

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203108Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	203108	<i>Submission Dates</i>	0000 (05/14/2012)
<i>Brand Name (Proposed)</i>	(b) (4)® RESPIMAT® Inhalation Spray		
<i>Generic Name</i>	Olodaterol		
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<i>OCP Division</i>	Division of Clinical Pharmacology-II		
<i>OND Division</i>	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)		
<i>Sponsor</i>	Boehringer Ingelheim Pharmaceuticals inc.		
<i>Relevant IND(s)</i>	76,362		
<i>Submission Type; Code</i>	505 (b) (1)	S	
<i>Formulation; Strength(s)</i>	Oral inhalation using Respimat inhaler; 2.5 mcg per actuation		
<i>Indication</i>	Maintenance bronchodilator treatment in patients with COPD.		
<i>Proposed Dosing Regimen</i>	5 mcg once daily		

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1 Executive Summary

1.1 Recommendations

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Olodaterol, a long acting beta-agonist, is indicated for a once daily maintenance bronchodilator treatment in patients with COPD. The proposed dosage regimen is 5 mcg once daily via oral inhalation using Respimat inhaler.

Clinical pharmacokinetics of olodaterol has been studied in healthy subjects in 12 Phase 1 studies and in COPD patients in 4 studies to evaluate pharmacokinetics after single and multiple doses, in vivo metabolism, effect of renal and hepatic impairment, QTc prolongation effect, and drug-drug interactions.

Pharmacokinetics

Inhaled olodaterol has approximately 30% bioavailability resulting from pulmonary absorption; oral bioavailability is very low (<1%). Following inhalation of a single dose of olodaterol, C_{max} values were generally reached within 10 to 20 minutes post-dose, with an elimination half-life of approximately 45 hours. Pharmacokinetics are linear, and steady state was reached after 8 days. Population pharmacokinetic analyses showed approximately 2-fold higher systemic exposure in Asians compared to Caucasians. Olodaterol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety mainly by CYP2C9 followed by conjugation. The active metabolite, SOM 1522 BS, however, is not detectable in plasma after chronic inhalation of the recommended therapeutic dose or doses of up to 4-fold higher. Olodaterol is a substrate for the efflux pump P-gp. A cross-study comparison suggests somewhat higher systemic exposure in COPD patients than in the healthy subjects.

Hepatic Impairment

A hepatic impairment study (1222.35) showed that olodaterol levels were not affected in subjects with hepatic impairment. Olodaterol exposure was comparable between normal and mild & moderate hepatic impairment patients. Severe hepatic impairment group was not studied.

Renal Impairment

A renal impairment study (1222.20) showed that olodaterol levels increased by approximately 40% in subjects with severe renal impairment.

Drug-drug Interaction

Three drug-drug interaction studies were conducted to evaluate the interaction of olodaterol with tiotropium (1237.3), ketokonazole (1222.47), and fluconazole (1222.48). Olodaterol exposure when administered alone was comparable with that when coadministered with fluconazole and tiotropium. However, its exposure increased by ~70% when coadministered with ketoconazole.

Effect on QTc Prolongation

The effect of Inhaled olodaterol on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo- and active (moxifloxacin) controlled study at single doses of 10, 20, 30, and 50 mcg (1222.8). Dose-dependent QTcF prolongation was observed. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 3.4 (7.1) ms, 5.9 (9.6) ms, 7.4 (10.9) ms and 8.5 (12.4) ms following doses of 10, 20, 30 and 50 mcg, respectively.

Dose-response

There is evidence of a dose-response relationship with regard to the pertinent pulmonary endpoints. The doses explored in both COPD and asthma patients included 2 µg, 5 µg, 10 µg and 20 µg. A clear dose-response relationship is observed, with an increasing effect with increasing dose, for all endpoints evaluated. With regard to the dosing posology of olodaterol, once-daily vs. twice daily dosing was assessed in both COPD and asthma patients. All olodaterol dose regimens showed a significant increase in FEV1 AUC0-12 and FEV1 AUC12-24 compared with baseline. Moreover, the 24 hr bronchodilatory profile of olodaterol 5 µg once daily was superior to the profile of olodaterol 2 µg twice daily, and olodaterol 10 µg once daily did not induce a greater FEV1 response than olodaterol 5 µg once daily. Based on the gathered Phase 2 data in both COPD and asthma patients, 5 µg and 10 µg doses, given once daily, were appropriate to use in the phase 3 trials. Both 5 µg and 10 µg olodaterol once daily regimen were investigated in the controlled Phase 3 trials and no dose related safety issues were identified. The efficacy was comparable between the two regimens.

