 40.77)	34.04 (27.83, 41.62)

Geometric mean (68% range); Median (min, max) for T_{max}
250 mcg: 9 subjects, 500 mcg: 9 subjects

The ratio of pharmacokinetic parameters between ages

Pharmacokinetic parameter	Roflumilast		Roflumilast N-oxide
$AUC_{(0-inf)}$	1.626 (1.378, 1.918)		1.558 (1.341, 1.809)
C_{max}	1.012 (0.857, 1.194)		1.083 (0.989, 1.187)
$t_{1/2}$	250 mcg	3.386 (2.556, 4.484)	1.568 (1.354, 1.817)
	500 mcg	2.012 (1.519, 2.665)	
CLt or CLmet	0.615 (0.521, 0.726)		0.642 (0.552, 0.746)
Vd/F	250 mcg	2.023 (1.623, 2.522)	1.007 (0.905, 1.120)
	500 mcg	1.275 (1.023, 1.590)	

The point estimate of the ratio (95% confidence interval)
Elderly subjects (250 mcg: 9 subjects and 500 mcg: 9 subjects)
Non-elderly subjects (250 mcg: 9 subjects and 500 mcg: 9 subjects)

Conclusions: Compared with young subjects, the AUC(0-inf.) and t1/2 were higher, and CLt and CLmet were lower in elderly subjects for both roflumilast and roflumilast N-oxide.

JP703

Study Title: A clinical Pharmacological (Phase I) Study of APTA-2217 in healthy adult volunteers (Gender factor, Single oral dose)

Objectives: To compare the pharmacokinetics between males and females, and evaluate the safety of APTA-2217 after single oral administration of 500 mcg under fasting condition in healthy adult volunteers.

Study Design:

	Male group: 10 subjects (+ 2 substitutes)	Female group: 10 subjects (+ 2 substitutes)
Administration period	500 mcg: 8 subjects Placebo: 2 subjects	500 mcg: 8 subjects Placebo: 2 subjects
Subjects were hospitalized from 2 days before administration to Day 6 for 8 days (8 days and 7 nights).		

Study Population: Overall, 20 subjects (10 males and 10 females) were enrolled and completed the study for analysis.

Data Analysis: The pharmacokinetic parameters of roflumilast and roflumilast N-oxide were calculated for each subject by non-compartment model analysis. The geometric mean and 68% range for each parameter (median, and min to max for Tmax) were calculated by each dose.

Results:
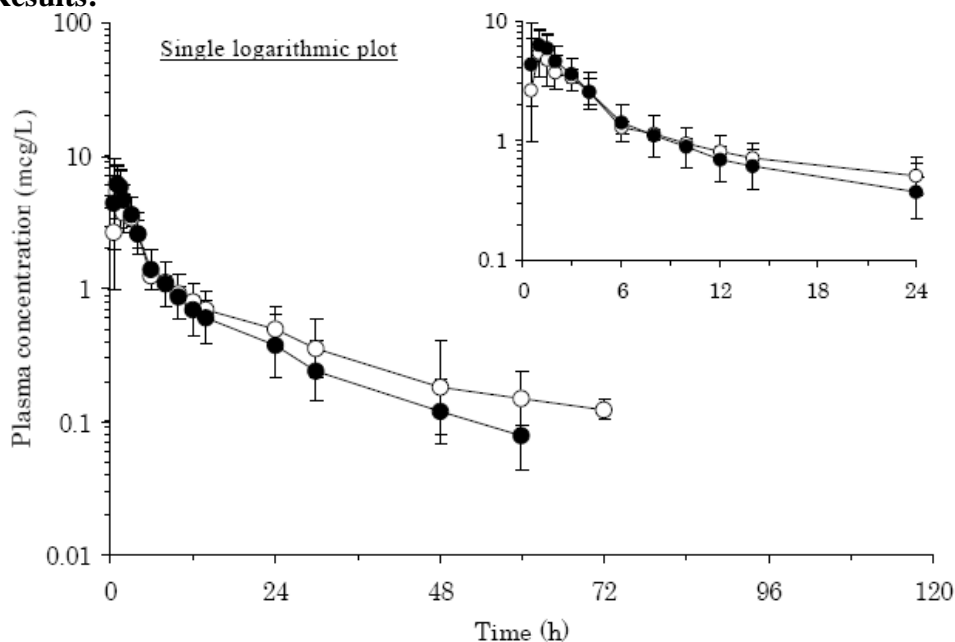
(Geometric mean, 68% range, Male Group: n=5 to 8, Female Group: n=4 to 6)

●: Male Group, ○: Female Group

Figure 11.4-1 Time-course of plasma concentrations of roflumilast after single oral administration of APTA-2217

Gender	Roflumilast		Roflumilast N-oxide	
	Male	Female	Male	Female
$AUC_{(0-inf.)}$ [mcg·h/L]	43.0 (31.3, 59.2)	46.6 (36.4, 59.8)	513.6 (452.7, 582.8)	581.5 (457.8, 738.6)
C_{max} [mcg/L]	7.240 (5.126, 10.224)	6.049 (3.670, 9.971)	12.130 (10.594, 13.889)	13.324 (11.590, 15.319)
T_{max} [h]	1.00 (0.50, 3.00)	1.00 (0.50, 3.00)	4.00 (4.00, 4.00)	4.00 (4.00, 4.00)
$t_{1/2}$ [h]	20.87 (10.28, 42.37)	19.42 (12.90, 29.24)	22.78 (19.61, 26.45)	25.72 (19.68, 33.62)
CLt or CLmet [L/h]	11.61 (8.45, 15.96)	10.72 (8.36, 13.74)	1.01 (0.89, 1.15)	0.89 (0.70, 1.14)
Vd/F [L]	349.68 (180.85, 676.12)	300.35 (243.46, 370.53)	33.25 (27.69, 39.94)	33.17 (29.07, 37.86)

Geometric mean (68% range); Median (min, max) for T_{max}.
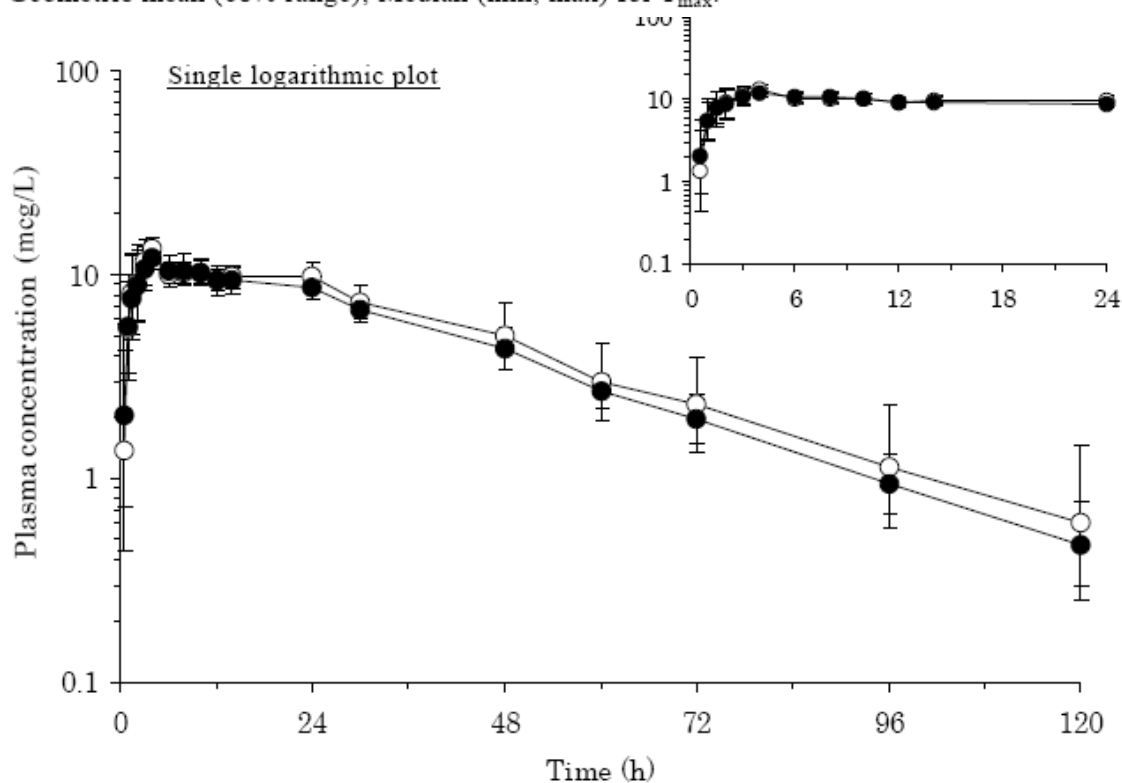
(Geometric mean, 68% range, Male Group: n=7 to 8, Female Group: n=6)
●: Male Group, ○: Female Group

Figure 11.4-2 Time-course of plasma concentrations of roflumilast N-oxide after single oral administration of APTA-2217

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Table 11.4-5 Comparison between males and females in pharmacokinetic parameters of roflumilast and roflumilast N-oxide

Drug	Pharmacokinetic parameter	Intergender difference [Note 1] (log-transformed)					Intergender ratio [Note 2]		
		Point estimate	SE	90% confidence interval		p value	Point estimate	90% confidence interval	
				Lower	Upper			Lower	Upper
Roflumilast	$AUC_{(0-inf)}$	-0.081	0.157	-0.361	0.200	0.618	0.923	0.697	1.222
	C_{max}	0.180	0.225	-0.221	0.581	0.440	1.197	0.801	1.787
	$t_{1/2}$	0.072	0.325	-0.507	0.651	0.829	1.074	0.602	1.918
	CLt	0.080	0.157	-0.200	0.361	0.618	1.084	0.819	1.434
	Vd/F	0.152	0.282	-0.350	0.654	0.599	1.164	0.705	1.923
Roflumilast N-oxide	$AUC_{(0-inf)}$	-0.124	0.098	-0.299	0.051	0.231	0.883	0.741	1.052
	C_{max}	-0.094	0.074	-0.226	0.038	0.229	0.910	0.798	1.039
	$t_{1/2}$	-0.122	0.112	-0.321	0.078	0.299	0.886	0.725	1.081
	CLmet	0.122	0.099	-0.055	0.298	0.243	1.129	0.947	1.347
	Vd/F	0.002	0.089	-0.155	0.160	0.978	1.002	0.856	1.174

[Note 1]: Male–Female, [Note 2]: Male/Female

Conclusions: After single oral administration of APTA-2217 at 500 mcg to healthy adult subjects (male and female) under fasting condition, no major differences in the pharmacokinetics of roflumilast and roflumilast N-oxide were observed between males and females. Adverse events after administration of the investigational drug to hospital discharge in this study were reported only in the female group.

CP-048

Study Title: Pharmacokinetics of roflumilast and roflumilast N-oxide after single and repeated oral administration of 250 μg and 500 μg roflumilast in Japanese and Caucasian subjects – a double blind, randomized, dose escalating, two-period, two parallel group comparison.

Objectives: Primary: The pharmacokinetics of repeated oral administration of 250 μg and 500 μg roflumilast were compared between Japanese and Caucasian subjects (steady state pharmacokinetics).
Secondary: The pharmacokinetics of a single oral administration of 250 μg and 500 μg roflumilast were compared between Japanese and Caucasian subjects (single dose pharmacokinetics). The safety, tolerability and metabolic activity were compared between Japanese and Caucasian subjects.

Study Design: This study was conducted as a double blind, randomized, dose escalating, two-period, two parallel group comparison. During the first period, subjects received either 250 μg roflumilast or placebo on Day 1 and then on Days 5 to 15. During the second period, after a washout period of at least 15 days, subjects received 500 μg roflumilast or placebo on Day 1, and then Days 5 to 15.

Subjects remained resident in the Unit from admission on Day -2 until the morning of Day 4, then returned every day until Day 13, and were re-admitted on Day 14 until the morning of Day 18. A post-study examination was conducted within two weeks of Day 19 of Period 2.

Study Population: A total of 30 subjects were randomized, and a total of 27 subjects (14 subjects of the Japanese group and 13 subjects of the Caucasian group) completed the study.

Data Analysis: AUCT (AUC0-24h) of roflumilast and roflumilast N-oxide and Cmax of roflumilast (steady state pharmacokinetics). Analyses via ANOVA, point estimates and 90%-confidence intervals.

Results:
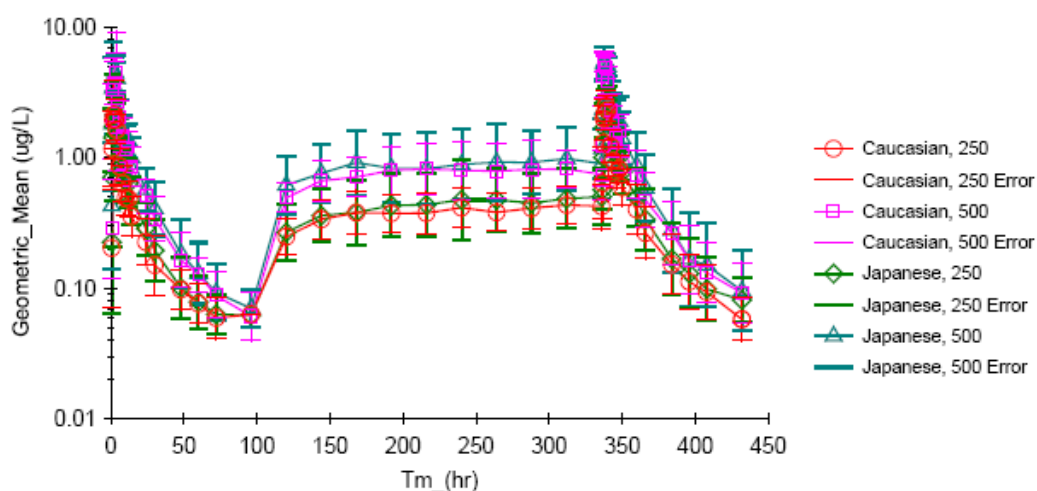
Figure 11.4.1.1 – 1: Roflumilast – Geometric means (68% ranges denoted as error in graph legend) in Japanese and Caucasian male subjects from Day 1 to Day 15, following oral administration of 250 μg and 500 μg roflumilast, **semilog** scale

Table 11.4.1.1 – 1: Roflumilast – Summary of pharmacokinetic parameter estimates in healthy male Japanese and Caucasian subjects at **Day 15** (steady state) following multiple once-daily oral administration [geometric mean, (68% range); t_{max}: median (min/ max)]

Variable	Caucasians				Japanese			
	n	Geom Mean	Upper 68%	Lower 68%	n	Geom Mean	Upper 68%	Lower 68%
250 roflumilast								
AUCT [h*ug/L]	11	23.3291	28.8942	18.8359	12	27.6070	36.3972	20.9396
AUCTB*	11	29.0588	37.1023	22.7590	12	29.1341	38.2146	22.2112
$CL_{ss}FB$ [L/h/kg]	11	0.1434	0.1831	0.1123	12	0.1430	0.1876	0.1090
C_{max} [g/L]	11	2.8730	3.6187	2.2809	12	3.1267	3.7299	2.6211
$C_{max}B$*	11	3.5786	4.6557	2.7507	12	3.2997	3.9217	2.7763
C_{min} [ug/L]	11	0.3849	0.5846	0.2535	12	0.4678	0.7684	0.2848
$C_{min}B$*	11	0.4795	0.7542	0.3048	12	0.4937	0.8060	0.3024
HL [h]	11	21.1516	26.1179	17.1297	12	19.4147	23.3156	16.1664
t_{max} [h](median, min/ max)	11	3	4	1	12	3	4	1.5
$V_{ss}FB$ [L/kg]	11	4.3755	5.1530	3.7154	12	4.0058	5.0734	3.1629
500 roflumilast								
AUCT [h*ug/L]	10	46.0300	58.0016	36.5294	11	52.8854	70.9105	39.4422
AUCTB*	10	57.8791	74.8314	44.7672	11	55.2329	72.5865	42.0281
$CL_{ss}FB$ [L/h/kg]	10	0.1440	0.1861	0.1114	11	0.1509	0.1983	0.1148

Variable	Caucasians				Japanese			
	n	Geom Mean	Upper 68%	Lower 68%	n	Geom Mean	Upper 68%	Lower 68%
C_{max} [ug/L]	10	5.9335	6.8929	5.1077	11	6.2175	7.1917	5.3753
$C_{max}B$*	10	7.4609	8.7208	6.3831	11	6.4935	7.1957	5.8599
C_{min} [ug/L]	10	0.7008	1.0626	0.4622	11	0.8086	1.4854	0.4401
$C_{min}B$*	10	0.8812	1.3866	0.5600	11	0.8444	1.5338	0.4649
HL [hr]	10	20.3501	25.7313	16.0942	11	17.6999	22.5868	13.8704
t_{max} [h](median, min/ max)	10	1.75	3	1	11	2	3	1.5
$V_{ss}FB$ [L/kg]	10	4.2271	5.1799	3.4495	11	3.8527	4.6675	3.1801

* normalized to 60 kg body weight

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Table 11.4.1.1 – 2: Roflumilast – Summary of pharmacokinetic parameter estimates in healthy male Japanese and Caucasian subjects at **Day 1** following single oral administration [geometric mean (68% range); t_{max}: median (min/ max)]

Variable	Caucasians				Japanese			
	n	Geom Mean	Upper 68%	Lower 68%	n	Geom Mean	Upper 68%	Lower 68%
250 µg roflumilast								
AUCI [h*ug/L]	12	22.5254	29.994	16.917	12	26.0323	35.947	18.852
AUCIB*	12	28.4956	37.955	21.394	12	27.4722	37.647	20.048
AUCT [h*ug/L]	12	16.6991	20.164	13.830	12	19.4439	24.535	15.409
AUCTB*	12	21.1250	25.135	17.755	12	20.5194	25.707	16.379
CLFB [L/h/kg]	12	0.1462	0.195	0.110	12	0.1517	0.208	0.111
C_{max} [ug/L]	12	2.6680	3.301	2.157	12	2.9998	3.853	2.336
HL [h]	12	16.9140	25.174	11.364	12	15.2024	19.139	12.075
t_{max} [h](median, min/ max)	12	2	4	1.5	12	3	4	1
V_dFB [L/kg]	12	3.5681	4.416	2.883	12	3.3265	4.045	2.736
500 µg roflumilast								
AUCI [h*ug/L]	10	49.3512	64.226	37.921	12	54.4463	69.413	42.707
AUCIB*	10	62.0553	82.337	46.770	12	57.4580	72.817	45.339
AUCT [h*ug/L]	10	36.4051	45.716	28.991	12	40.2294	46.985	34.445
AUCTB*	10	45.7766	57.726	36.300	12	42.4547	49.537	36.385
CLFB [L/h/kg]	10	0.1343	0.178	0.101	12	0.1450	0.184	0.114
C_{max} [ug/L]	10	5.2338	6.855	3.996	12	6.1342	8.020	4.692
HL [h]	10	20.3923	27.138	15.324	12	17.3364	22.116	13.590

Variable	Caucasians				Japanese			
	n	Geom Mean	Upper 68%	Lower 68%	n	Geom Mean	Upper 68%	Lower 68%
t_{max} [h](median, min/ max)	10	3	4	1.5	12	3	4	1
V_dFB [L/kg]	10	3.9508	4.705	3.317	12	3.6274	4.306	3.056

*normalized to 60 kg body weight

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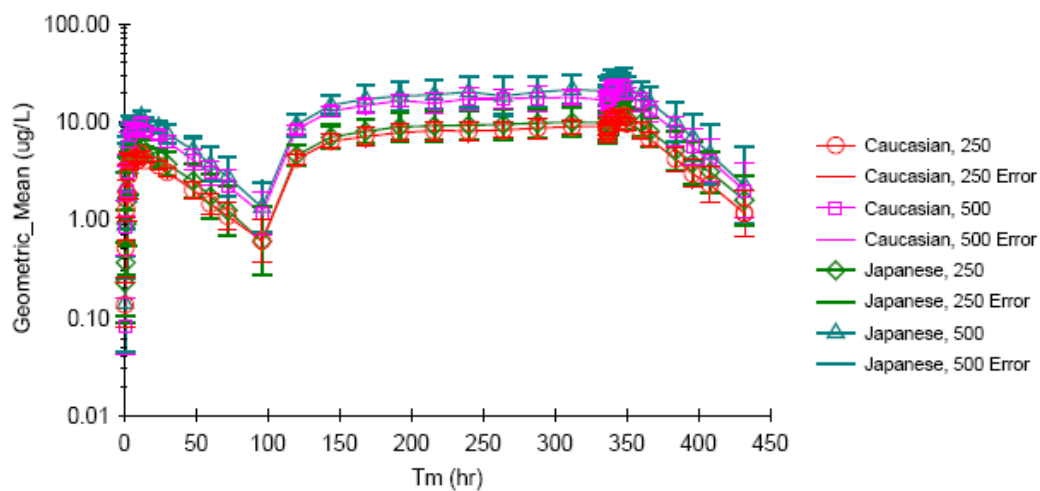
Figure 11.4.2.1 – 2: Roflumilast N-oxide – Geometric means (68% ranges, denoted as error in graph legend) in Japanese and Caucasian male subjects from Day 1 to Day 15, following oral administration of 250 µg and 500 µg roflumilast, **semilog** scale

Table 11.4.2.1 – 1: Roflumilast N-oxide – Summary of pharmacokinetic parameter estimates in healthy male Japanese and Caucasian subjects at **Day 15** (steady state) following multiple once-daily oral administrations of roflumilast [geometric mean (68% range); t_{max}: median (min/ max)]

Variable	Caucasians				Japanese			
	n	Geom Mean	Upper 68%	Lowe 68%	n	Geom Mean	Upper 68%	Lower 68%
250 µg roflumilast								
AUCT [h*ug/L]	11	233.9058	265.5538	206.0295	12	264.8329	340.5626	205.9429
AUCTB*	11	291.3531	345.5836	245.6328	12	279.4822	360.1963	216.8548
$CL_{ss}FB$ [L/h/kg]	11	0.0143	0.0170	0.0121	12	0.0149	0.0192	0.0116
C_{max} [ug/L]	11	12.2232	13.5190	11.0516	12	13.3713	16.8199	10.6299
$C_{max}B$*	11	15.2253	17.7982	13.0243	12	14.1110	17.9031	11.1221
C_{min} [ug/L]	11	7.5028	9.1230	6.1703	12	8.1919	11.1333	6.0275
$C_{min}B$*	11	9.3455	11.7181	7.4533	12	8.6450	11.7780	6.3454
HL [h]	11	26.5118	32.1154	21.8859	12	26.8532	33.3350	21.6317
t_{max} [h](median, min/ max)	11	8	12	4	12	10	12	4
$V_{ss}FB$ [L/kg]	11	0.5470	0.5806	0.5153	12	0.5776	0.6451	0.5171
500 µg roflumilast								
AUCT [h*ug/L]	10	468.5096	542.9594	404.2682	11	545.7876	708.5242	420.4290
AUCTB*	10	589.1140	723.2393	479.8623	11	570.0140	733.3531	443.0553
$CL_{ss}FB$ [L/h/kg]	10	0.0141	0.0174	0.0115	11	0.0146	0.0188	0.0114
C_{max} [ug/L]	10	23.9921	26.7426	21.5244	11	28.1727	35.6318	22.2751
$C_{max}B$*	10	30.1681	36.2318	25.1193	11	29.4233	37.1193	23.3229
C_{min} [ug/L]	10	14.2813	17.7730	11.4755	11	16.6315	22.7929	12.1357
$C_{min}B$*	10	17.9576	23.4577	13.7471	11	17.3697	23.5553	12.8085
HL [h]	10	24.7527	30.4388	20.1289	11	24.3587	31.8066	18.6548
t_{max} [h](median, min/ max)	10	6	12	4	11	12	12	4
$V_{ss}FB$ [L/kg]	10	0.5051	0.5487	0.4651	11	0.5138	0.5675	0.4651

* normalized to 60 kg body weight

Table 11.4.2.1 - 2: Roflumilast N-oxide – Summary of pharmacokinetic parameter estimates in healthy male Japanese and Caucasian subjects at **Day 1** following a single oral administration of roflumilast [geometric mean (68% range); t_{max}: median (min/ max)]

Variable	Caucasians				Japanese			
	n	Geom Mean	Upper 68%	Lower 68%	n	Geom Mean	Upper 68%	Lowe _68%
250 µg roflumilast								
AUCI [h*ug/L]	12	242.6402	300.213	196.109	12	277.8446	371.359	207.878
AUCIB*	12	306.9500	401.561	234.630	12	293.2137	394.155	218.123
AUCT [h*ug/L]	12	87.9040	93.926	82.268	12	102.2098	118.268	88.332
AUCTB*	12	111.2023	126.557	97.711	12	107.8636	123.845	93.944
CLFB [L/h/kg]	12	0.0136	0.018	0.010	12	0.0142	0.019	0.011
C_{max} [ug/L]	12	4.7750	5.179	4.403	12	5.6123	6.609	4.766
HL [h]	12	28.9777	43.348	19.371	12	24.1537	30.666	19.024
t_{max} [h](median, min/ max)	12	12	12	4	12	12	14	4
V_dFB [L/kg]	12	0.5675	0.682	0.472	12	0.4952	0.581	0.422
500 µg roflumilast								
AUCI [h*ug/L]	10	485.4110	591.050	398.653	12	577.7281	731.231	456.449
AUCIB*	10	610.3663	788.276	472.610	12	609.6854	773.207	480.746
AUCT [h*ug/L]	10	176.9808	190.801	164.162	12	208.2303	236.820	183.092
AUCTB*	10	222.5395	253.974	194.996	12	219.7487	247.332	195.242
CLFB [L/h/kg]	10	0.0137	0.018	0.011	12	0.0137	0.017	0.011
C_{max} [ug/L]	10	9.9790	10.986	9.064	12	11.4606	13.055	10.061
HL [h]	10	28.1329	37.091	21.338	12	25.8579	31.568	21.181
t_{max} [h](median, min/ max)	10	12	12	4	12	12	24	4
V_dFB [L/kg]	10	0.5541	0.640	0.480	12	0.5099	0.565	0.460

* normalized to 60 kg body weight

Conclusions: After a single dose, no significant population effect was observed for any roflumilast parameter estimate. In contrast, population effects following a single dose, were observed for AUCT and Cmax of roflumilast N-oxide.

FHP019

Study Title: Pharmacokinetics of roflumilast after single oral dose administration of 0.25 mg to patients with liver cirrhosis Child Pugh A in comparison to healthy subjects

Objectives: Primary: The investigation of the pharmacokinetics of roflumilast (89302-107) in patients with liver cirrhosis Child-Pugh A in comparison to a matched control group of healthy subjects.
Secondary: To assess the safety and tolerability of roflumilast and to investigate the pharmacokinetics of its active metabolite 89502-044.

Study Design: Open label parallel group comparison.

Study Population: A total of 24 subjects were enrolled with 12 hepatic impaired and 12 healthy subjects.

Data Analysis: Point estimates and 90%-confidence limits for the ratio of the population medians of AUC(o-∞j and Cmax of Test (patients with liver cirrhosis) and Reference (healthy subjects).

Results:

The following tables show a summary of the pharmacokinetic characteristics of roflumilast (89302-107) and the metabolite 89502-044 after single oral administration of 0.25 mg roflumilast to patients with liver impairment (n=12) and healthy control subjects (n=12). Values are given as geometric means with 68%-range except for tmax which is given as mean ± SEM (N=12)

Patents with liver impairment:	B9302-107	B9502-044
$AUC_{(0-\infty)}$ (µgxh/l)	29.11 (20.55, 41.24)	282.32 (189.94, 419.63)
C_{max} (µg/l)	2.926 (1.827, 4.684)	3.787 (2.594, 5.528)
$t_{\frac{1}{2}}$ (h)	32.36 (17.09, 61.29)	37.35 (27.35, 51.02)
t_{max} (h)	1.21 ± 0.18	28.70 ± 8.74

Healthy Control subjects:	B9302-107	B9502-044
$AUC_{(0-\infty)}$ (µgxh/l)	13.59 (9.51, 19.43)	161.76 (117.80, 222.11)
C_{max} (µg/l)	2.690 (1.825, 3.964)	3.751 (3.053, 4.608)
$t_{\frac{1}{2}}$ (h)	9.82 (4.84, 19.93)	25.87 (17.40, 38.48)
t_{max} (h)	1.67 ± 0.30	5.54 ± 1.16

Comparison of the two groups for roflumilast was assessed by using AUC (extent of absorption) and Cmax (rate of absorption) as primary criteria. The point estimates (90%-CI) for these characteristics were as follows: AUC: 2.142 (1.636, 2.805) and Cmax: 1.088 (0.804, 1.472).

The secondary characteristics AUC and t1/2 of metabolite 89502-044 were also analyzed in an explorative intention, yielding the following point estimates and 90%-confidence intervals: AUC: 1.745 (1.310, 2.326) and t1/2: 1.444 (1.081, 1.929). The point estimate (90%-CI) of tmax was -0.458 (-1.054, 0.138) for roflumilast and 23.158 (6.999, 39.318) for the metabolite 89502-044.

Conclusions: This study showed that plasma AUCs and half-lives for both roflumilast and its metabolite 89502-044 were significantly increased in hepatic impairment patients compared to healthy controls, while peak plasma concentrations did not change significantly.

Roflumilast and metabolite 89502-044 AUC in patients with liver disease was increased by about 114% and 75% respectively. In addition, a prolongation of the half-life by 230% and 44% was observed for roflumilast and its metabolite respectively.

Therefore, clearance is reduced when liver function is impaired.

CP-062

Study Title: Pharmacokinetics and safety of roflumilast after once-daily repeated oral administration of 250 μg to patients with liver cirrhosis Child-Pugh A and B in comparison to healthy subjects.

Objectives: The aim of this study was to evaluate the steady-state pharmacokinetics of roflumilast and roflumilast N-oxide after repeated oral doses of 250 μg roflumilast administered once-daily for 14 days in patients with impaired hepatic function, i.e. liver cirrhosis Child-Pugh stage A and B as compared to matched healthy controls. Further, the study provided information on the safety and tolerability of this roflumilast treatment.

Study Design: The study was conducted in a single center and had an open, non-randomized, one-period, repeated dose parallel group study design stratified according to hepatic function. It consisted of a screening examination, a treatment period (Study Day -2 to 15 with a morning administration of 250 μg roflumilast on Study Days 1-14), and a post-study examination.
Subjects were assigned to 3 groups: healthy subjects (Group 1), patients with liver cirrhosis Child-Pugh stage A (Group 2), patients with liver cirrhosis Child-Pugh stage B (Group 3).
Healthy subjects were matched to patients with liver cirrhosis Child-Pugh A according to sex, age and body weight.

Blood samplings for pharmacokinetic purposes were performed on the following days for roflumilast and roflumilast N-oxide:
 ̣Study Day 14 (steady state): at pre-dose, 0.25 h, 0.5 h, 0.75 h 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 h after morning dosing
 ̣Study Days 12, 13, and 14: sampling within 30 min before dosing for determination of trough values. The trough plasma concentration on Study Day 14 served as pre-dose value.
Plasma protein binding: The blood samples taken 1 h, 4 h, 12 h, and 24 h after dosing were also used to determine protein binding i.e. the fraction of roflumilast and roflumilast N-oxide bound to plasma protein.
Monoethylglycinexylidide (MEGX) test: In the morning of Study Day −1, the MEGX-test was performed. Serum samples for determination of lidocaine and its metabolite(s) were taken 15 and 30 minutes after i.v. administration of lidocaine (1 mg/kg body weight).

Study Population: A total of 25 subjects (8 healthy subjects, 17 patients with liver cirrhosis) were enrolled in this study. All subjects were of Caucasian origin. One patient was withdrawn due to a prolongation of the QTc-interval already present at screening, so that 24 subjects (8 per group) were available for the analysis of the primary pharmacokinetic variables.

Demographic characteristics for the study population (full analysis set)

Characteristic	Healthy Subjects (n=8)	Liver Cirrhosis Child-Pugh A (n=8)	Liver Cirrhosis Child-Pugh B (n=9)
Age [years]			
median (min, max)	52 (43, 67)	51 (44, 63)	52 (43, 66)
Height [cm]			
median (min, max)	164 (145, 180)	166 (162, 175)	165 (156, 171)
Weight [kg]			
median (min, max)	69 (54, 92)	69 (52, 102)	68 (52, 80)
Sex, n (%)			
Male	3 (37.5%)	5 (62.5%)	6 (66.7%)
Female	5 (62.5%)	3 (37.5%)	3 (33.3%)

Data Analysis: Point estimates and 90%-confidence limits for the ratio of the population medians of AUC(o-∞) and Cmax of Test (patients with liver cirrhosis) and Reference (healthy subjects).

Results: Plasma concentrations of roflumilast and roflumilast N-oxide were determined by using a erformance Liquid Chromatography with tandem Mass Spectrometry (HPLC-MS/MS) assay. For measurements of pharmacokinetic samples, the lower limit of quantitation (LLOQ) was 0.04 µg/L for both compounds, using a sample volume of 0.5 mL.
For measurements of plasma protein binding samples, the LLOQ was 0.00499 µg/L for both compounds, using a sample volume of 0.5 mL.
Serum concentrations of MEGX and lidocaine were also determined using a validated HPLC-MS/MS assay. The LLOQ was 2 µg/L and 20.0 µg/L for MEGX and lidocaine, respectively, using a sample volume of 0.1 mL.

Primary pharmacokinetic parameter estimates of roflumilast following a 14-day oral administration of roflumilast (250 µg once daily) in patients with liver cirrhosis Child-Pugh A and B as compared with healthy subjects; geometric mean, 68% range

Parameter	N[a]	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
$AUC_{(0-24h)}$	8	30.018	45.279	57.711
(hr*µg/L)		19.907, 45.265	32.435, 63.211	29.953, 111.191
CLssFBW	8	0.119	0.075	0.066
(L/hr/kg)		0.077, 0.183	0.050, 0.113	0.031, 0.140
C_{max}	8	4.705	4.828	5.950
(µg/L)		3.822, 5.791	3.693, 6.311	4.149, 8.531

[a]There were 8 observations in each of the 3 groups

Primary pharmacokinetic parameter estimates of roflumilast N-oxide following a 14-day oral administration of roflumilast (250 µg once daily) in patients with liver cirrhosis Child-Pugh A and B as compared with healthy subjects; geometric mean, 68% range

Parameter	N[a]	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
$AUC_{(0-24h)}$	8	308.69	382.66	436.13
(hr*µg/L)		210.35, 453.02	283.27, 516.94	309.55, 614.47
C_{max}	8	17.61	22.12	24.65
(µg/L)		12.71, 24.39	16.89, 28.96	17.55, 34.63

[a]There were 8 observations in each of the 3 groups

Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast primary pharmacokinetic parameter estimates following 14-day oral administration of roflumilast (250 µg once daily)

Compound	Dependent	Reference (N=8)	Test (N=8)	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast	$AUC_{(0-24h)}$ [hr*µg/L]	Healthy	Child-Pugh A	30.018	45.279	150.84	99.24	229.27
		Healthy	Child-Pugh B	30.018	57.711	192.25	126.49	292.21
	CLssFBW [L/hr/kg]	Healthy	Child-Pugh A	0.119	0.075	63.37	39.38	101.97
		Healthy	Child-Pugh B	0.119	0.066	55.45	34.46	89.22
	C_{max} [µg/L]	Healthy	Child-Pugh A	4.705	4.828	102.62	80.26	131.22
		Healthy	Child-Pugh B	4.705	5.950	126.47	98.9	161.71

Test/Reference ratios refer to Group 2/Group 1 and Group 3/Group 1 as defined in the study protocol
i.e. Child-Pugh A (Test)/Healthy Subjects (Reference) and Child-Pugh B (Test)/Healthy Subjects (Reference)

Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast N-oxide primary pharmacokinetic parameter estimates following 14-day oral administration of roflumilast (250 µg once daily)

Compound	Dependent	Reference (N=8)	Test (N=8)	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast N-Oxide	$AUC_{(0-24h)}$ [hr*µg/L]	Healthy	Child-Pugh A	308.694	382.668	123.96	92.2	166.68
		Healthy	Child-Pugh B	308.694	436.135	141.28	105.08	189.97
	C_{max} [µg/L]	Healthy	Child-Pugh A	17.609	22.124	125.64	95.95	164.51
		Healthy	Child-Pugh B	17.609	24.656	140.02	106.93	183.34

Test/Reference ratios refer to Group 2/Group 1 and Group 3/Group 1 as defined in the study protocol
i.e. Child-Pugh A (Test)/Healthy Subjects (Reference) and Child-Pugh B (Test)/Healthy Subjects (Reference)

Free fraction of roflumilast and roflumilast N-oxide expressed as percentage in healthy subjects and patients with liver cirrhosis Child-Pugh stage A and B on Study Day 14 following once-daily administration of 250 µg roflumilast

Compound	% free fraction, mean (standard deviation)		
	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
Roflumilast	0.61 (0.45)	0.41 (0.33)	0.49 (0.22)
Roflumilast N-oxide	1.51 (0.21)	1.47 (0.22)	2.03 (0.37)

The mean free fraction of roflumilast N-oxide was approximately 38% higher in patients with moderate liver cirrhosis (Child-Pugh B patient population) than in patients with mild liver cirrhosis (Child-Pugh A) and healthy subjects.