Dose adjustments for intrinsic/extrinsic factors

No dose adjustments are warranted for extrinsic or intrinsic factors. Baseline FEV1, weight, height and age were found to be the most significant covariates that influence systemic olodaterol exposure. Accounting for these factors, it is expected that a ~2-fold maximum increase of olodaterol exposure would be observed, compared to a typical COPD patient. As the proposed dosing regimen is 5 µg once daily and the PK is linear, increase of systemic exposure up to 2-fold would not lead to clinically meaningful differences in terms of safety. It is of note that the efficacy of olodaterol is not correlated with systemic exposure as the effect site is in the lung. As such, the following factors including elderly, gender, race, renal impairment, hepatic impairment, and genetic polymorphism would not need dose adjustment as the impact on PK is less than 2-fold.

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?

Olodaterol is a selective agonist of the human β 2-adrenoceptor discovered by Boehringer Ingelhem pharmaceuticals Inc. and developed for administration by inhalation using the RESPIMAT inhaler. It was also referred as BI 1744 during the development program. The Type B EOP2 meeting was held on Aug 11, 2008. The key Clinical Pharmacology and Biopharmaceutics agreements were: no food effect was needed, evaluate PK in the Phase 3 trials, sponsor will explore PKPD analysis from phase 3 trials. The NDA is reviewed under standard review timelines.

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?

Olodaterol hydrochloride is a white to off-white powder that is sparingly-slightly soluble in water and slightly soluble in ethanol. The molecular weight is 422.9 g/mole (salt): 386.5 g/mole (base), and the molecular formula is $C_{21}H_{26}N_2O_5 \times HCl$ as a hydrochloride.

The drug product, (b) (4) RESPIMAT, is composed of a sterile, aqueous solution of (b) (4) filled into a 4.5 mL plastic container crimped into an aluminum cylinder for use with the (b) (4) RESPIMAT inhaler. When used with the (b) (4) RESPIMAT inhaler each cartridge, containing a minimum of 4 grams of a sterile aqueous solution, delivers 60 metered actuations after preparation for use, the equivalent of 30 days medication when used as two actuations once a day. Each dose (1 dose equals 2 actuations) from the (b) (4) RESPIMAT inhaler delivers 5 mcg olodaterol in 22.1 mL of solution from the mouthpiece.

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

(b) (4) RESPIMAT Inhalation Spray is a long-acting beta₂-adrenergic agonist indicated for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

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

The recommended dosage for patients with COPD is 5 mcg once daily.

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?

There are a total of 19 in vitro studies to investigate the protein binding, enzyme and transporter profiling.

Index	Study	Objective
1	8222052	<i>In vitro</i> plasma protein binding in hepatic impairment and healthy volunteers
2	U06-1541	In vitro study to investigate the effect of tiotropium on the oxidative in vitro metabolism of [¹⁴ C]olodaterol
3	B2436 (U04-1983)	Determination of the In Vitro Binding of [¹⁴ C]BI 1744 CL to the Plasma Proteins and Blood Cells of Rat, Dog and Man Using Equilibrium Dialysis
4	PB08-003	Determination of in vitro plasma protein binding of [3H]OLODATEROL, in plasma of rat, dog and human
5	A180_05LU	Effect of tiotropium bromide on the oxidative in vitro metabolism of [¹⁴ C]BI 1744 CL
6	A180_05LU	Effect of BI 54903 XX (ciclesonide) on the oxidative in vitro metabolism of [¹⁴ C]BI 1744 CL
7	A206_06LU	Effect of BI 1744 CL on the oxidative in vitro metabolism of [¹⁴ C]tiotropium
8	A212_07LU	Effect of BI 1744 CL on the oxidative in vitro metabolism of [¹⁴ C] BI 54903 XX
9	A167_04LU	BI 1744 CL: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions
10	A180_05LU	Investigation of the human cytochrome P450 enzymes involved in the metabolism of [¹⁴ C]BI 1744 CL
11	A469_05BC	Investigations on the metabolism of BI 1744 CL in humans
12	A452_05BC, A646_05BC, A465_05BC, A467_06BC, A468_06BC, A470_06BC, A475_06BC, A476_06BC,	Investigations on the in vitro metabolism of BI 1744 CL
13	A473_06BC	In vivo metabolism of BI 1744 CL: Enantioselective analysis of the parent compound in samples of humans and animal species
14	A544-08bc	Metabolism of BI 1744 in humans
15	A258-09lu	BI 1744-Glucuronide (CD 992): In vitro inhibition studies on cytochrome P450 dependent metabolic reactions
16	A031-09os	BI 1744 CL: In vitro cytochrome P450 enzyme induction in primary human hepatocytes
	A282-08te	In vitro phase II metabolism of BI 1744
17	PK0720T	Investigation in the permeability of BI 1744 CL and its interaction