Conclusions: When comparing patients with liver cirrhosis to healthy subjects a gradual increase in exposure was observed in patients with liver cirrhosis Child-Pugh stage A and B for both roflumilast and roflumilast N-oxide.

FHP020

Study Title: Pharmacokinetics of roflumilast after single oral dose administration of 0.5 mg to patients suffering from severe renal impairment

Objectives: Primary: The investigation of the pharmacokinetics of roflumilast (89302-107) in patients with severe renal impairment in comparison to a matched control group of healthy subjects.
Secondary: To assess the safety, tolerability and pharmacokinetics of the pharmacologically active metabolite 89502-044.

Study Design: Open label parallel group comparison. Single dose of 0.5 mg roflumilast was given to the subjects.

Study Population: A total of 24 subjects (12 patients with severe renal impairment and 12 healthy control subjects).

Data Analysis: Point estimates and 90%-confidence limits for the ratio of the population medians of AUC(o-∞j and Cmax of Test (patients with renal impairment) and Reference (healthy subjects).

Results: The following tables show a summary of the pharmacokinetic characteristics of roflumilast (89302-107) and the metabolite 89502-044 after single oral administration of 0.5 mg roflumilast to patients with renal impairment (n=12) and healthy control subjects (n=12). Values are given as geometric means with 68%-range except for tmax which is given as mean ± SEM (N=12).

Patients with renal impairment:	B9302-107	B9502-044
$AUC_{(0-\infty)}$ (µgxh/l)	35.48 (23.73, 53.04)	428.93 (334.19, 550.54)
C_{max} (µg/l)	4.266 (2.744, 6.633)	6.840 (5.350, 8.745)
$t_{1/2}$ (h)	22.08 (14.18, 34.41)	37.40 (21.88, 63.94)
t_{max} (h)	1.38 ± 0.16	19.82 ± 4.41

Healthy control subjects:	B9302-107	B9502-044
$AUC_{(0-\infty)}$ (µgxh/l)	44.69 (33.47, 59.68)	461.18 (366.23, 580.74)
C_{max} (µg/l)	5.072 (3.625, 7.097)	7.780 (6.350, 9.534)
$t_{1/2}$ (h)	18.52 (11.43, 30.00)	28.70 (21.97, 37.49)
t_{max} (h)	1.79 ± 0.18	16.92 ± 2.88

Comparison of the two groups for roflumilast was assessed by using AUC (extent of absorption) and Cmax (rate of absorption) as primary criteria. The point estimates (90%-CI) for these characteristics were as follows: AUC: 0.794 (0.618, 1.019) and Cmax: 0.841 (0.639, 1.107). The point estimate (90%-CI) of t1/2 as a secondary criterion (explorative intention) was 1.193 (0.862, 1.650). The point estimate (90%-CI) of tmax was -0.417 (-0.834, 0.001) for roflumilast.
The secondary characteristics AUC and t1/2 of metabolite 89502-044 were also analyzed in an explorative intention, yielding the following point estimates and 90%-confidence intervals: AUC: 0.930 (0.775, 1.116) and *t1/2:* 1.303 (0.951, 1.787).

Conclusions: Following single oral administration of 0.5 mg roflumilast to 12 patients comparable to the corresponding values of a control group of healthy volunteers. A dose adjustment was not considered to be necessary in the investigated population subgroup.

CP-053 (report 21/2003)

Study Title: Determination of cytochrome P450 1A2 activity in Subject No. 10 of Study BY217/FHP 027 - a case control study

Objectives: To determine the enzyme activity of cytochrome P450 1A2 in a female subject who exhibited high roflumilast and roflumilast-N-oxide plasma concentrations during Study BY217/FHP027 (Subject ⁽ᵇ⁾ ⁽⁶⁾) as compared to six healthy female subjects.

Study Population: A total of 7 healthy, female, Caucasian subjects with normal body weight according to the Broca index (0.8 ≤ weight[kg]/(height[cm]-100) ≤ 1.25) were enrolled. The case subject from Study BY217/FHP027 (Subject ⁽ᵇ⁾ ⁽⁶⁾ showed increased plasma concentrations of roflumilast and roflumilast N-oxide. The median (range) age was 42 (24 to 45); 2 of the subjects were smokers.

Study Design: This study was a single-center, case control study. Subjects underwent a pre-study medical examination (within one week before study start), followed by administration of 200 mg of caffeine with urine collection from 0-4 hours and 4-8 hours, followed by a post-study medical examination.

Data Analysis: The primary variable was determination of the activity of cytochrome P450 enzyme 1A2 as evaluated by the ratio of the metabolites of caffeine in urine: (1X+1U+AFMU)/17U. The ratio of caffeine metabolites in the urine of subject (b) (6) was compared with the respective median (mean) ratio of the control study subjects. The secondary variables of this study included the NAT activity (NATi) and XO activity (XOi), which were also calculated using the metabolite concentrations of caffeine in urine. NATi was assessed by the ratio AFMU/1X. XOi was assessed by the ratio 1U/1X

Results: Individual urine concentrations of AFMU, 1U, 1X, and 17U and individual activity indices CYP1A2i, XOi, and NATi are shown for each collection period in the table below.

Subject ID	Initials	collection time	AFMU [mg/L]	1U [mg/L]	1X [mg/L]	17U [mg/L]	AFMU+1U+1X	CYP1A2i (AFMU+1U+1X) / 17U	NATi AFMU / 1X	XOi 1U / 1X
010	(b) (6)	pre dose	1.25	1.74	0.00	3.63	2.99	0.82	-	-
010		0-4h	0.00	1.27	1.02	1.38	2.28	1.65	0.00	1.25
010		4-8h	3.93	5.75	4.70	9.69	14.38	1.48	0.84	1.23
001		pre dose	0.67	8.64	1.42	1.80	10.73	5.95	0.47	6.08
001		0-4h	0.76	6.93	4.03	3.33	11.72	3.52	0.19	1.72
001		4-8h	5.12	23.74	16.60	13.97	45.46	3.25	0.31	1.43
002		pre dose	3.63	9.16	1.83	3.87	14.62	3.78	1.99	5.02
002		0-4h	2.27	3.03	1.44	2.43	6.74	2.78	1.57	2.10
002		4-8h	19.17	7.21	4.52	9.19	30.90	3.36	4.24	1.59
003		pre dose	3.17	11.88	4.98	6.03	20.03	3.32	0.64	2.38
003		0-4h	0.00	2.01	1.10	1.07	3.12	2.92	0.00	1.82
003		4-8h	1.77	5.07	3.63	2.69	10.47	3.89	0.49	1.40
004		pre dose	0.70	3.39	0.00	1.10	4.09	3.71	-	-
004		0-4h	0.00	1.85	1.36	0.81	3.21	3.94	0.00	1.36
004		4-8h	6.65	12.67	12.56	7.86	31.88	4.06	0.53	1.01
005		pre dose	1.37	30.79	2.64	2.98	34.79	11.67	0.52	11.68
005		0-4h	0.54	8.73	1.57	2.66	10.84	4.08	0.34	5.57
005		4-8h	3.43	11.44	8.40	10.09	23.27	2.31	0.41	1.36
006		pre dose	0.59	5.66	1.71	2.01	7.95	3.96	0.34	3.32
006		0-4h	2.30	11.69	10.84	5.36	24.83	4.63	0.21	1.08
006		4-8h	7.92	36.24	26.54	11.42	70.69	6.19	0.30	1.37

Median indices of CYP1A2, XO, and NAT activity are shown in the following table, relative to subject No. 10.

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subject ID	Initials	collection time	CYP1A2i (AFMU+1U+1X) 17U	Median	NATi AFMU 1X	Median	XOi 1U 1X	Median
010	(b) (6)	4-8h	1.48	**1.48**	0.84	**0.84**	1.23	**1.23**
001			3.25		0.31		1.43	
002			3.36		4.24		1.59	
003		4-8h	3.89	**3.84**	0.49	**1.05**	1.40	**1.36**
004			4.06		0.53		1.01	
005			2.31		0.41	**0.41**	1.36	
006			6.19		0.30	(without BT)	1.37	

❖ *Reviewer comment: Subjects* (b) (6) *and* (b) (6) *were smokers. They had higher CYP1A2 activities than other control subjects, which may overestimate comparisons to the case subject.*

In comparison with the control group, the CYP1A2 activity was reduced in Subject (b) (6) by a factor of 2.6. The Test/Reference ratio was 0.41, where CYP1A2i of subjec (b) (6) was considered as "Test" and the arithmetic mean of CYP1A2i of the control group was considered "Reference".

For NAT, no difference was found between the activity in subject (b) (6) and the control group. The Test/Reference ratio for NATi was 0.8. However, one study subject of the control group (b) (6) showed a NATi that was raised about 10-fold. If subjec (b) (6) is excluded from the control group, a Test/Reference ratio of 2.0 is found for NATi.

The Test/Reference ratio for XOi was 0.90. The XOi for study subjec (b) (6) was similar to XOi values found for the individuals from the control group that ranged between 1.01 and 1.51. Therefore, the XOi activity of subject (b) (6) was similar to the XOi activity found for the control group.

Conclusions: In subjec (b) (6) the activity of CYP1A2 was reduced by a factor of 2.6 when compared with the control group. NAT activity in study subject (b) (6) was similar to controls, although an increase by a factor of two is observed if the elevated study subjec (b) (6) who had 10 times higher activity than other controls) was excluded from the control group. XO activity in study subjec (b) (6) was similar to that of the control group.

CP-054 (report 22/2003)

Study Title: Determination of cytochrome P450 3A4 activity in Subject (b) (6) of Study BY217/FHP027 - a case control study

Objectives: The objective of this study was to determine the cytochrome P450 3A4 activity in subject (b) (6) of Study BY217/FHP027 *in vivo* and to compare this activity with the results of historic data of control subjects.

Study Population: Case: 1 case subject (subject ▮▮▮(b) (6) from Study BY217/FHP027, Clinical Study Report Number 208/2001). Control: Historical control group of healthy subjects taken from Floyd et al. Pharmacogenetics 2003; 13(10):595-606).

Study Design: This study was conducted as a single-center case-control study. The study consisted of a pre-study medical examination (including blood pressure, heart rate, and ECG) within one week prior to study start, one treatment period of 12h on Day 1 (subject was hospitalized the afternoon before study start, Day -1 and remained in hospital until conclusion of the study, Day 2), and a post study medical examination conducted on Day 2 after study termination (including blood pressure, heart rate, and ECG). Blood samples for determination of midazolam and its metabolites were collected predose (before intravenous administration of midazolam) and during the study period (after administration of midazolam) for up to 12h. Blood pressure, heart rate, and ECG were recorded at pre-dose, 5 minutes, 15 min, 0.5h, 1h, 2h, 4h, 6h, 8h, 10h, and 12h after administration of study drug. Adverse events were monitored throughout.

Data Analysis: The primary variable of the study was the midazolam weight normalized systemic clearance [dose/(AUC x weight)] of case subject ▮▮▮(b) (6) of Study BY217/FHP027 as compared with the published data of a control group (historical controls).

The secondary variables were:
− ratio of AUC 1-hydroxymidazolam/AUC of midazolam
− ratio of AUC 4-hydroxymidazolam/AUC midazolam
− ratio t1/2 1-hydroxymidazolam/ t1/2 midazolam
− ratio AUC 4-hydroxymidazolam/ratio t1/2 midazolam
− AUC and t1/2 midazolam;
− results of safety measurements and adverse eventswas the midazolam weight normalized systemic clearance [dose/(AUC x weight)] of subject ▮▮▮(b) (6)

Results: The weight normalized clearance determined for case subject ▮▮▮(b) (6) after administration of 1 mg of midazolam intravenously was 2.99 mL/(min-kg). Comparison with reference data showed that the subjects weight normalized clearance falls in the lower percentile (range: 2.61 - 3.88 mL/(min-kg) of the reference data set.

Individual pharmacokinetic results for midazolam and its metabolite 1-hydroxy-midazolam (after deconjugation) determined for case subject ▮▮▮(b) (6) after administration of one single intravenous dose of 1 mg midazolam are shown in the following table.

Pharmacokinetic characteristics (AL10)	Midazolam	1-Hydroxy-Midazolam
AUC [µg / L x h]	84.4	23.5
$t_{1/2}$ [h]	6.80	5.15
CL* [L / (h x kg)]	0.1794	–
CL [mL/(min × kg)]	2.99	–

Source of data: Pharmacokinetic data, Table 14.2.1.2 (midazolam) and Table 14.2.1.4 (1-hydroxymidazolam) CL = clearance; The correction factor for converting clearance from L/(h × kg) to ml/(min × kg) is 1000/60 (L-ml/h-min). The term CL* indicates that this clearance with the unit of L/(h × kg) is the initial clearance value as calculated by KINTPC. The second CL value is obtained by multiplying CL* with the correction factor 1000/60. The reason for doing so is that all clearance values for the reference data set in the publication by Floyd et al. 2003 are shown as ml/(min × kg).

Reference data obtained from a historical population of 57 healthy subjects (23 Caucasians, 34 African Americans, 32 female and 25 male subjects, aged between 18 and 55 years and weighing 52 to 123 kg) are presented in the following table (Floyd et al. 2003).

Parameter for Historical Data	Midazolam Clearance [mL/(min × kg)]
Range	2.61 – 15.20*
Mean ± SD	5.54 ± 2.04
Lower quartile	2.61 - 3.88
Upper quartile	6.01 – 15.20

Source of data: (Floyd et al 2003);*53 out of the 57 healthy control subjects were within the range of 2.61 to 8.64

In the Reference population, for 53 (93.0%) out of 57 study subjects, the midazolam clearance ranged between 2.61 to 8.64 mL/(min-kg)]. The lower quartile for the reference population ranged between 2.61 and 3.88 mL/(min-kg).

CYP 3A4 and CYP 3A5 activities as determined by the ratio of the AUC(0-inf.) for 1-hydroxymidazolam over the AUC(0-inf.) for midazolam for case subject (b) (6) are given in the

following table. Concentrations used for the determination of pharmacokinetic parameters of the metabolite 1-hydroxymidazolam were determined after treating the sample with ß-glucuronidase/ arylsulfatase.

Ratio analysis	(1-OHMDZ / MDZ)
AUC$_{(0-inf.)}$ (CYP 3A4 activity)	0.29

Source of data: The ratio of AUC from 1-OHMDZ over MDZ represents the metabolic ratio in subject (b) (6) This is a standard parameter to assess metabolic activity *in vivo*.

For the metabolite 4-hydroxymidazolam, all concentrations were below the lower limit of quantitation of 0.95 ng/ml; therefore, no pharmacokinetic parameters could be calculated.

Conclusions: The results of the present study show that the activity of the cytochrome P450 3A4 of the case subject was reduced when compared with reference data from (historical) control group (Floyd et al. 2003). Because cytochrome P450 3A4 contributes considerably to the metabolism of roflumilast, such a decrease of CYP 3A4 activity could be responsible for decreased rate of metabolism of roflumilast and consequently may contribute to the increased plasma levels of roflumilast and roflumilast N-oxide found in the case subject.

FHP027 (report 269-2003)

Study Title: Summary/expert report – Pharmacokinetic and pharmacogenetic analysis of subject (b) (6) of study BY217/FHP027 showing an increased systemic exposure to roflumilast.

Objectives: To summarize the following: i) pharmacokinetic data of subject (b) (6) for roflumilast and roflumilast-N-oxide following single and repeated oral administration of 500 µg roflumilast, ii) data on the subject's individual activity of the enzymes involved in roflumilast metabolism are compiled; third, iii) data on the subject's pharmacogenetic background of these enzymes

Study Population: Subject (b) (6) was a female Caucasian. By the time of the study FHP027, the subject was 41 years of age, with a height of 162 cm, weight of 62 kg, and a Broca Index of 1.00. Subject (b) (6) was included in the study with no clinically relevant medical history and was taking desogestrel/ethinylestradiol (Marvelon®) as concomitant medication. The subject reported not to smoke and stated an occasional consumption of alcohol. Subject (b) (6) reported aversion towards coffee; she reported this feature to be present throughout her family.

Study Design: Not applicable as this is a summary report.

Study FHP027 was conducted according to an open, randomized, two-period crossover design. Subjects received either Treatment A (digoxin 250 μg o.d. on Days 1 and 14, and Roflumilast 500 μg o.d. on Days 1 to 14) or Treatment B (digoxin 250 μg o.d. on Day 1). The treatment periods were separated by a washout period of at least 10 days. Blood sampling for determination of pharmacokinetic parameters was done on Day 1 of Treatment A and on Days 13 and 14 of Treatment A.

CYP1A2 and CYP3A4 phenotyping, DNA sequencing, and in vitro functional studies were performed to characterize the etiology of the high roflumilast exposure.

Data Analysis: Subject ____(b) (6)____ weight-normalized clearance was compared with a female reference population receiving the same roflumilast dose, i.e. 500 μg as single dose and at steady state compiled in report No. 144/2002. Other analyses are descriptive.

Results:

Pharmacokinetics

The pharmacokinetic characteristics of roflumilast and its major and pharmacologically active metabolite roflumilast N-oxide in subject ____(b) (6)____ following intake of 500 μg roflumilast on Day 13 (Reference, administration of roflumilast alone) and Day 14 (Test, administration of roflumilast with concomitant digoxin treatment) revealed an increased systemic exposure to roflumilast and roflumilast N-oxide. There was no change in the pharmacokinetic parameters for digoxin.

Comparison of the respective geometric mean data for roflumilast and roflumilast N-oxide from all study subjects are shown in the following tables. A five-fold increase of AUC(0-24h) for roflumilast and a three-fold increase for roflumilast N-oxide AUC(0-24h) was observed on both study days. A significant increase in elimination half-lives (t1/2) was also observed. The trough values of subject ____(b) (6)____ compared with the trough levels of all other study subjects were higher. The accumulation index Rac for roflumilast in subjec ____(b) (6)____ was 1.85 for roflumilast and 2.93 for roflumilast-N-oxide. The metabolic ratio, calculated as AUC(0-24h) roflumilast over AUC(0-24h) roflumilast–N-oxide, was elevated two-fold compared with the mean of all other study subjects. Subjec ____(b) (6)____ was re-exposed to a single dose of 500 μg roflumilast in order to confirm the low clearance of roflumilast and roflumilast-N-oxide in ____(b) (6)____ [1]. A similar elevation of the pharmacokinetic characteristics AUC and t1/2 previously found for roflumilast in subject ____(b) (6)____ during the roflumilast digoxin interaction study was confirmed.