Table 2.2.1A: A list of in vitro enzyme profiling studies.		
Index	Study	Objective
1	8222052	<i>In vitro</i> plasma protein binding in hepatic impairment and healthy volunteers
		with P glycoprotein using the Caco-2 cell in vitro absorption model
18	PK0723T	In vitro evaluation of the transport and the interaction of BI 1744 CL with human organic anion transporting polypeptide (OATP) isoforms
19	PK0724T	In vitro interacting potential for P-gp

The clinical program for olodaterol was comprised of 12 Phase 1 trials (9 in healthy volunteers, 1 in patients with COPD, 1 in patients with renal impairment and 1 in patients with hepatic impairment), 3 Phase 2 trials in COPD, 4 Phase 2 trials in asthma and 10 Phase 3 trials in COPD.

Basic pharmacokinetics in healthy subjects was assessed in 6 Phase 1 trials: 1222.1 (single rising dose study), 1222.2 (14 day multiple rising dose study), 1222.7 (single rising dose trial with intravenous (i.v.) dosing), 1222.19 (single rising dose trial with oral dosing), 1222.9 (single dose ADME trial, with oral and i.v. dosing), 1222.21 (14 day multiple rising dose study in Japanese healthy subjects). Pharmacokinetics was also assessed in a thorough QT/QTc study in healthy subjects (1222.8). In addition, 3 drug-drug interaction studies were conducted: 1237.3 (3 weeks dosing to assess interaction of olodaterol and tiotropium), 1222.47 (3 weeks dosing to assess interaction of olodaterol and ketoconazole) and 1222.48 (3 weeks dosing to assess interaction of olodaterol and fluconazole). Pharmacokinetics was also studied in patients with renal impairment (1222.20) and in patients with hepatic impairment (1222.35).

Pharmacokinetics in COPD patients was assessed in 4 Phase 2 studies: 1222.3 (single dose Study), 1222.5 (4 weeks once daily dosing), 1222.22 (4 weeks once daily dosing in Japanese COPD patients), 1222.26 (3 weeks once daily vs. twice daily dosing). Pharmacokinetics in COPD patients was also assessed in 4 Phase 3 studies: 1222.11 (48 weeks once daily dosing), 1222.12 (48 weeks once daily dosing), 1222.13 (48 weeks once daily dosing), 1222.14 (48 weeks once daily dosing). Pharmacokinetics in asthma patients was assessed in 3 Phase 2 studies: 1222.4 (single dose study), 1222.6 (4 weeks once daily dosing) and 1222.27 (4 weeks once daily dosing).

Table 2.2.1B: A list of clinical studies with PK assessment.		
Index	Study	Objective
1	1222.1	SAD in healthy subjects
2	1222.2	MAD in healthy subjects
3	1222.7	IV study
4	1222.19	Oral study
5	1222.9	Human ADME study
6	1222.8	TQT study

Table 2.2.1B: A list of clinical studies with PK assessment.		
Index	Study	Objective
1	1222.1	SAD in healthy subjects
7	1222.35	Renal impairment study
8	1222.20	Hepatic impairment study
9	1222.21	MAD in Japanese healthy volunteers
10	1222.22	Dose finding in Japanese COPD patients
11	1222.47	DDI with ketoconazole
12	1237.3	DDI with tiotropium
13	1222.48	DDI with fluconazole
14	1222.4	Single dose in asthma patients
15	1222.6	Dose finding in asthma patients
16	1222.27	Dose finding in asthma patients
17	1222.3	Phase 2 dose ranging in COPD (2, 5, 10, 20, 40 mcg); Single dose
18	1222.5	Phase 2 dose ranging in COPD (2, 5, 10, 20 mcg QD)
19	1222.26	Posology in COPD patients
20	1222.11	Phase 3 in COPD patients
21	1222.12	Phase 3 in COPD patients
22	1222.13	Phase 3 in COPD patients
23	1222.14	Phase 3 in COPD patients

2.2.3 What are the PK characteristics of olodaterol?

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

A single ascending dose study of olodaterol via inhalation with Respimat was conducted in healthy subjects at escalating doses of 0.5 µg, 1.0 µg, 2.5 µg, 5.0 µg, 10.0 µg, 15.0 µg, 20.0 µg, 30.0 µg, 40.0 µg, 50.0 µg, 60.0 µg, 70.0 µg (Study 1222.1). After oral inhalation, olodaterol exhibits multi-exponential disposition kinetics. The maximum concentrations were measured 14 to 22 minutes after end of drug inhalation. The exposure is approximately dose proportional. Renal excretion unchanged accounted for approximately 5-6% of administered dose following 96 hours after inhalation. The terminal half life averaged 25 hours.

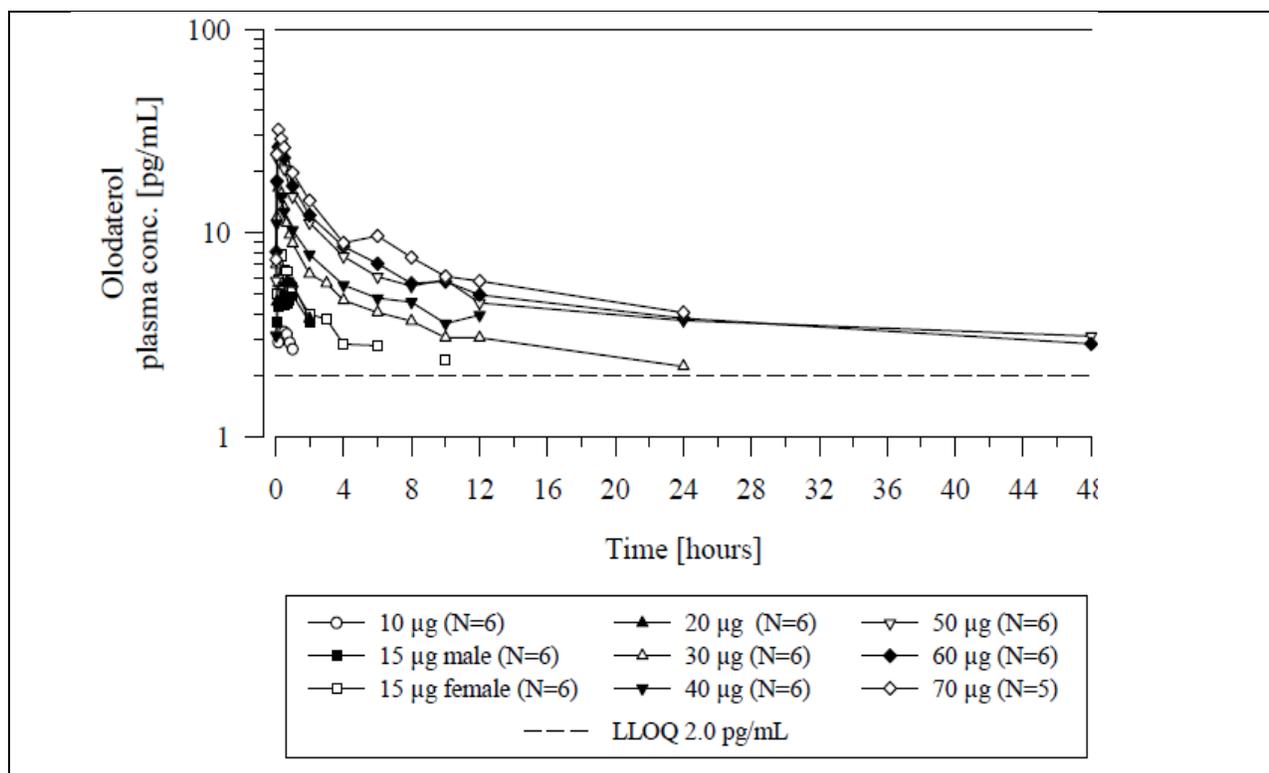


Figure 2.2.3A1: The concentration time profiles of olodaterol after a single oral inhalation of 10 to 70 mcg (Study 1222.1).