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Table 1: Individual pharmacokinetic on roflumilast data of subject (b) (6) after a single as well as steady state administration of 500 μg roflumilast taken compared with geometric mean data of all study subjects included in study FHP027 (208/2001)

	Subject (b) (6) 500 μg roflumilast single dose[1]	Subject (b) (6) after steady state administration of 500 μg roflumilast (Day 13)	Geometric mean of all study subjects after steady state administration of 500 μg roflumilast	
			Geom Mean	68%-range
AUC [μg/lxh]	144.6^2 53.8^3	267.6^3	50.2	29.8 – 84.6
Cmax [μg/l]	10.2	18.91	9.93	6.96 – 14.15
t ½ [h]	79.0	n.a.	14.44	9.08 – 22.96
R_{ac}^4		4.97		
metabolic ratio[5]	0.304	0.192	0.096	0.092 – 0.104

n.a. = not ascertained

[1] = data are taken from re-exposure of subject (b) (6) with a single dose of 500 μg roflumilast

[2] = $AUC_{(0-96h)}$, [3] = $AUC_{(0-24h)}$,

[4] the accumulation rate R_{ac} was calculated by dividing AUC_{ss} over $AUC_{(1, \tau \, 1st \, dose}$ according to Rowland and Tozer [25]

[5] the metabolic ratio was calculated as $AUC^{roflumilast}$ over $AUC^{roflumilast -N-oxide}$

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Table 2: Individual pharmacokinetic on roflumilast N-oxide data of subject (b) (6) after a single as well as steady state administration of 500 µg roflumilast compared with geometric mean data of all study subjects included in study FHP027 (208/2001)

	Subject (b) (6) 500 µg roflumilast single dose[1]	Subject (b) (6) after steady state administration of 500 µg roflumilast (Day 13)	Geometric mean of all study subjects after steady state administration of 500 µg roflumilast	
			Geom Mean	68%-range
AUC [µg/lxh]	476.4[2] 146.6[3]	1396.5[3]	504.4	339.6 – 749.2
Cmax [µg/l]	5.6	68.71	30.92	22.78 – 41.98
t ½ [h]	n.a.	n.a.	34.53	23.29 – 51.19
R_{ac}[4]		9,52		

n.a. = not ascertained

[1] = data are taken from re-exposure of subject (b) (6) with a single dose of 500 µg roflumilast

[2] = $AUC_{(0-96h)}$, [3] = $AUC_{(0-24h)}$,

[4] the accumulation rate R_{ac} was calculated by dividing AUC_{ss} over $AUC_{(1, \tau)}$

Mild nausea, mild to moderate diarrhea and moderate headache was reported following treatment with 500 µg roflumilast at steady state from Day 1 to 14 in combination with 250 µg digoxin by subject (b) (6) These adverse events were assessed by the investigator as likely related to roflumilast treatment. Upon re-exposure of subject (b) (6) to a single dose of 500 µg roflumilast, no adverse effects were reported.

In order to statistically assess the extent of exposure of subject (b) (6) to roflumilast, the subject's weight-normalized clearance was compared with a female reference population receiving the same roflumilast dose, i.e. 500 µg as single dose and at steady state compiled in report No. 144/2002. Weight-normalized clearance of roflumilast was lowest in subjec (b) (6) when compared with the female reference population after single dose administration of 500 µg roflumilast (n = 46) as well as at steady state (n = 21), as shown in the following figure and table.

Figure 1: Scatter plot of weight-normalized oral clearances of roflumilast after administration of 500 µg roflumilast as a single dose or at steady state to Caucasian women compiled in discussion No. 144/2002. Medians are indicated as horizontal bars. * Weight-normalized roflumilast clearance of subject (b) (6)

- ● CI single dose
- ○ CI repeated dose
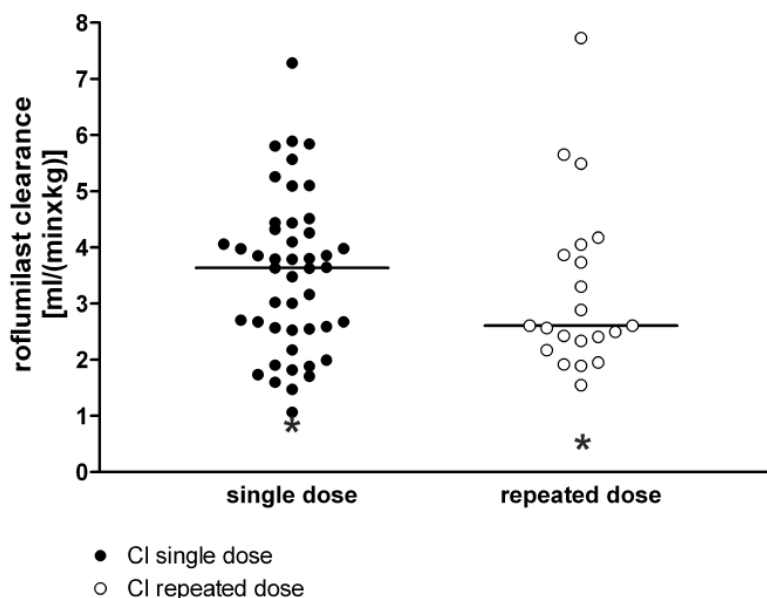
Table 3: Statistical analysis of weight-normalized oral clearances of roflumilast after administration of 500 µg roflumilast as a single dose or at steady state to Caucasian women compiled in discussion No. 144/2002.

	CI roflumilast [ml/ (min x kg)] single dose	CI roflumilast [ml/(minxkg)] repeated dose
Minimum	1.064	1.547
25% Percentile	2.538	2.252
Median	3.638	2.605
75% Percentile	4.379	3.958
Maximum	7.284	7.728
Mean	3.526	3.228
Std. Deviation	1.391	1.526
Std. Error	0.2051	0.3329
n	46	21
Subject (b) (6)	0.929	0.502

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<u>Phenotyping</u>

Subject   (b) (6) underwent caffeine (CYP1A2) and midazolam (CYP3A4) phenotyping. The results of this analysis are described in the summaries for CP053 and CP054.

<u>Gene sequencing and functional studies</u>

(b) (4)

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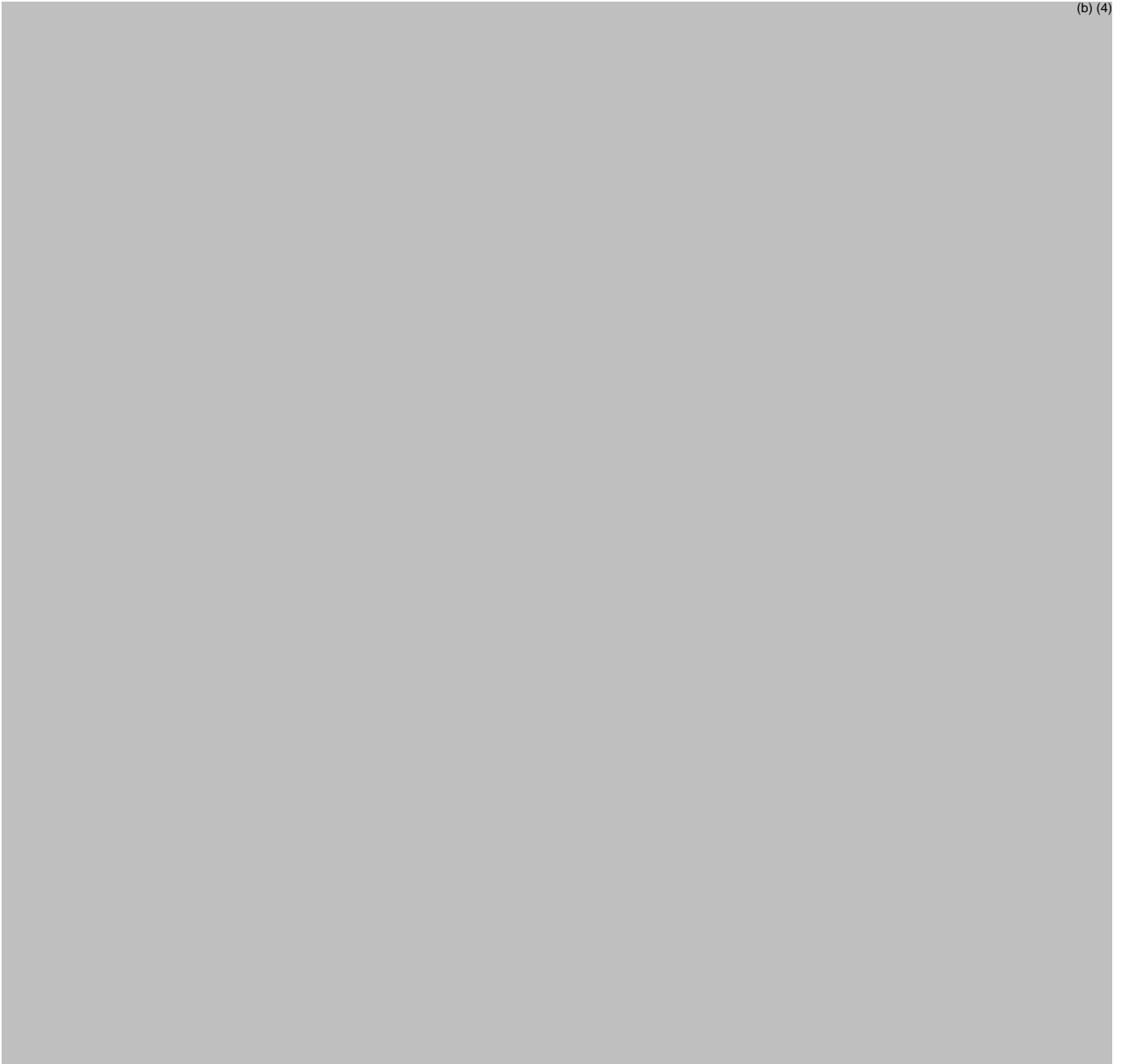
FHP033

Study Title: Male endocrine function after single and repeated oral administration of 250 μg or 500 μg roflumilast - a double blind, placebocontrolled, randomized, three-period changeover study

Objectives: Primary: Male endocrine function after single and repeated oral administration of 250 μg or 500 μg roflumilast.
Secondary: Adrenal cortex function (glucocorticoid and mineralocorticoid) after single and repeated oral administration of 250 μg or 500 μg roflumilast. Safety and tolerability.

Study Population: A total of 25 subjects were included in the study. A total of 24 per-protocol subjects for each treatment (500 μg roflumilast, 250 μg roflumilast, placebo) completed the study.

Study Design: A double-blind, placebo-controlled, randomized, three-period changeover design. Levels of testosterone, FSH, LH, inhibin-B, progesterone, ACTH and aldosterone, as well as concentrations of sodium and potassium were determined at the screening examination, and on study days 1 and 14 at pre-dose, and at 2h after the administration of study medication (500 μg roflumilast, 250 μg roflumilast and placebo). Cortisol levels before and after ACTH stimulation test (0.25 mg of Synacthen\ intravenously) was determined in the morning of study day −7 of the first study period, and on study day 15 of each study period.

Data Analysis: Only pharmacokinetic asssements of the study are summarized here. Noncompartmental analysis was used in the pharmacokinetic assessments.

Results:

Table 11.4.1-1: 500 µg roflumilast: Geometric means (68% range) of roflumilast and ro-flumilast-N-oxide plasma concentrations in healthy male subjects before (pre-dose) and after (2h post-dose) the administration of study medication at study day 1, as well as study days 14 and 15 (steady state)

	Roflumilast		Roflumilast-N-oxide	
	Geometric means	(68% range)	Geometric means	(68% range)
Day 1/ pre-dose	n.v.	---	n.v.	---
Day 1/ 2 h post-dose	3.42	(2.42, 4.84)	5.74	(4.22, 7.82)
Day 14/ pre-dose	0.47	(0.25, 0.89)	10.27	(6.82, 15.47)
Day 14/ 2 h post-dose	3.73	(2.55, 5.46)	16.12	(12.07, 21.52)
Day 15/ pre-dose	0.42	(0.22, 0.79)	9.92	(6.59, 14.93)
Day 15/ 2 h post-dose	2.92	(1.87, 4.55)	15.05	(11.18, 20.25)

Table 11.4.1-2: 250 µg roflumilast: Geometric means (68% range) of roflumilast and ro-flumilast-N-oxide plasma concentrations in healthy male subjects before (pre-dose) and after (2h post-dose) the administration of study medication at study day 1, as well as study days 14 and 15 (steady state)

	Roflumilast		Roflumilast-N-oxide	
	Geometric means	(68% range)	Geometric means	(68% range)
Day 1/ pre-dose	n.v.	---	n.v.	---
Day 1/ 2 h post-dose	1.59	(1.17, 2.17)	2.81	(2.07, 3.82)
Day 14/ pre-dose	0.26	(0.14, 0.48)	5.36	(3.69, 7.77)
Day 14/ 2 h post-dose	1.88	(1.32, 2.68)	8.24	(6.46, 10.50)
Day 15/ pre-dose	0.25	(0.14, 0.45)	4.79	(3.35, 6.86)
Day 15/ 2 h post-dose	1.65	(1.18, 2.30)	8.16	(6.37, 10.45)

Conclusions: The pharmacokinetic results revealed that all subjects received the respective dose. Trough values at study days 14 and 15 showed comparable values. The trough values of roflumilast and roflumilast-N-oxide at study days 14 and 15 were approximately as double as high after 500 µg roflumilast compared to trough values after 250 µg roflumilast.

IN108

Study Title: Comparison of safety and efficacy of 250 µg roflumilast versus 500 µg roflumilast versus placebo over 12 weeks in patients with chronic obstructive pulmonary disease (COPD).

Objectives: To study the safety and tolerability of roflumilast 250 µg vs. roflumilast 500 µg vs. placebo.

To investigate the effect of roflumilast 250 µg vs. roflumilast 500 µg vs. placebo on pulmonary function, efficacy rating, and exacerbation rate.

To evaluate plasma levels of roflumilast and its major metabolite roflumilast N-oxide.

Note: only the third objective is discussed here.

Study Population: A total of 152 patients were recruited from five centers in India.

Study Design: The study was designed as a double-blind, randomized (2:2:1, roflumilast 250 µg vs. roflumilast 500 µg vs. placebo), parallel group study, with a single blind-baseline period.

Enrolled patients received salbutamol metered dose inhalers (MDIs) as rescue medication on demand and were randomly assigned to one of the 3 treatment groups (2:2:1 randomization):

Group 1: roflumilast (250 µg/day tablet, orally)
Group 2: roflumilast (500 µg/day tablet, orally)
Group 3: placebo (tablet, od, orally)

The tablet was taken in the morning after breakfast with plenty of water, at least 200 ml.

Data Analysis: The pharmacokinetic profile of roflumilast (B9302-107) and its major metabolite roflumilast N-oxide (B9502-044) in steady state were investigated based on plasma levels at visit T4.
For this purpose blood samples were taken from the patients **prior** to intake of the study medication at the site.
Additionally, in a subset of predefined centers the pharmacokinetic profile was investigated in 60 patients according to the following schedule:
Blood samples were taken immediately prior to intake of the study medication, and at 2 hours (± 15 min), 4 hours (± 15 min) and 9 hours (± 15 min) after intake of the study medication, respectively.

Results: Determination of roflumilast and metabolite plasma concentrations was performed using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

Conclusions: The PK was assessed independently in a population PK report.

JP706

Study Title: A verification study of APTA-2217 in patients with chronic obstructive pulmonary disease (A placebo-controlled doubleblind, parallel group study)

Objectives: To investigate the efficacy and safety after 24-week treatment of APTA-2217 at doses of 500 mcg and 250 mcg in patients with COPD using placebo as a control and to investigate the pharmacokinetics of roflumilast and roflumilast N-oxide after repeated administration of APTA-2217 at doses of 500 mcg and 250 mcg

Study Population: The demographic information is shown in the following table.

Table 11.2–1   Patient background (at the allocation, FAS)

		500 mcg	250 mcg	Placebo
Total		204	205	191
Gender	Male	197 (96.6)	196 (95.6)	185 (96.9)
	Female	7 (3.4)	9 (4.4)	6 (3.1)
Age (years)		70.0 ± 7.3	69.4 ± 8.3	69.8 ± 6.8
Height (cm)		162.9 ± 5.9	162.2 ± 6.4	162.2 ± 6.6
Body weight (kg)		57.2 ± 9.5	57.3 ± 9.5	57.0 ± 9.1
Smoking history (pack year)		55.8 ± 26.5	56.4 ± 28.2	58.0 ± 33.2
Smoking status	Ex-smokers	127 (62.3)	126 (61.5)	122 (63.9)
	Smokers	77 (37.7)	79 (38.5)	69 (36.1)
Constant dose of short-acting anticholinergics	No	133 (65.2)	137 (66.8)	116 (60.7)
	Yes	71 (34.8)	67 (32.7)	75 (39.3)
	Other	0 (0.0)	1 (0.5)	0 (0.0)
COPD severity	Moderate	113 (56.5)	128 (63.7)	103 (54.5)
	Severe	87 (43.5)	73 (36.3)	86 (45.5)
	NA	4	4	2

Age, height, body weight, smoking history: mean±SD. Others: number of patients (%).
Pack year = number of cigarettes a day ÷ 20 × years smoking, SD = standard deviation,
NA = not available
Data source: Table 14.2.1–2

Study Design: The study scheme is shown in the following graph.
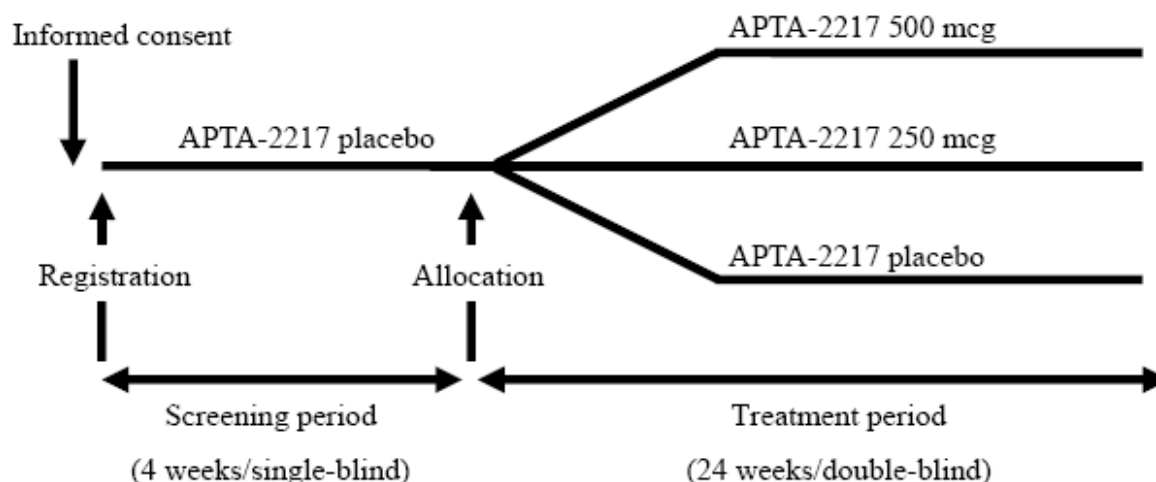
Results:

Table 11.4.1–3   ANCOVA for changes in pulmonary function tests at T_{last}
(within-treatment differences, FAS)

		LSmean	SE	95%CI (Lower)	95%CI (Upper)	p-value
FEV_1(L)						
Pre-bronchodilator	500mcg - Placebo	0.086	0.016	0.054	0.118	<.001
	250mcg - Placebo	0.079	0.016	0.048	0.111	<.001
	500mcg - 250mcg	0.006	0.016	-0.026	0.038	0.698
FVC(L)						
Pre-bronchodilator	500mcg - Placebo	0.123	0.030	0.064	0.182	<.001
	250mcg - Placebo	0.093	0.030	0.035	0.151	0.002
	500mcg - 250mcg	0.030	0.030	-0.029	0.089	0.317
Post-bronchodilator	500mcg - Placebo	0.076	0.027	0.022	0.130	0.006
	250mcg - Placebo	0.054	0.027	0.001	0.108	0.046
	500mcg - 250mcg	0.022	0.028	-0.032	0.076	0.430
MMEF(L/sec)						
Pre-bronchodilator	500mcg - Placebo	0.036	0.015	0.007	0.065	0.015
	250mcg - Placebo	0.035	0.014	0.007	0.064	0.015
	500mcg - 250mcg	0.001	0.015	-0.028	0.029	0.961
Post-bronchodilator	500mcg - Placebo	0.038	0.015	0.008	0.068	0.012
	250mcg - Placebo	0.050	0.015	0.020	0.079	<.001
	500mcg - 250mcg	-0.012	0.015	-0.042	0.018	0.438
V'_{50}/V'_{25}						
Pre-bronchodilator	500mcg - Placebo	0.033	0.083	-0.131	0.197	0.689
	250mcg - Placebo	0.166	0.082	0.005	0.328	0.043
	500mcg - 250mcg	-0.133	0.083	-0.297	0.031	0.111
Post-bronchodilator	500mcg - Placebo	-0.008	0.101	-0.208	0.191	0.934
	250mcg - Placebo	0.121	0.100	-0.076	0.318	0.229
	500mcg - 250mcg	-0.129	0.103	-0.330	0.072	0.209
PEF(L/min)						
Pre-bronchodilator	500mcg - Placebo	7.805	2.910	2.087	13.522	0.008
	250mcg - Placebo	7.950	2.869	2.314	13.587	0.006
	500mcg - 250mcg	-0.146	2.904	-5.850	5.558	0.960
Post-bronchodilator	500mcg - Placebo	6.866	2.651	1.658	12.074	0.010
	250mcg - Placebo	7.486	2.626	2.328	12.645	0.005
	500mcg - 250mcg	-0.621	2.675	-5.876	4.635	0.817

FEV_1 = Forced expiratory volume in the first second, FVC = Forced vital capacity,
MMEF = Maximum mid-expiratory flow rate, V'_{50}/V'_{25} = V max 50%/ V max 25%,
PEF = Peak expiratory flow, LSmean = Least squares mean, SE = Standard error, CI = Confidence interval
Data source: Table 14.2.2–2, Table 14.2.2–4, Table 14.2.2–6, Table 14.2.2–8, Table 14.2.2–10.

The number of COPD exacerbations did not differ significantly between any pair of the treatment groups. For "moderate or severe exacerbation" and "moderate exacerbation", the number of days to the first COPD exacerbation was significantly longer in 500 mcg group than in placebo group.

AE profie:

Table 12.2.1   Summary of adverse events reported during the treatment period

(Safety analysis set for the treatment period)

	500mcg n=204			250mcg n=205			Placebo n=191		
	n'	(%)	n"	n'	(%)	n"	n'	(%)	n"
AEs	187	(91.7)	582	177	(86.3)	534	161	(84.3)	437
Drug-related AEs	118	(57.8)	242	76	(37.1)	145	52	(27.2)	80
AEs leading to premature study discontinuation	48	(23.5)	89	27	(13.2)	36	12	(6.3)	18
SAEs	20	(9.8)	21	20	(9.8)	20	12	(6.3)	13
Drug-related SAEs	6	(2.9)	7	1	(0.5)	1	1	(0.5)	1

n' :Number of patients with at least one event in the category, %: Based on the total number of patients in the respective treatment group, n":Number of events in the category,
AE=adverse event, SAE=serious adverse event
Data source: Table 14.3.1–3, Table 14.3.1–4, Table 14.3.1–8, Table 14.3.2–2, Table 14.3.2–3.

Conclusions: This study demonstrated the efficacy of APTA-2217 at doses of 500 mcg and 250 mcg once daily for 24 weeks based on post-bronchodilator FEV_1 of patients with moderate or severe COPD. APTA-2217 was shown to improve pulmonary function. On the other hand, the study did not show the efficacy of APTA-2217 for most secondary endpoints based on COPD symptoms scores, the puff number of short-acting inhaled β_2-stimulator, SGRQ, and COPD exacerbations.
The incidence of adverse events was higher for APTA-2217 than for placebo. Common adverse events were gastrointestinal symptoms. The incidence of individual adverse events tended to be higher in 500 mcg group than in 250 mcg group. No meaningful changes were detected in laboratory tests, vital signs measurements, or 12-lead ECG findings.
These results indicate that APTA-2217 can improve the pulmonary function of COPD patients at doses of 500mcg and 250 mcg once daily. For the safety, 250 mcg of APTA-2217 was shown to be more tolerable than 500 mcg of the study drug.

JP708

Study Title: A long-term study of APTA-2217 in patients with chronic obstructive pulmonary disease

Objectives: An extension study of APTA-2217-06 study (Multi-center, placebo-controlled, randomized, double-blind, parallel-group study). After the key-open of APTA-2217-06 study, administration to placebo group would be terminated.

Study Population: The demographic information is shown in the following table.

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Table 11.2–1   Patient background (at allocation, FAS)

		500 mcg	250 mcg	Placebo
Total		40	54	58
Gender	Male	39 (97.5)	51 (94.4)	57 (98.3)
	Female	1 (2.5)	3 (5.6)	1 (1.7)
Age (years)		69.9 ± 6.5	67.9 ± 8.0	70.0 ± 7.2
Height (cm)		163.1 ± 6.6	163.5 ± 6.7	161.8 ± 6.1
Body weight (kg)		58.7 ± 11.3	59.0 ± 11.1	57.8 ± 10.2
Smoking status	Ex-smokers	25 (62.5)	31 (57.4)	36 (62.1)
	Smokers	15 (37.5)	23 (42.6)	22 (37.9)
Smoking history (pack year)		56.0 ± 28.8	58.0 ± 29.7	53.2 ± 27.0
Constant dose of short-acting anticholinergics	No	23 (57.5)	33 (61.1)	33 (56.9)
	Yes	17 (42.5)	20 (37.0)	24 (41.4)
	Other	0 (0.0)	1 (1.9)	1 (1.7)
COPD severity	Moderate	18 (45.0)	35 (67.3)	34 (58.6)
	Severe	22 (55.0)	17 (32.7)	24 (41.4)
	NA	0	2	0

Age, height, body weight, smoking history: mean ± SD. Others: number of patients (%). SD = standard deviation.

Concomitant short-acting anticholinergic use status: Others = discontinued, started the concomitant treatment or changed the dosage during Study APTA-2217-06.

Pack year = number of cigarettes a day / 20 × years smoking.

Severity: NA = not available, the pulmonary function test at allocation was not assessed as good session.

Data source: Table 14.2.1–1

Study Design: The study scheme is shown in the following graph.
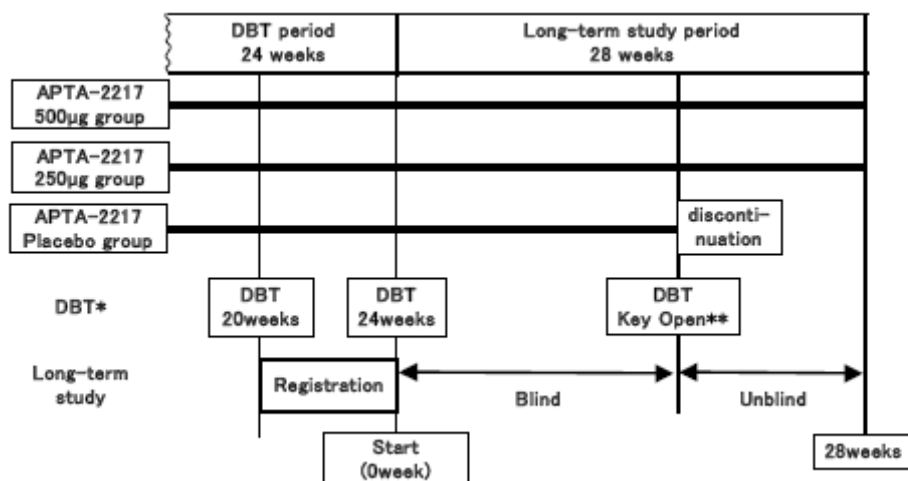
Results:

Table 11.4.1–5   Number of COPD exacerbations per 52 weeks (FAS for APTA-2217-06 study)

| | | n | No. of COPD exacerbations | No. of COPD exacerbations per 52 weeks | | | |
				Mean	Median	Min	Max
Moderate or severe	500mcg	204	25	1.19	0.00	0.00	40.44
	250mcg	205	21	2.00	0.00	0.00	104.00
	Placebo	191	16	0.50	0.00	0.00	21.67
Severe	500mcg	204	1	0.00	0.00	0.00	1.00
	250mcg	205	4	0.40	0.00	0.00	52.00
	Placebo	191	0	0.00	0.00	0.00	0.00
Moderate	500mcg	204	24	1.18	0.00	0.00	40.44
	250mcg	205	19	1.60	0.00	0.00	72.80
	Placebo	191	16	0.50	0.00	0.00	21.67
Mild	500mcg	199	13	0.70	0.00	0.00	30.33
	250mcg	201	14	0.61	0.00	0.00	22.00
	Placebo	186	16	0.59	0.00	0.00	21.60

The number of COPD exacerbations did not differ significantly between any pair of the treatment groups. For "moderate or severe exacerbation" and "moderate exacerbation", the number of days to the first COPD exacerbation was significantly longer in 500 mcg group than in placebo group.

AE profie:

Table 12.2.1   Summary of adverse events reported during the treatment period

(Safety analysis set)

| | 500mcg n=40 | | | 250mcg n=54 | | | Placebo n=58 | | |
	n'	(%)	n"	n'	(%)	n"	n'	(%)	n"
AEs	39	(97.5)	230	53	(98.1)	285	56	(96.6)	249
Drug-related AEs	22	(55.0)	41	21	(38.9)	54	22	(37.9)	43
AEs leading to premature study discontinuation	6	(15.0)	7	4	(7.4)	4	4	(6.9)	5
SAEs	11	(27.5)	13	7	(13.0)	8	6	(10.3)	8
Drug-related SAEs	1	(2.5)	1	1	(1.9)	1	1	(1.7)	1

n' :Number of patients with at least one event in the category, %: Based on the total number of patients in the respective treatment group, n":Number of events in the category.
Data source: Table 14.3.1–1, Table 14.3.1–2, Table 14.3.1–3, Table 14.3.2–1, Table 14.3.2–2.

Conclusions: In this study, the effects of APTA-2217 250 mcg or 500 mcg on pulmonary function measurements were evaluated in moderate to severe COPD patients. The pulmonary function measurements showed an initial improvement followed by a decline was observed.in these type of patients. Rregarding safety, once daily dosing of APTA-2217 for 52 weeks is more tolerable at 250 mcg than at 500 mcg. No conclusion can be drawn from this study concerning long term efficacy of APTA 2217.

IN108

Study Title: Comparison of safety and efficacy of 250 μg roflumilast versus 500 μg roflumilast versus placebo over 12 weeks in patients with chronic obstructive pulmonary disease (COPD).

Objectives: To study the safety and tolerability of roflumilast 250 μg vs. roflumilast 500 μg vs. placebo.

To investigate the effect of roflumilast 250 µg vs. roflumilast 500 µg vs. placebo on pulmonary function, efficacy rating, and exacerbation rate.

To evaluate plasma levels of roflumilast and its major metabolite roflumilast N-oxide.

Note: only the third objective is discussed here.

Study Population: A total of 152 patients were recruited from five centers in India.

T-Table 5: Demographic and baseline lung function parameters (full analysis set; n = 118)

		Roflumilast 500 µg od (n = 47)	Roflumilast 250 µg od (n = 46)	Placebo (n = 25)	Total (n = 118)
Patients	(n)	47	46	25	118
Sex (male/female)	(n)	46/1	45/1	25/0	116/2
Age	(years)	59 (40-73)	61 (42-75)	63 (41-74)	60 (40-75)
Current/Ex-Smokers	(n)	19/28	18/28	11/14	48/70
Smoking habits (Current smokers)	(pack year)	28 ± 21.6	23 ± 12.8	25 ± 13.8	25 ± 16.8
Smoking habits (Ex-smokers)	(pack year)	27 ± 18.1	28 ± 20.9	27 ± 18.5	27 ± 19.1
FEV_1 pre-bronchodilator	(l)	1.21 ± 0.45	1.20 ± 0.47	1.32 ± 0.49	n.d.
post-bronchodilator	(l)	1.30 ± 0.48	1.31 ± 0.47	1.43 ± 0.51	n.d.
reversibility	(%)	5.17 ± 6.2	5.83 ± 7.9	6.36 ± 6.7	n.d.
	(ml)	58.72 ± 75.5	64.35 ± 88.6	76.80 ± 101.9	n.d.
pre-bronchodilator	(% of predicted)	46 ± 14	47 ± 16	49 ± 15	n.d.
post-bronchodilator		49 ± 15	51 ± 16	53 ± 14	n.d.
PEF post-bronchodilator	(l/min)	198 ± 78	205 ± 77	223 ± 75	n.d.
FEF_{25-75} post-bronchodilator	(l/sec)	0.71 ± 0.42	0.72 ± 0.56	0.81 ± 0.49	n.d.
FVC post-bronchodilator	(l)	2.20 ± 0.66	2.23 ± 0.58	2.38 ± 0.74	n.d.
FEV_1/FVC post-bronchodilator	(%)	57 ± 9	59 ± 11	61 ± 10	n.d.

Data are presented as mean ± SD, except age: median (range).
FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, n = number of patients, n.d. = not done.
Data on reversibility and FEV_1/FVC are from patients at visit B0. All other lung function baseline data are given for randomized patients at B2 (= T0), i.e. at randomization. The baseline lung function parameters did not necessarily include data from all patients in the full analysis set (see Section 10.2 for details).
Pack year = number of cigarettes a day/20 x years smoking.
Data source: demographics: Table 14.1.2.1, Table 14.1.2.2, Table 14.1.2.4, Table 14.1.2.5; FEV_1: Table 14.2.1.1, Table 14.2.1.2; reversibility: Table 14.1.4.1; FEV_1/FVC: Table 14.1.4.2.

Study Design: The study was designed as a double-blind, randomized (2:2:1, roflumilast 250 µg vs. roflumilast 500 µg vs. placebo), parallel group study, with a single blind-baseline period.

Enrolled patients received salbutamol metered dose inhalers (MDIs) as rescue medication on demand and were randomly assigned to one of the 3 treatment groups (2:2:1 randomization):

Group 1: roflumilast (250 µg/day tablet, orally)
Group 2: roflumilast (500 µg/day tablet, orally)
Group 3: placebo (tablet, od, orally)

The tablet was taken in the morning after breakfast with plenty of water, at least 200 ml.

Data Analysis: The pharmacokinetic profile of roflumilast (B9302-107) and its major metabolite roflumilast N-oxide (B9502-044) in steady state were investigated based on plasma levels at visit T4.

For this purpose blood samples were taken from the patients prior to intake of the study medication at the site.

Additionally, in a subset of predefined centers the pharmacokinetic profile was investigated in 60 patients according to the following schedule:

Blood samples were taken immediately prior to intake of the study medication, and at 2 hours (± 15 min), 4 hours (± 15 min) and 9 hours (± 15 min) after intake of the study medication, respectively.

Results: Determination of roflumilast and metabolite plasma concentrations was performed using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.
Primary efficacy variable: post-bronchodilator FEV1

T-Table 9: Post-bronchodilator FEV_1 [l] - within- and between-treatment differences (ITT last-value analysis)

WITHIN	n	T0 Mean % pred.	T0 LSMean	T_{last} LSMean	$T_{last} - T0$ LSMean ± SEM	$T_{last} - T0$ 95%CI	p-value[a]
Rof500	42	1.326 50%	1.349	1.377	0.028 ± 0.075	-0.121, 0.178	0.7107
Rof250	43	1.325 51%	1.349	1.362	0.013 ± 0.075	-0.136, 0.162	0.8604
Placebo	25	1.429 54%	1.349	1.225	-0.124 ± 0.081	-0.286, 0.038	0.1308

BETWEEN	Test	Reference	n Test	n Reference	ΔTest – ΔReference LSMean ± SEM	ΔTest – ΔReference 95%CI	p-value[b]
	Rof500	Placebo	42	25	0.152 ± 0.050	0.053, 0.251	0.0028
	Rof500	Rof250	42	43	0.015 ± 0.043	-0.070, 0.100	0.7300
	Rof250	Placebo	43	25	0.137 ± 0.049	0.040, 0.235	0.0064

[a] p-value for within-treatment differences (ANCOVA), two-sided, significance level 5%.
[b] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.

CI = confidence interval, Δ = within-treatment difference, FEV_1 = forced expiratory volume in one second, LS = least squares, n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).
Data source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.6, Table 14.2.1.9.

T-Table 13:   COPD exacerbations (ITT last value analysis)

Treatment Parameter	No. of patients N# (%)	No. of exacerbations or visits n	Time [days] to onset of first exacerbation or drop-out Median	Time [days] to onset of first exacerbation or drop-out Range
Severe exacerbations				
Placebo	1 (4)	1	90	90 - 90
Rof250	0 (0)	0	n.a.	n.a.
Rof500	1 (2.1)	1	67	67 - 67
Severe or moderate exacerbations				
Placebo	3 (12)	4	54	2 - 70
Rof250	7 (15.2)	7	55	2 - 62
Rof500	3 (6.4)	3	28	26 - 67
Mild exacerbations		n#		
Placebo	4 (16)	4	n.a.	n.a.
Rof250	5 (10.9)	5	n.a.	n.a.
Rof500	8 (17)	9	n.a.	n.a.
Exacerbations leading to drop-out		n		
Placebo	1 (4)	1	90	90 - 90
Rof250	0 (0)	n.a.	n.a.	n.a.
Rof500	0 (0)	n.a.	n.a.	n.a.