Table 2.2.3A1: Geometric means and geometric coefficients of variation [%] of pharmacokinetic parameters of olodaterol after inhalation of 2.5 µg up to 70 µg BI 1744 CL via the Respimat® inhaler (Study 1222.1).

Dose (ug) (n=6)	C _{max}	T _{max} ¹	AUC _{0-inf}	T _{half}	Fe ²
2.5	-	-	-	-	-
5	-	-	-	-	-
10	3.62 (24.0)	0.3 (0.17-0.5)	-	-	-
15 male	4.89 (52.6)	0.37 (0.2-0.5)	-	-	-
15 female	7.89 (26.1)	0.37 (0.2-0.38)	-	-	-

20	5.33 (76.2)	0.35 (0.18-0.85)	-	-	-
30	17.7 (57.3)	0.28 (0.17-0.5)	126 (90%)	16.8 (116)	-
40	15.4 (68.2)	0.37 (0.12-0.5)	145 (80%)	16.7 (50.8)	5.63 (55.3)
50	26.2 (28.3)	0.29 (0.2-0.55)	356 (90%)	38.0 (91.0)	6.30 (31.8)
60	29.8 (71.1)	0.29 (0.22-0.55)	398 (44%)	39.5 (43.4)	5.05 (36.0)
70 (n=5)	32.7 (54.3)	0.23 (0.22-0.38)	304 (105%)	21.5 (81.0)	5.98 (62.5)

¹: median and range. ²: fraction excreted in the urine over 24 hours

The multiple dose study was conducted in healthy subjects in study 1222.2 after repeated inhalation of 2.5, 10 and 30 mcg olodaterol once daily for 14 days. The exposure of 2.5 mcg group could not be detected. Steady state was achieved after 8 days. ~3% to 10% of the inhaled dose is excreted unchanged in urine at steady state. Accumulation of drug in plasma based on C_{max} values was low and accounted for a factor of 1.25 for dose group 10 µg BI 1744 CL (female), 1.27 for dose group 10 µg BI 1744 CL (male) and 1.45 for dose group 30 µg BI 1744 CL. The geometric mean terminal half-life at steady state was around 45 hours. Excretion of olodaterol in urine accounted for approximately 2-3% of the BI 1744 CL dose following 24 hours after single inhalation and 5-7% within the dosing interval at steady state. Thus, accumulation based on urinary excretion of drug within the dosing interval 0-24 hours revealed a factor of about 2. The results of the statistical analysis of dose proportionality indicated that AUC and C_{max} values increased sub-proportionally within the dose range.