Placebo: N = 25; Rof250: N = 46; Rof500: N = 47;

n = number of exacerbations, n# = number of visits with mild exacerbations, N# = number of patients with exacerbations, n.a. = not applicable, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily.
Data source: Table 14.2.3.1.

AE profie:

T-Table 2: Discontinued patients (full analysis set)

Reason for withdrawal	Roflumilast 500 µg od n	Roflumilast 500 µg od %	Roflumilast 250 µg od n	Roflumilast 250 µg od %	Placebo n	Placebo %
Adverse event	0	0	2	29	0	0
Non-medical reasons	13	100	5	71	9	90
Withdrawal due to escape criteria	0	0	0	0	1	10
Total	13	100	7	100	10	100

[a] The percentage is based on the total number of discontinued patients in a treatment group.

Note that only the major reason is given in case one patient discontinued due to several criteria.
Source of data: Table 14.1.1.6 and Table 16.2.1.2.

T-Table 17: Overview of treatment-emergent AEs by treatment group (full analysis set; n = 118)

	Number (%) of patients[a]			
	Roflumilast 500 µg od (n = 47)	Roflumilast 250 µg od (n = 46)	Placebo (n = 25)	Total (n = 118)
No. of AEs	29	26	12	67
No. of patients reporting at least one AE	18 (38.3)	17 (37.0)	7 (28.0)	42 (35.6)
No. of patients with SAEs	1 (2.1)	2 (4.3)	1 (4.0)	4 (3.4)
No. of patients with AEs judged to be at least 'likely' related to study drug[b]	2 (4.3)	0 (0.0)	0 (0.0)	2 (1.7)
No. of patients with AEs leading to premature study discontinuation	0 (0)	2 (4.3)	1 (4.0)	3 (2.5)
No. of patients with AEs not yet known to be recovered	1 (2.1)	0 (0)	0 (0)	1 (0.8)

[a] Percentages are based on the total number of patients in the respective treatment group.
[b] by investigator.
n = number of patients.
Data source: Table 14.3.1.2, Table 14.3.1.3, Table 14.3.1.9, and Table 16.2.7.10.

Conclusions: The PK was assessed independently in a population PK report. When compared to placebo, both roflumilast 250µg and roflumilast 500 µg improved the post-bronchodilatory lung function parameters. This study showed that roflumilast was safe and well tolerated.

CP-065

Study Title: Pharmacokinetics of 250 µg, 375 µg and 500 µg roflumilast in children and adolescents with mild to moderate asthma and healthy adult subjects – an open, one-period, three parallel group design with repeated oral doses of once daily roflumilast for 14 days

Objectives: The primary objective of the study was to characterize dose-corrected AUCTAU and Cmax of roflumilast and roflumilast N-oxide at steady-state on Day 14 in pediatric and adolescent patients with mild to moderate asthma and in healthy adults.

Study Design: This study was conducted according to an open, one-period, three parallel group design with repeated doses of once daily roflumilast for 14 days. It consisted of a screening examination, a treatment period (14 days), and a post-study examination. Children and adolescents were allocated to treatment groups according to body weight.
Children (aged 6 to 8, and 9 to 11 years) were assigned to the following treatment groups:
• 250 µg roflumilast for < 40 kg body weight
• 375 µg roflumilast for ≥ 40 kg to < 60 kg body weight
Adolescents (aged 12 to 14, and 15 to 17 years) were assigned to the following treatment groups:
• 375 µg roflumilast for ≥ 40 kg < 60 kg body weight

• 500 µg roflumilast for ≥60 kg body weight
Healthy adults (aged 18 to 40 years) received 500 µg roflumilast.
Blood samplings for pharmacokinetic purposes were performed on Day 14 at the following time points:
• At pre-dose (within 5 min prior to study drug administration) and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 14 h, and 24 h (10 samples) after oral administration of roflumilast once daily for 14 days.
• Trough levels of roflumilast and roflumilast N-oxide were determined using only the samples collected at pre-dose and 24 h post-dosing.

Study Population:
The sample size of 36 patients/ subjects was chosen due to feasibility.

	Full analysis set	Valid cases set
Children	12	12
Adolescents	12	12
Adults	14	12
Total	38	36

Demographic and anthropometric data are summarized in the following:

Characteristic	Children (N=12)	Adolescents (N=12)	Adults (N=12)
Age [years]			
Mean ±SD	9 ±1.8	15 ±1.4	25 ±6.3
Median (min, max)	9 (6, 11)	15 (12, 17)	24 (18, 34)
Gender			
Male, n (%)	6 (50)	6 (50)	6 (50)
Female, n (%)	6 (50)	6 (50)	6 (50)
Height [cm]			
Mean ±SD	139 ±12.8	166 ±9.6	170 ±11.5
Median (min, max)	135 (124, 163)	162 (155, 183)	168 (155, 196)
Body weight [kg]			
Mean ±SD	39.7 ±8.7	61.4 ±11.1	73.3 ±16.3
Median (min, max)	39 (28, 57)	59 (46, 86)	68.5 (52, 107)
Body mass index [kg/m^2]			
Mean ±SD	20.5 ±2.7	22.3 ±2.7	25.0 ±2.8
Median (min, max)	19.9 (18.2, 27.1)	22.2 (19.1, 28.1)	24.7 (20.9, 28.7)
Smoking			
Ex-smokers, n (%)	0 (0)	0 (0)	2 (17)
Non-smokers, n (%)	12 (100)	12 (100)	10 (83)
Race			
White, n (%)	5 (42)	8 (67)	11 (92)
Black or African American, n (%)	2 (17)	2 (17)	0 (0)
American Indian or Alaska native, n (%)	1 (8)	0 (0)	0 (0)
Other, n (%)	4 (33)	2 (17)	1 (8)

Data Analysis: The pharmacokinetic parameter estimates (AUCcorr, AUCTAU, Cmax corr and Cmax) for plasma roflumilast and roflumilast N-oxide were calculated by a non-compartmental analysis using WinNonlin.

Results: Plasma concentrations of roflumilast and roflumilast N-oxide were measured using a validated high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) detection. The calibration ranges were 0.1 to 20 μg/L for
roflumilast and 0.1 to 40 μg/L for roflumilast N-oxide using a sample volume of 400 μL.
The free fraction of roflumilast was measured in different age groups from samples taken on Day 14 at 2 h and 14 h for pharmacokinetic analysis.

T-Table 27   **Fraction unbound of roflumilast* and roflumilast N-oxide [%], and tPDE4i activity**: Geometric mean and 68%-ranges in children, adolescents, and adults, following repeated oral doses of roflumilast, on Day 14 (BY217/CP-065)

Treatment Group		N	Geometric Mean	Lower 68%	Upper 68%
Children	fu Roflumilast*	12	0.011	0.011	0.011
	fu Roflumilast N-oxide	12	0.018	0.013	0.025
	tPDE4i	12	0.525	0.422	0.652
Adolescents	fu Roflumilast*	12	0.011	0.011	0.011
	fu Roflumilast N-oxide	12	0.022	0.019	0.026
	tPDE4i	12	0.469	0.345	0.638
Adults	fu Roflumilast*	12	0.011	0.011	0.011
	fu Roflumilast N-oxide	12	0.021	0.019	0.023
	tPDE4i	12	0.576	0.411	0.805

* Since the fu roflumilast-values were not available, the population values reported in ALTANA Pharma Study Report 107/2005 were taken.
Data source: Table 15.2.3.1
Parameters are defined in T-Table 10

The unbound fractions of roflumilast N-oxide were similar in children, adolescents and adults. The unbound fractions of roflumilast were not available.

T-Figure 5   **Roflumilast:** Plasma concentration-time profiles (geometric mean, 68%-range) in children, adolescents, and adults, following repeated oral doses of roflumilast, on Day 14 (BY217/CP-065)
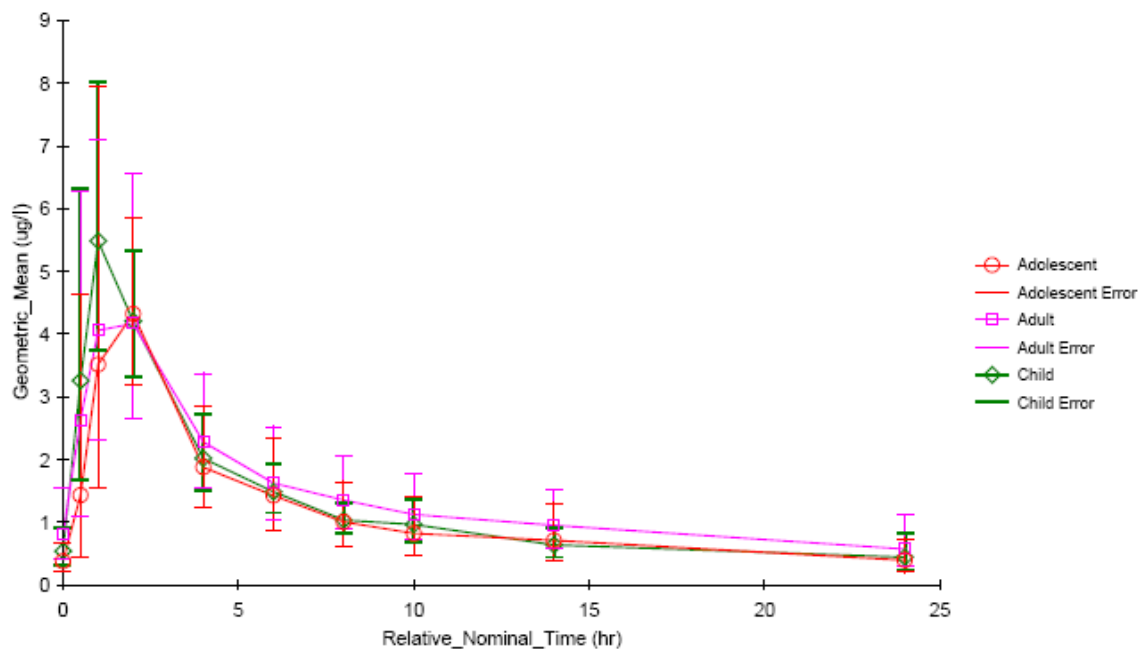
For roflumilast, similar pattern of mean plasma concentration-time curves were seen in children, adolescents and adults. Roflumilast concentrations declined in a biexponential fashion. A higher mean C_{max} value was noted in the children, as compared to adults.

T-Figure 15   **Roflumilast N-oxide:** Plasma concentration-time profiles (geometric mean, 68%-range) in children, adolescents, and adults, following repeated oral doses of roflumilast, on Day 14 (BY217/CP-065)
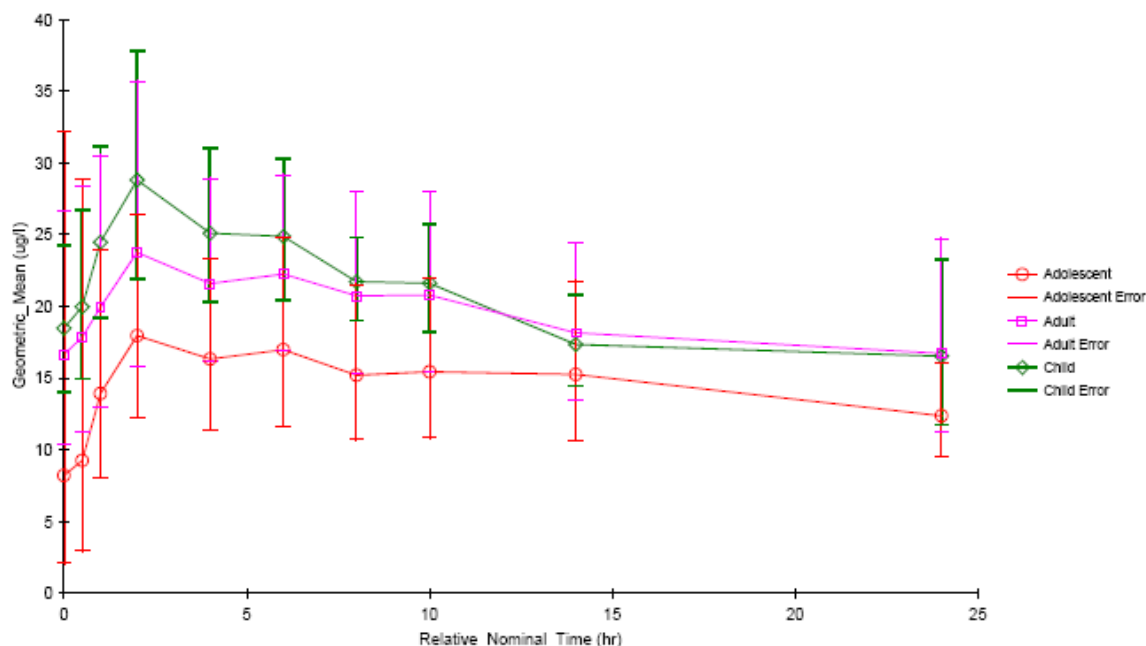
For roflumilast N-oxide, similar pattern of mean plasma concentration-time curves were seen in children, adolescents and adults. A higher mean C_{max} value was noted in children and a lower mean C_{max} value was noted in adolescents, when compared to adults.

Conclusions: Following single oral administration of 0.5 mg roflumilast to 12 children and adolescents, a higher exposure of roflumilat and roflumilat N-oxide in children and a lower exposure for roflumilast N-oxide in adolescents were found when compared to adults.

M2-117

Study Title: Effects of roflumilast 500 µg on inflammatory cells and mediators in BALF after segmental pulmonary LPS challenge in healthy volunteers – ERIC

Objectives: Assessment of anti-inflammatory properties of roflumilast in humans by means of segmental pulmonary lipopolysaccharide (LPS; endotoxin)-challenge

Study Design: Double-blind, randomized, 2-parallelgroup comparison.
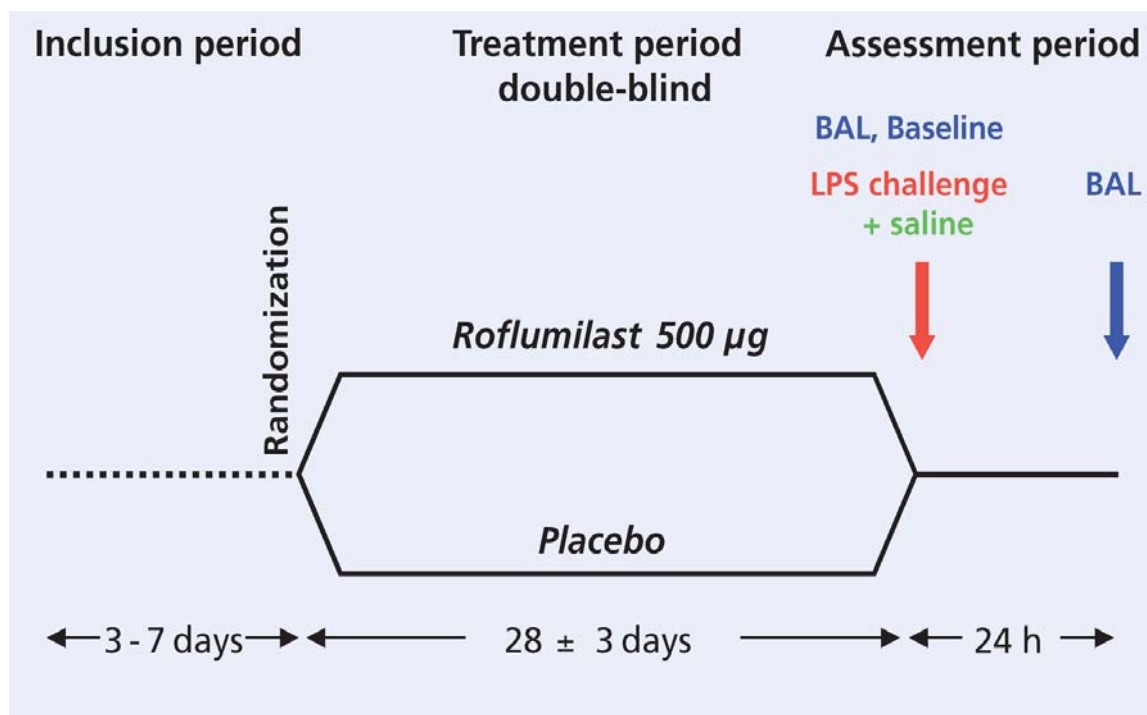
Roflumilast 500 μg, QD, p.o. or placebo for 4 weeks.

In a randomized, placebo-controlled, double-blind, single-center parallel-group study, 37 per-protocol healthy subjects of either gender were treated for 28 days with either roflumilast 500 μg, QD, p.o., or placebo. At Day 29, a baseline bronchoalveolar lavage (BAL) was performed, followed by segmental endotoxin challenge (4 ng/kg) and saline control challenge. After 24 hours, baseline bronchoalveolar lavage fluide (BALF) was sampled from the challenged segments and cells were counted and differentiated.

Study Population: Healthy subjects, N=43 (23M/20F); aged 20 to 43 years, median: 25 years. Roflumilast-group, N=22 (12M/10F), aged 20 to 43 years, median: 27 years. Placebo-group, N=21 (11M/10F), aged 20 to 41 years, median: 25 years.