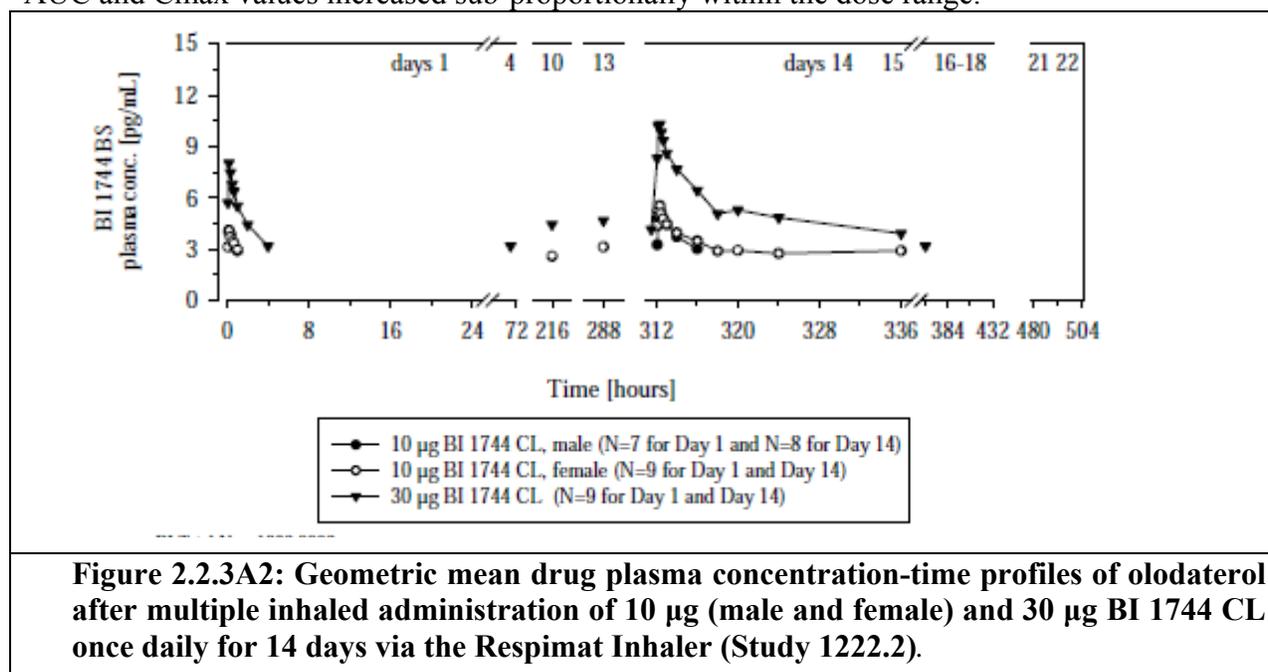


Table 2.2.3A2: Geometric means and geometric coefficients of variation [%] of pharmacokinetic parameters of olodaterol following single inhalation of 10 µg and 30 µg BI 1744 CL via the Respimat® Inhaler (Study 1222.2).					
Dose (ug)	C _{max} (pg/mL) (n=7/9/9)	T _{max} ¹ (h) (n=8/9/9)	AUC ₀₋₂₄ (pg h/mL) (n=4/6/9)	T _{half} (h) (n=8/8/9)	Fe ² (n=9/9/9)
Day 1					
10 µg male	4.12 (26.3%)	0.3 (0.15- 0.3)	-	-	3.39 (47%)
10 µg female	4.28 (29.2%)	0.18 (0.15- 0.3)	-	-	3.17 (37%)
30 µg	8.47 (63.8%)	0.17 (0.08- 0.5)	-	-	2.45 (51%)
Day 14					
10 µg male	5.33 (57%)	0.342 (0.3- 1)	80.5 (27%)	22.9 (20%)	6.97 (57%)
10 µg female	5.34(35%)	0.18 (0.17- 0.7)	76.7 (20%)	45.9 (30%)	6.21 (66%)
30 µg	10.7 (45%)	-3 (0.17- 0.7)	126 (35%)	45.1 (36%)	4.53 (40%)
¹ : median and range. ² : fraction excreted in the urine over 24 hours					

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

The PK of olodaterol in COPD patients were studied in four Phase 2 studies and 4 Phase 3 studies. In addition, the PK of olodaterol in asthma patients were assessed in 3 Phase 2 studies. The concentration-time profiles of olodaterol follow multi-exponential decline after oral inhalation in COPD patients. C_{max} in COPD patients is generally higher than those in healthy and asthma subjects.