Results:

T-Table 2.7.2 - 104 Inflammatory cells ($\times 10^5$/mL) in BALF: Mean change (differences of LSM) from baseline 24 hours after segmental pulmonary LPS challenge in healthy subjects after roflumilast 500 µg, QD, p.o. (test) or placebo (reference) for 4 weeks [M2-117 (273/2005)]

	Mean change from baseline (LSM)		Mean difference of change from baseline of treatment effect (roflumilast – placebo)	
	Test	Reference	Point estimate	(95% CI)
Monocyte	123	146	-23.9	(-82.3, 34.5)
Neutrophil	792	1292	-499	(-991, -8.32)
Eosinophils	2.51	9.59	-7.08	(-13.0, -1.11)
Lymphocytes	5.44	7.27	-1.82	(-10.4, 6.82)
Sum of monocytes and macrophages	352	356	-3.85	(-155, 147)
Total cell count[a]	1.10	1.71	-0.61	(-1.19, -0.02)

[a] Total cell count measured in recovered BALF.
BALF=Broncho-alveolar lavage fluid, CI=confidence interval, LPS=lipopolysaccharide, LSM=least squares mean

T-Table 2.7.2 - 105 Biochemical inflammatory markers in BALF and blood: Mean change (differences of LSM) from baseline 24 hours after segmental LPS challenge in healthy subjects after roflumilast 500 µg, QD, p.o. (test) or placebo (reference) for 4 weeks [M2-117 (273/2005)]

	Mean change from baseline (LSM)		Mean difference of change from baseline of treatment effect (roflumilast – placebo)	
	Test	Reference	Point estimate	(95% CI)
Biochemical inflamatory markers in BALF				
TNFα [pg/mL]	35.7	43.0	-7.24	(-20.8, 6.36)
IL-6 [pg/mL]	205	195	9.83	(-91.2, 110)
IL-8 [pg/mL]	48.6	36.5	12.1	(-9.07, 33.3)
MMP-9 [ng/mL]	6.24	5.64	0.61	(-1.37, 2.58)
MCP-1 [pg/mL]	41.0	49.1	-8.10	(-39.5, 23.3)
Nitrate [µmol/L]	0.02	-0.11	0.13	(-0.07, 0.34)
Nitrite [µmol/L]	-0.09	-0.04	-0.06	(-0.17, 0.06)
Biochemical inflamatory markers in blood				
CRP [mg/L]	4.66	4.62	0.04	(-2.79, 2.86)
E-selectine [ng/mL]	1.41	0.92	0.49	(-1.94, 2.92)
TNFα [pg/mL]	0.03	0.38	-0.35	(-1.18, 0.48)
IL-6 [pg/mL]	1.19	3.10	-1.91	(-4.04, 0.22)
IL-8 [pg/mL]	0.00	0.00	0.00	NA

CI=confidence interval, CRP=C-reactive protein, IL-6=Interleukin 6, IL-8=Interleukin 8, LPS=lipopolysaccharide, MCP-1 = Monocyte chemoattractant protein-I, MMP = Matrix metalloproteinase-9, LSM=least squares mean, NA=not analyzed, TNFα=Tumor necrosis factor α., BALF=Broncho-alveolar lavage fluid

T-Figure 2.7.2 - 10 Total cells (A), neutrophils (B), eosinophils (C) and monocytes (D): Change of BALF cells from baseline (mean ± SEM) at 24 hours after endotoxin (LPS) or saline challenge [M2-117 (273/2005)]
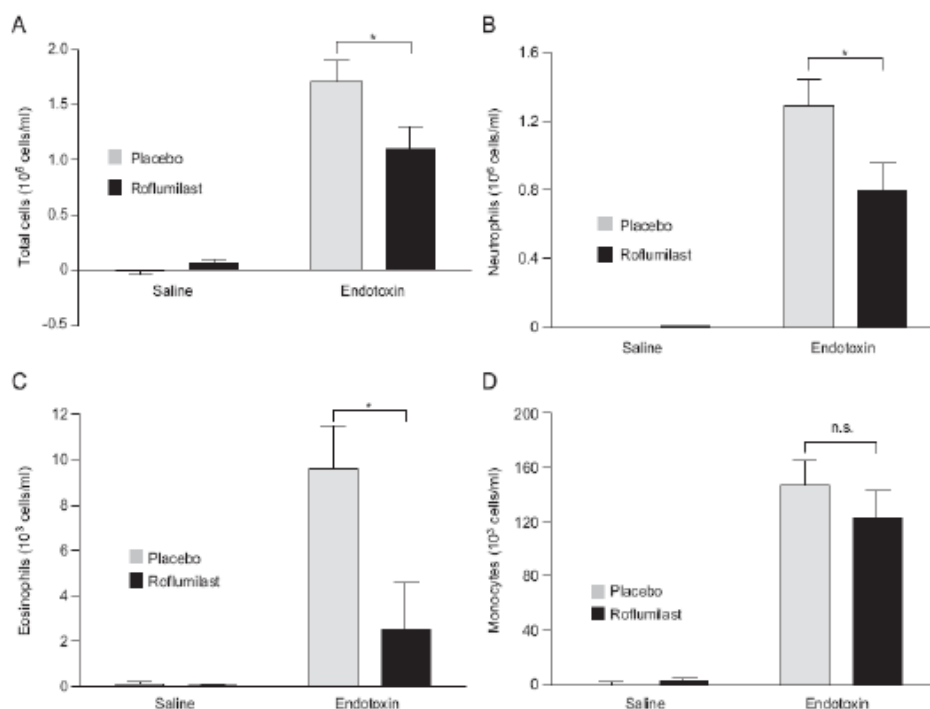
*One-sided p=0.025 for differences versus placebo; n.s.=not significant

After endotoxin challenge, influx of total cells (difference from baseline) in BALF of roflumilast treated subjects was 35% lower than with placebo (p=0.02). Correspondingly, the influx of neutrophils and eosinophils of roflumilast treated subjects was 38% (p=0.02) and 73% (p=0.01) lower than with placebo, respectively. In contrast, endotoxin-induced influx of monocytes was not different between roflumilast- and placebo treated subjects. No statistically significant differences existed between the groups pertaining to endotoxin
induced influx of macrophages and lymphocytes. There were no significant differences between the treatments for any of the soluble inflammatory markers in BALF and in blood. Roflumilast was well tolerated. No unexpected or serious treatment-emergent signs and symptoms were observed.

Conclusions: Roflumilast attenuated the endotoxin induced influx of neutrophils and eosinophils into the airways. This study demonstrates the anti-inflammatory properties of
roflumilast on bronchoalveolar granulocytes in endotoxin-induced airway inflammation in healthy subjects.

336

FHP030

Study Title: Anti-inflammatory activity of roflumilast. Study on the effect of oral roflumilast 500 µg over 4 weeks on sputum neutrophils in COPD patients

Objectives: To assess the anti-inflammatory activity of a 4-week treatment with roflumilast 500 µg, QD, in COPD patients by non-parametric endpoint analysis of the following surrogate markers of inflammation: (i) Sputum neutrophils, expressed as percentage of total non-squamous cells (neutrophils %), as primary variable. (ii) Other sputum inflammatory cells expressed as percentage of total non-squamous cells. (iii) Biochemical markers in sputum supernatant and in blood. Furthermore, lung function, safety and tolerability were assessed. For the primary (neutrophils %) and most of the secondary variables no statistically significant difference between roflumilast and placebo was seen.

Study Design: Randomized, double-blind, placebo-controlled, 2-period crossover study.
Treatment: The regimen is summarized in below table.

T-Table 2.7.2 - 106 Treatments [FHP030 (187/2002)]

	Baseline period (2 weeks)	Period 1 (4 weeks)	Period 2ᵃ (4 weeks)
Sequence 1	Placebo, QD, p.o.	Roflumilast 500 µg, QD, p.o.	Placebo QD, p.o.
Sequence 2	Placebo, QD, p.o	Placebo QD, p.o.	Roflumilast 500 µg, QD, p.o.

ᵃ The washout period between treatment period 1 and 2 was 4 to 6 weeks.

Study Population: Patients with a history of COPD for at least 1 year, N=41 (31M/10F), aged 48 to 75 years, median; 65 years.

Results and Conclusions:

T-Table 2.7.2 - 107 Absolute numbers of sputum inflammatory cells, biochemical inflammatory markers in sputum supernatant and blood: Mean change from baseline test/reference ratios (point estimate [% reference], 95% confidence interval) after repeated doses of roflumilast 500 μg, QD, p.o. (test) or placebo (reference) for 4 weeks (ITT analysis using a repeated measures model) [FHP030 (379/2004)]

	Roflumilast*	Placebo*	Ratio (roflumilast/placebo)	
			Point estimate	95% CI
Sputum inflammatory cells				
Neutrophils	0.80	1.15	0.69	(0.53, 0.91)
Eosinophils	0.76	1.30	0.58	(0.40, 0.84)
Macrophages	0.77	0.95	0.81	(0.61, 1.09)
Lymphocytes	0.63	0.87	0.73	(0.51, 1.04)
Total cell counts	0.89	1.21	0.74	(0.57, 0.95)
Bronchial epithelial cells	0.95	1.12	0.85	(0.61, 1.19)
Biochemical inflammatory markers in sputum supernatant				
Neutophil elastase	1.04	1.20	0.86	(0.65, 1.15)
Interleukin-8	0.96	1.16	0.83	(0.64, 1.07)
Biochemical inflammatory markcer in blood				
TNFα formation *ex vivo*	0.96	1.09	0.89	(0.80, 0.98)
E-selectin	0.96	0.97	0.99	(0.96, 1.02)

* Geometric mean

T-Table 2.7.2 - 108 Lung function variables: Mean difference of changes from baseline (point estimate [% reference], 95% confidence interval) after repeated doses of roflumilast 500 μg, QD, p.o. (test) or placebo (reference) for 4 weeks (ITT analysis using repeated a measures model) [FHP030 (379/2004)]

		Mean change from baseline		Mean difference of change from baseline of treatment effect (roflumilast – placebo)	
		Roflumilast*	Placebo*	Point estimate	95% CI
FEV$_1$ [L]	Pre	0.054	-0.017	0.071	(0.047, 0.095)
	Post	0.036	-0.028	0.064	(0.013, 0.116)

* Least square mean

Inflammatory cells in sputum: The total cell count was significantly decreased by 26% under roflumilast when compared with placebo. In addition, absolute numbers of sputum neutrophils and eosinophil decreased by 31% and 42%, respectively, under roflumilast. In contrast to absolute cell numbers, differential cell counts for neutrophils, macrophages and lymphocytes, expressed as a percentage of total non-squamous cells, were not affected by roflumilast and placebo treatment (187/2002). Biochemical marker of inflammation in sputum supernatant: Levels of the neutrophil chemo-attractant IL-8 and the neutrophil degranulation product neutrophil elastase decreased not significantly under roflumilast when compared with placebo. Biochemical marker of inflammation in blood: TNFα secretion in whole blood cultures following *ex vivo* stimulation by LPS was significantly reduced by 11% during roflumilast treatment when compared with placebo. In contrast, E-selectin levels in blood were not different

between the two treatments. Lung function: Pre- and post-bronchodilator FEV1 improved significantly under roflumilast when compared with placebo.

No major safety problems were seen during treatment with roflumilast in COPD patients.

The anti-inflammatory effect of roflumilast in patients with COPD was demonstrated by the reduction of absolute number of sputum neutrophils. This effect, however, could not be demonstrated by the relative number of sputum neutrophils expressed as percentage of total non-squamous cells because of the almost parallel decrease in bothu parameters. The pre- and post-bronchodilator FEV1 improvement under roflumilast may be explained by the parallel reduction of absolute sputum neutrophil and eosinophil numbers in COPD patients.

FK1101

Study Title: 26 weeks treatment with 250 μg vs. 500 μg roflumilast vs. placebo in patients with chronic obstructive pulmonary disease (dose range finding trial)

Objectives: The study was designed as a dose-range finding study comparing the effects of 250 μg/d roflumilast, 500 μg/d roflumilast and placebo, administered orally over a period of 26 weeks, on pulmonary function, quality of life, clinical symptoms and use of rescue medication in patients with COPD. The study was also to provide information on the safety and tolerability of roflumilast in the patient population enrolled.

Study Design: This was a 26-week, randomized, double-blind, multi-center, multi-national phase Ila study including three parallel treatment arms (250 μg roflumilast, 500 μg roflumilast and placebo). Patients suffering from COPD presenting with a smoking history of at least 10 pack years (one pack year was defined as smoking 20 cigarettes per day for one year) were eligible for entry into the study. The study consisted of a 2-week, single-blind baseline period and a 26-week treatment period.

Study Population: All of the 516 randomized patients had received at least one dose of study medication and were included in the ITT population. Eighty (80) patients were excluded from the PP population due to major protocol deviations (see Section 10.2). The PP population thus consisted of 436 patients.

T-Table 5:
Demographic and baseline characteristics (ITT, n = 516)

Parameter		Placebo	Roflumilast 250 µg	Roflumilast 500 µg
Patients	(n)	172	175	169
Sex (male/female)	(n)	129/43	121/54	122/47
Age	(years)	62 (42 - 75)	60 (41 - 75)	61 (41 - 75)
Current/ex-smokers	(n)	92/80	95/80	88/81
Smoking habit	pack year	38±22	37±21	36±18
FEV$_1$ pre-bronchodilator	(l)	1.48±0.40[a]	1.55±0.42[b]	1.53±0.43
	(% pred.)	51±10[a]	52±10[b]	52±11
post- bronchodilator	(l)	1.54±0.40[c]	1.61±0.44	1.57±0.44
	(% pred.)	53±10[c]	54±11	54±11
Reversibility: change in FEV$_1$	(%)	3.6±5.7	4.0±6.0	3.2±5.9
Morning PEF (diary)	(l/min)	243±78	246±80	242±85
FEV$_1$/FVC	(%)	58±8	59±9	59±9

Data are presented as mean±SD, except age: median (range).
Lung function baseline data are given at T0, i.e. prior to randomization.
[a] n = 170   [b] n = 173   [c] n = 171
Data source: demographics: Table 14.1.1-5, Table 14.1.1-9 and Table 14.1.1-9, FEV$_1$: Table 14.2.2-2, Table 14.2.2-3, Table 14.2.2-3; reversibility: Table 14.1.2-1; morning PEF: Table 14.2.2-240, FEV$_1$/FVC: Table 14.1.2-3.

T-Table 2: Patient withdrawal (randomized patients, n = 516)

Reason for withdrawal	Number (%)[a] of patients			
	Placebo (n = 172)	Roflumilast 250 µg (n = 175)	Roflumilast 500 µg (n = 169)	Total (n = 516)
Non-medical reasons	12 (7)	11 (6)	12 (7)	35 (7)
Adverse event[b]	8 (5)	10 (6)	10 (6)	28 (5)
Escape criteria	2 (1)	3 (2)	2 (1)	7 (1)
Other medical reason	-	4 (2)	-	4 (1)
Total	22 (13)	28 (16)	24 (14)	74 (14)

[a] Percentages are calculated out of the total number of patients in a treatment group.
[b] Note, that a patient could have presented with more than one reason for premature withdrawal but only the main reason is included in the above table which causes the inconsistency between T-Table 2 and T-Table 66 (Section 12.3.1.3).
Abbreviations: n = number of patients.
Data source: Table 14.1.1-2.

Results and Conclusions:
Primary efficacy variables:
Pre-bonchodilator *FEV1:* In addition to the parametric analysis as specified in the protocol a non-parametric analysis was performed as suggested by the non-normal distribution of the FEV, values. The improvements seen were higher in the roflumilast groups as compared to placebo (with respect to LSMeans and medians), reaching statistical significance on the 2.5%-level (one-sided) with respect to both doses, but not for placebo (see below). Differences between roflurnilast and placebo were more pronounced when analyzed nonparametrically. A trend towards dose-dependency was found (LS Mean).

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Pre-bronchodilator FEV$_1$ (l): Within treatment differences: T$_{last}$ - T0 (ITT last value analysis)

Treatment group	n	LS Mean ± Std Err (median)	95% CI	p-value[a] parametric (non-parametric)
Placebo	169	0.029 ± 0.023 (-0.020)	-0.017, 0.075	0.2183 (0.8222)
250 µg roflumilast	173	0.064 ± 0.022 (0.030)	0.020, 0.108	0.0045 (0.0104)
500 µg roflumilast	167	0.069 ± 0.023 (0.030)	0.024, 0.114	0.0026 (0.0110)

[a] Two-sided.

Pre-bronchodilator FEV$_1$ (l): Between-treatment differences for T$_{last}$ - T0 (ITT last value analysis)

Treatment group	n	LS Mean ± Std Err	95% CI	p-value[a] parametric (non-parametric)
250 µg roflumilast vs placebo	b	0.035 ± 0.030	-0.024, 0.094	0.1199 (0.0475)
500 µg roflumilast vs placebo	b	0.041 ± 0.030	-0.018, 0.099	0.0884 (0.0471)
500 µg vs 250 µg roflumilast	b	0.005 ± 0.030	-0.053, 0.064	0.4284 (0.4980)

[a] one-sided   [b] n = 169, 173, 167 for placebo, 250 µg and 500 µg roflumilast, respectively.

SGRQ - total score: There were no differences between treatments. A comparable statistically significant and clinically relevant decrease in LSMean was seen in all three treatment groups mounting to -4.45, -4.41, and -4.73 in the placebo, 250 ug roflumilast and 500 ug roflumilast group, respectively.

Secondary variables: Exacerbations: The number of patients meeting "escape" criteria were three each in the placebo and 250 µg roflumilast, and two in the 500 µg roflumilast group. The overall number of exacerbations was reduced on 500 µg roflumilast as compared to the other two treatment groups. The corresponding numbers were 26, 25 and 15 exacerbations on placebo, 250 µg and 500 µg roflumilast, respectively, experienced by 16, 19 and 13 patients.

Safety evalutions: overall summary of the AEs are shown in the table below.

Overview of AEs

	Placebo (N = 172)	Roflumilast 250 µg (N = 175)	Roflumilast 500 µg (N = 169)
No. of patients with AEs[a]	85 (49%)	85 (49%)	82 (49%)
No. of AEs	182	170	176
"likely" and "definitely" related AEs[b]	6 (3%)	8 (5%)	30 (17%)
"unlikely" and "not" related AEs[b]	176 (97%)	162 (95%)	146 (83%)
No. of patients withdrawn due to AE[a]	10 (6%)	13 (7%)	12 (7%)
No. of patients with SAEs[a]	11 (6%)	14 (8%)	9 (5%)
No. of SAEs	14	18	12

[a] Percentages are based on the number of patients in each treatment group.
[b] Percentages are based on the total number of AEs in the respective treatment group.

Conclusions: Statistical significant was not reached for the primary efficacy endpoint preFEV1 and SGRQ values.

M2-107

Study Title: A comparison of treatment with 250 µg roflumilast versus 500 µg roflumilast versus placebo over 24 weeks in patients with chronic obstructive pulmonary disease (COPD)

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Objectives: The present study aimed to compare the efficacy of roflumilast 500 μg and 250 μg with placebo administered for 24 weeks on pulmonary function, QoL, symptoms, use of rescue medication and exacerbation rate in patients suffering from COPD. The primary comparison was roflumilast 500 μg versus placebo, based on FEV_1 (post-bronchodilator); the total score of the St. George's Respiratory Questionnaire (SGRQ) was co-primary. Both variables were analyzed with respect to change from randomization to endpoint. In addition, the study aimed to provide further information on the safety and tolerability of roflumilast.

Study Design: The study was designed as a 24-week multicenter, double-blind, randomized parallel group study with a single-blind placebo baseline period. The required sample size was calculated for the change in the primary variable of post-bronchodilator FEV_1 as follows: a sample size of 400 patients in the roflumilast 500 μg group and 200 patients in the placebo group was needed to achieve a power of approximately 90% for concluding superiority in the primary comparison of 500 μg roflumilast over placebo with regard to FEV_1. This corresponded to a total sample size of 1000 randomized patients (randomization scheme 2:2:1, i.e. 400 patients in the roflumilast 500 μg group, 400 patients in the roflumilast 250 μg group and 200 patients in the placebo group). At least 10 and at most 100 patients were requested per center.
The study consisted of the following periods:
   baseline period (4 weeks): visits B0, B2 and B4 (clinic visits at start of baseline, or 2 or 4 weeks after start of baseline period, respectively)
   treatment period (24 weeks): visits T0 (= baseline visit B4), T4, T8, T12, T16, T20, and T24 (clinic visits at zero, 4, 8, 12, 16, 20 and 24 weeks after randomization)
   safety follow-up, if necessary: visit F
Enrolled patients received salbutamol as rescue medication on demand, and were randomly assigned to one of the 3 treatment groups (2:2:1 randomization):
   group 1: roflumilast 500μg tablet, once daily (o.d.), per os (p.o.)
   group 2: roflumilast 250μg tablet, o.d., p.o.
   group 3: placebo tablet, o.d., p.o.

Study Population: The distribution of study subjects are shown belown.

T-Table 5: Demographic and baseline lung function parameters (full analysis set; n = 1411)

		Placebo	Roflumilast 250 µg	Roflumilast 500 µg	Total
Patients	(n)	280	576	555	1411
Sex (male/female)	(n)	207/73	419/157	410/145	1036/375
Age	(years)	63 (40-82)	65 (40-86)	64 (42-87)	64 (40-87)
Current/Ex-Smokers	(n)	125/155	267/309	254/301	646/765
Smoking habits	(pack year)	43 ± 22.0	43 ± 24.1	41 ± 20.6	42 ± 22.4
Constant anticholinergics/without anticholinergics	(n)	91/181	211/340	209/324	511/845
FEV$_1$ pre-bronchodilator	(l)	1.45± 0.48	1.40 ± 0.47	1.41 ± 0.49	n.d.
post-bronchodilator	(l)	1.57 ± 0.48	1.52 ± 0.47	1.50 ± 0.48	n.d.
reversibility	(%)	9.6 ± 13.1	9.6 ± 12.0	9.1 ± 13.1	n.d.
	(ml)	114.9 ± 153.9	113.6 ± 147.0	103.2 ± 151.6	n.d.
pre-bronchodilator	(% of predicted)	51.3 ± 13.8	50.1 ± 13.4	50.6 ± 13.7	n.d.
post-bronchodilator		55.2 ± 13.1	54.2 ± 13.0	54.2 ± 13.2	n.d.
Morning PEF (diary)	(l/min)	234 ± 82	224 ± 81	226 ± 83	n.d.
FEV$_1$/FVC	(%)	50 ± 11	50 ± 12	50 ± 12	n.d.

Data are presented as mean ± SD, except age: median (range).
FEV$_1$ = forced expiratory volume in one second, FVC = forced vital capacity, n = number of patients, n.d. = not done.
Morning PEF is given for randomized patients pre T0. All other lung function baseline data are given for randomized patients at B4 (= T0), i.e. prior to randomization. The baseline lung function parameters did not necessarily include data from all patients in the full analysis set (see Section 10.2 for details).
Pack year = number of cigarettes a day/20 x years smoking.
Data source: demographics: Table 14.1.2.1, Table 14.1.2.2, Table 14.1.2.4, Table 14.1.2.5, FEV$_1$: Table 14.2.1.1, Table 14.2.1.2; reversibility: Table 14.1.4.1; morning PEF: Table 14.2.5.1; FEV$_1$/FVC: Table 14.1.4.2.

T-Table 2: Discontinued patients (randomized patients; n = 1413)

Reason for termination	Number (%) of patients[a]		
	Placebo (n = 280)	Roflumilast 250 µg (n = 578)[b]	Roflumilast 500 µg (n = 555)
Adverse event	23 (72)	54[c] (54)	84[d] (68)
Other medical reasons	3 (9)	8 (8)	11 (9)
Non-medical reasons	6 (19)	38 (38)	29 (23)
Total	32 (100)	100 (100)	124 (100)

[a] Percentages are based on discontinued patients in the respective treatment group.
[b] 578 patients were randomized to the roflumilast 250 µg group, but since two of these patients did not receive any study medication, the full analysis set for the roflumilast 250 µg group consisted only of 576 patients.
[c] Note that a patient could have presented with more than one reason for premature withdrawal but only the main reason is included in the above table which causes the inconsistency in the roflumilast 250 µg group between this table and T-Table 44.
[d] Additionally, two patients in the roflumilast 500 µg group had an AE at T0, which was counted as baseline AE and, thus, is included in this table but not in T-Table 44.
n = number of patients.
Data source: Table 14.1.1.5.

Results and Conclusions:

Primary efficacy variables:
Post-bronchodilator FEV1:
A statistically significant increase in post-bronchodilator FEV1 was observed with both roflumilast doses in the ITT endpoint analysis. The increase was higher in the roflumilast 500 µg group (LSMean: 51 ml) than in the roflumilast 250 µg group (LSMean: 29 ml). In the

placebo group a statistically significant decrease in post-bronchodilator FEV1 was seen (LSMean: -45 ml). Statistically significant (p < 0.0001) between-treatment differences in favor of roflumilast were observed for the comparisons of roflumilast 500 µg with placebo (difference in LSMeans: 97 ml) and roflumilast 250 µg with placebo (difference in LSMeans: 74 ml). Although the differences between the two roflumilast doses were not statistically significant a statistically significant dose-response relationship in favor of roflumilast was observed in the Jonckheere-Terpstra test (p < 0.0001, one-sided).

T-Table 10: Post-bronchodilator FEV₁ [l] - within- and between-treatment differences (ITT last-value analysis)

WITHIN		T0		T_{last}	$T_{last} - T0$		
	n	Mean % pred.	LSMean	LSMean	LSMean ± SEM	95%CI	p-value[a]
Placebo	257	1.564 55%	1.521	1.476	-0.045 ± 0.016	-0.076, -0.014	0.0041
Rof250	528	1.511 54%	1.521	1.550	0.029 ± 0.012	0.006, 0.052	0.0134
Rof500	501	1.510 54%	1.521	1.572	0.051 ± 0.012	0.028, 0.075	<0.0001

BETWEEN			n	n	ΔTest – ΔReference		
	Test	Reference	Test	Reference	LSMean ± SEM	95%CI	p-value[b]
	Rof500	Placebo	501	257	0.097 ± 0.018	0.062, 0.131	<0.0001
	Rof500	Rof250	501	528	0.023 ± 0.014	-0.006, 0.051	0.1166
	Rof250	Placebo	528	257	0.074 ± 0.018	0.039, 0.108	<0.0001

[a] p-value for within-treatment differences (ANCOVA), two-sided, significance level 5%.
[b] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.
CI = confidence interval, Δ = within-treatment difference, FEV₁ = forced expiratory volume in one second, LS = least squares, n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).
Data source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.7, Table 14.2.1.10.

Total SGRQ score (co-primary efficacy variable): Statistically significant improvements (corresponding to a decrease in score) were observed in all three treatment groups from T0 to Tlast with the changes being higher in both roflumilast groups than in the placebo group. In the roflumilast groups the changes were close to the level of clinical significance (i.e. change of at least 4). The between-treatment differences between roflumilast 500 µg and placebo approached statistical significance in the ITT analysis (p = 0.053) and reached statistical significance in the PP analysis (p = 0.0492). The Jonckheere-Terpstra test revealed a statistically significant monotone dose-response relationship in favor of roflumilast.

Table 2: SGRQ total score - between-treatment differences change from T0 to T_{last} (ITT last-value analysis)

		n	n	ΔTest – ΔReference		
Test	Reference	Test	Reference	LSMean ± Std Err	95%CI	p-value[a]
Rof500	Placebo	496	267	-1.7 ± 0.9	-3.5, 0.0	0.0532
Rof500	Rof250	496	522	-0.2 ± 0.7	-1.6, 1.3	0.8270
Rof250	Placebo	522	267	-1.6 ± 0.9	-3.3, 0.2	0.0770

[a] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.
CI = confidence interval, Δ = within-treatment difference, LS = least squares, n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily, SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).
Data source: Table 14.2.3.7.

T-Table 20: SGRQ component scores - within- and between-treatment differences (ITT last-value analysis)

WITHIN		n	T0 Mean	T0 LSMean	T_{last} LSMean	$T_{last}-T0$ LSMean ± Std Err	$T_{last}-T0$ 95%CI	p-value[a]
Activity	Placebo	269	55.4	57.0	55.4	-1.6 ± 1.0	-3.5, 0.3	0.0948
	Rof250	525	57.7	57.0	53.8	-3.3 ± 0.7	-4.7, -1.9	<0.0001
	Rof500	501	57.1	57.0	54.0	-3.1 ± 0.7	-4.5, -1.6	<0.0001
Impacts	Placebo	269	28.3	31.1	29.9	-1.2 ± 0.9	-3.0, 0.5	0.1649
	Rof250	529	31.8	31.1	28.9	-2.2 ± 0.7	-3.5, -0.9	0.0010
	Rof500	500	32.0	31.1	28.1	-3.1 ± 0.7	-4.4, -1.7	<0.0001
Symptoms	Placebo	273	49.7	51.3	47.8	-3.6 ± 1.1	-5.8, -1.3	0.0017
	Rof250	539	52.2	51.3	45.3	-6.0 ± 0.9	-7.7, -4.3	<0.0001
	Rof500	509	51.4	51.3	46.7	-4.6 ± 0.9	-6.4, -2.9	<0.0001

BETWEEN	Test	Reference	n Test	n Reference	ΔTest – ΔReference LSMean ± Std Err	ΔTest – ΔReference 95%CI	p-value[b]
Activity	Rof500	Placebo	501	269	-1.5 ± 1.1	-3.6, 0.6	0.1724
	Rof500	Rof250	501	525	0.2 ± 0.9	-1.5, 2.0	0.8200
	Rof250	Placebo	525	269	-1.7 ± 1.1	-3.8, 0.4	0.1178
Impacts	Rof500	Placebo	500	269	-1.9 ± 1.0	-3.8, 0.1	0.0662
	Rof500	Rof250	500	529	-0.9 ± 0.8	-2.5, 0.7	0.2868
	Rof250	Placebo	529	269	-1.0 ± 1.0	-2.9, 1.0	0.3308
Symptoms	Rof500	Placebo	509	273	-1.1 ± 1.3	-3.6, 1.5	0.4109
	Rof500	Rof250	509	539	1.4, ± 1.1	-0.7, 3.5	0.1911
	Rof250	Placebo	539	273	-2.5 ± 1.3	-5.0, 0.1	0.0556

[a] p-value for within-treatment differences (ANCOVA), two-sided, significance level 5%.
[b] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.
CI = confidence interval, Δ = within-treatment difference, LS = least squares, n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).
Data source: Table 14.2.3.1, Table 14.2.3.4, Table 14.2.3.7.

Secondary efficacy variables:
Only COPD excerbations are summarized here as.

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T-Table 21: COPD exacerbations (ITT last value analysis)

Treatment Parameter	No. of patients N# (%)	No. of exacerbations n	Time [days] to onset of first exacerbation or drop-out Median	Time [days] to onset of first exacerbation or drop-out Range
Severe exacerbations				
Placebo	5 (1.8)	5	100	17-144
Rof250	12 (2.1)	12	61	15-143
Rof500	14 (2.5)	16	24	3-167
Severe or moderate exacerbations				
Placebo	59 (21.1)	84	83	0-171
Rof250	131 (22.7)	183	64	1-170
Rof500	108 (19.5)	154	64	0-173
Severe, moderate or mild exacerbations				
Placebo	97 (34.6)	317	58	0-171
Rof250	207 (35.9)	593	52	0-170
Rof500	157 (28.3)	418	56	0-173
Exacerbations leading to drop-out				
Placebo	7 (2.5)		98	77-144
Rof250	23 (4.0)		52	3-141
Rof500	15 (2.7)		60	3-143

Placebo: N = 280; Rof250: N = 576; Rof500: N = 555;
n = number of exacerbations, N = number of patients in treatment group, N# = number of patients with exacerbations,
Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily.
Small differences (n = 3, 2, 1 for roflumilast 500, 250, placebo) in the comparison of patients who discontinued due to the AE 'COPD exacerbation' and the survival analysis are present. This is due to the fact that these patients had no regular visit after discontinuation, and one investigator refused to enter the AE as an exacerbation (for a roflumilast 500 µg patient). Thus these were not considered in the survival analysis.
Data source: Table 14.2.9.1.

Safety evalutions: overall summary of the AEs are shown in the table below.

T-Table 32: Overview of treatment-emergent AEs by treatment group (full analysis set; n = 1411)

	Number (%) of patients*			
	Placebo (n = 280)	Roflumilast 250 µg (n = 576)	Roflumilast 500 µg (n = 555)	Total (n = 1411)
No. of AEs	419	896	944	2259
No. of patients reporting at least one AE	174 (62.1)	382 (66.3)	370 (66.7)	926 (65.6)
No. of patients with SAEs	21 (7.5)	41 (7.1)	53 (9.5)	115 (8.2)
No. of patients with AEs judged to be at least 'likely' related to study drug[b]	12 (4.3)	46 (8.0)	92 (16.6)	150 (10.6)
No. of patients with AEs leading to premature study discontinuation	23 (8.2)	56 (9.7)	82 (14.8)	161 (11.4)
No. of patients with AEs not yet known to be recovered	22 (7.9)	54 (9.4)	55 (9.9)	131 (9.3)

* Percentages are based on the total number of patients in the respective treatment group.
[b] by investigator.
n = number of patients.
Data source: Table 14.3.1.2 and Table 14.3.1.3.

Conclusions: Statistical significant was reached for the primary efficacy endpoint postFEV1 and SGRQ values. In total, 62.1% of patients treated with placebo, 66.3% of patients receiving 250 µg roflumilast and 66.7% of patients treated with 500 µg roflumilast experienced AEs.

4.4 New Drug Application Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	022522	**Brand Name**	DAXAS
OCP Division (I, II, III, IV, V)	II	**Generic Name**	Roflumilast
Medical Division	DPAP	**Drug Class**	PDE4 inhibitor
OCP Reviewer	Ping Ji	**Indication(s)**	Maintenance treatment of chronic obstructive pulmonary disease (COPO) associated with chronic bronchitis in patients at risk of exacerbations
OCP Team Leader	Xu Yun	**Dosage Form**	Tablet
Pharmacometrics Reviewer	Venkatesh Bhattaram	**Dosing Regimen**	1 tablet per day, with or without food
Date of Submission	July 15, 2009	**Route of Administration**	oral
Estimated Due Date of OCP Review	March 24, 2009	**Sponsor**	Forest Lab
Medical Division Due Date	April 7, 2009	**Priority Classification**	S
PDUFA Due Date	May 17, 2009		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE	x			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	2	2	
I. Clinical Pharmacology				
Mass balance:	x	3	2	
Isozyme characterization:	x	17	14	
Blood/plasma ratio:				
Plasma protein binding:	x	2	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3	3	

multiple dose:	x	**3**	**3**	
Patients-	x	9	9	
single dose:				
multiple dose:				
Dose proportionality -	x			
fasting / non-fasting single dose:		**1**	**1**	
fasting / non-fasting multiple dose:		**2**	**2**	
Drug-drug interaction studies -		**21**	**21**	
In-vivo effects on primary drug:	x			
In-vivo effects of primary drug:	x			
In-vitro:	x			
Subpopulation studies -		**15**	**15**	
ethnicity:	x	4	4	
gender:	x	1	1	
pediatrics:	x	1	1	
geriatrics:	x	6	6	
renal impairment:	x	1	1	
hepatic impairment:	x	2	2	
PD -				
Phase 2:	x	**5**	**5**	
Phase 3:	x			
PK/PD -	x			
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x			
Population Analyses	x	**5**	**5**	
Data rich:				
Data sparse:				
II. Biopharmaceutics		**10**	**5**	
Absolute bioavailability	x			
Bioequivalence studies -	x			
Food-drug interaction studies	x			
III. Other CPB Studies		**19**	**3**	
Genotype/phenotype studies	x			
Chronopharmacokinetics				
Pediatric development plan	x			
Literature References	x			
Total Number of Studies/Reports		**98**	**82**	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
--------------------	--------------------	--------------------	---
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ping Ji
03/23/2010

ARUN K AGRAWAL
03/23/2010

VENKATESH A BHATTARAM
03/23/2010

MICHAEL A PACANOWSKI
03/23/2010

YANING WANG
03/23/2010

ISSAM ZINEH
03/23/2010

YUN XU
03/23/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<table>
<tr><td colspan="4" align="center">Office of Clinical Pharmacology

<i>New Drug Application Filing and Review Form</i></td></tr>
</table>

General Information About the Submission

	Information		Information
NDA/BLA Number	022522	**Brand Name**	TBD
OCP Division (I, II, III, IV, V)	II	**Generic Name**	Roflumilast
Medical Division	DPAP	**Drug Class**	
OCP Reviewer	Ping Ji	**Indication(s)**	Maintenance treatment of chronic obstructive pulmonary disease (COPO) associated with chronic bronchitis in patients at risk of exacerbations
OCP Team Leader		**Dosage Form**	Tablet
Pharmacometrics Reviewer	Hao Zhu	**Dosing Regimen**	1 tablet per day, with or without food
Date of Submission	July 15, 2009	**Route of Administration**	oral
Estimated Due Date of OCP Review	March 10, 2009	**Sponsor**	Nycomed GmbH
Medical Division Due Date	March 24, 2009	**Priority Classification**	S
PDUFA Due Date	May 17, 2009		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	x			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	2		
I. Clinical Pharmacology				
Mass balance:	x	3		
Isozyme characterization:	x	17		
Blood/plasma ratio:				
Plasma protein binding:	x	2		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	x	3		

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Patients-	x	9		
single dose:				
multiple dose:				
Dose proportionality -	x	3		
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	11		
In-vivo effects of primary drug:	x	12		
In-vitro:	x			
Subpopulation studies -				
ethnicity:	x	4		
gender:	x	1		
pediatrics:	x	1		
geriatrics:	x	6		
renal impairment:	x	1		
hepatic impairment:	x	2		
PD -		10		
Phase 2:	x			
Phase 3:	x			
PK/PD -	x			
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x			
Population Analyses -	x	5		
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	x	1		
Relative bioavailability -	x	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	x	1		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	x	1		
Chronopharmacokinetics				
Pediatric development plan	x			
Literature References	x			
Total Number of Studies		100		

On **initial** review of the NDA/BLA application for filing:

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			N/A	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?				
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	another language needed and provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_y_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Ping Ji	Sep 25, 2009
Reviewing Clinical Pharmacologist	Date

Dakshina M. Chilukuri	Sep 25, 2009
Team Leader(Actg.)	Date