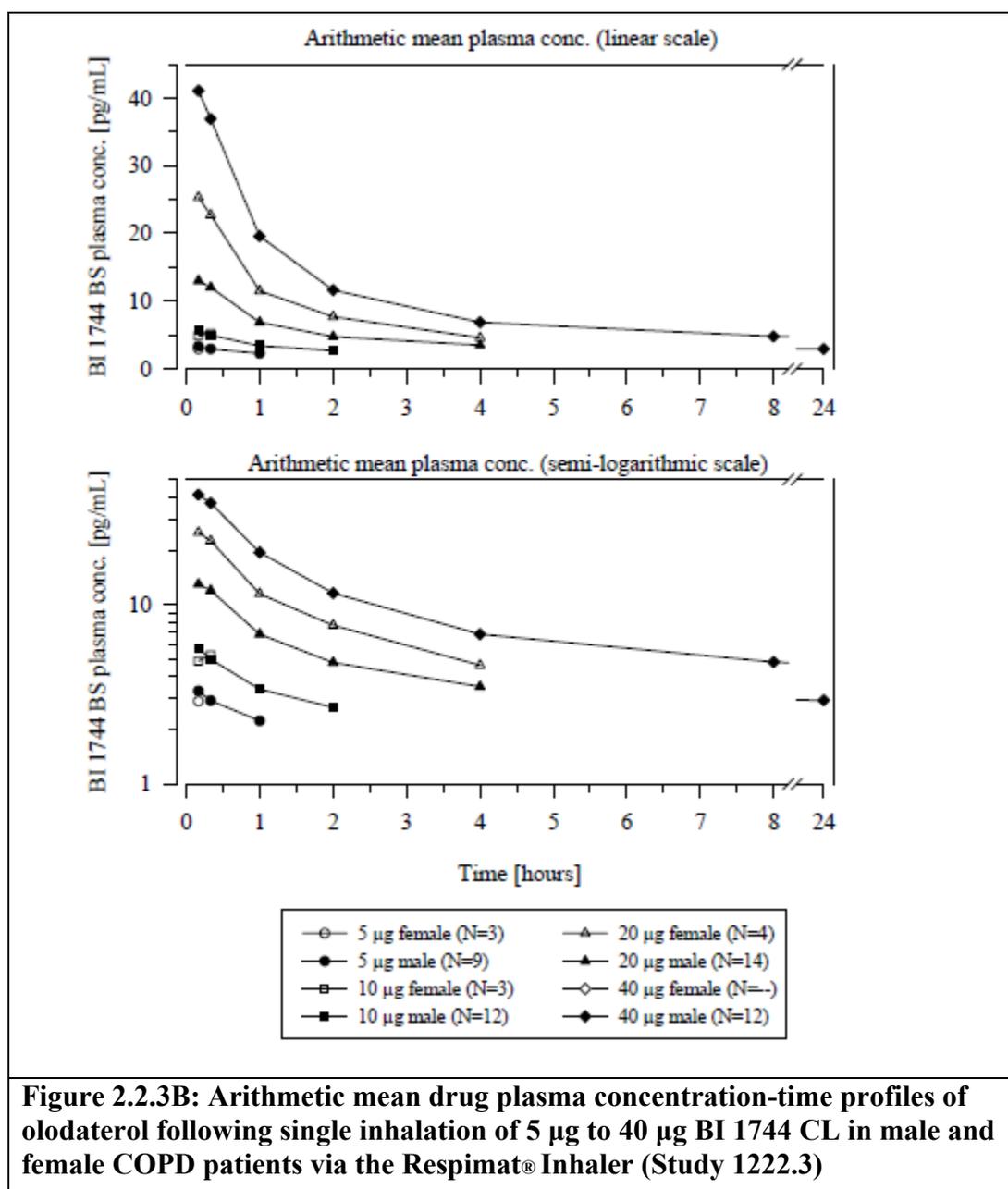


Table 2.2.3B: Cross-study Comparison of olodaterol systemic exposure after inhalation of 5 and 10 µg olodaterol by healthy volunteers, asthma patients and COPD patients

5 µg

Parameter [Unit]	Healthy volunteers			Asthma patients			COPD patients		
	N	gMean (gCV%)	Source	N	gMean (gCV%)	Source	N	gMean (gCV%)	Source
C _{max} [pg/mL]	---	---	1222.1	9	2.95 (33.9)	1222.4	12	3.16 (26.3)	1222.3
				21	3.54 (48.4)	1222.6	40	3.58 (51.4)	1222.5
	7 [#]	2.82 (23.8) [#]	1222.21 [#]				53 [#]	4.17 (46.7) [#]	1222.22 [#]
AUC ₀₋₁ [pg·h/mL]	---	---	1222.1	---	---	1222.4	---	---	1222.3
				---	---	1222.6	---	---	1222.5
	---	---	1222.21 [#]				30 [#]	3.67 (35.6) [#]	1222.22 [#]
C _{max,15} [pg/mL]				39	3.19 (35.0)	1222.6	46	4.02 (46.7)	1222.5
	9 [#]	3.35 (23.8) [#]	1222.21 [#]				67 [#]	5.92 (57.4) [#]	1222.22 [#]
AUC _{0-1,15} [pg·h/mL]				27	2.94 (30.7)	1222.6	28	3.38 (39.2)	1222.5
	9 [#]	2.66 (26.3) [#]	1222.21 [#]				64 [#]	4.85 (54.6) [#]	1222.22 [#]

--- no descriptive statistics available, since parameter available in less than 1/3 of the subjects (healthy volunteer studies) or less than 1/3 of the subjects (asthma and COPD patient studies)

Japanese study

10 µg

Parameter [Unit]	Healthy volunteers			Asthma patients			COPD patients		
	N	gMean (gCV%)	Source	N	gMean (gCV%)	Source	N	gMean (gCV%)	Source
C _{max} [pg/mL]	6	3.62 (24.0)	1222.1	26	4.54 (39.5)	1222.4	16	4.95 (53.8)	1222.3
	16 ¹	4.21 (27.1) ¹	1222.2	44	4.63 (59.7)	1222.6	71	5.45 (63.5)	1222.5
	17	3.29 (42.1)	1222.8						
	9 [#]	5.44 (29.4) [#]	1222.21 [#]				81 [#]	8.22 (58.3) [#]	1222.22 [#]
AUC ₀₋₁ [pg·h/mL]	5	2.90 (16.3)	1222.1	21	3.91 (30.9)	1222.4	11	4.22 (39.0)	1222.3
	12 ¹	3.36 (23.7) ¹	1222.2	31	3.95 (49.4)	1222.6	48	4.93 (45.7)	1222.5
	---	---	1222.8						
	8 [#]	4.21 (26.0) [#]	1222.21 [#]				77 [#]	6.08 (50.8) [#]	1222.22 [#]
C _{max,15} [pg/mL]	17 ¹	5.33 (44.4) ¹	1222.2	45	5.09 (53.0)	1222.6	72	7.13 (63.8)	1222.5
	26 [§]	3.32 (24.1) [§]	1222.47 [§]				44 [§]	5.30 (54.2) [§]	1237.3 [§]
	30 [§]	5.36 (34.4) [§]	1222.48 [§]						
	9 [#]	6.80 (53.5) [#]	1222.21 [#]				78 [#]	13.1 (58.6) [#]	1222.22 [#]
AUC _{0-1,15} [pg·h/mL]	16 ¹	4.67 (38.1) ¹	1222.2	43	4.37 (50.3)	1222.6	68	5.76 (55.8)	1222.5
	24 [§]	2.78 (23.5) [§]	1222.47 [§]				37 [§]	4.30 (62.3) [§]	1237.3 [§]
	31 [§]	4.01 (30.3) [§]	1222.48 [§]						
	8 [#]	6.17 (35.8) [#]	1222.21 [#]				77 [#]	10.8 (54.0) [#]	1222.22 [#]

--- no descriptive statistics is available, since parameter was available for less than 1/3 of the subjects

1 The given numbers include males and females, hence differ from numbers given in CTR 1222.2 (males and females presented separately).

Japanese study

§ Olodaterol mono arm in the tiotropium+olodaterol FDC Study 1237.3

c) What are the characteristics of drug absorption?

The absolute bioavailability of olodaterol following inhalation based on a cross-study comparison is estimated to be approximately 30%. In contrast, the absolute bioavailability of an orally administered olodaterol solution due to incomplete absorption and considerable first-pass metabolism is below 1% (Study 1222.9)

d) What are the characteristics of drug distribution?

Olodaterol exhibits multi-compartmental disposition kinetics. The volume of distribution (V_{ss} : 1110 L) by far exceeds the total body volume, indicating extensive distribution of olodaterol into tissues. The blood cell-to-plasma concentration ratio of olodaterol is about 2.5 to 3.0, implying that olodaterol associates with red blood cells. Moderate (~60%) and concentration independent binding of olodaterol to human plasma proteins has been observed, which was unchanged in renal or hepatic insufficiency.

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

The mass balance study indicated that both renal (38%) and hepatic (53%) play a role in eliminating olodaterol after IV dosing.

The mass balance study was conducted in healthy male subjects in study 1222.9 at (20 µg i.v. and 40 µg oral treatments). It was an open-label, parallel design with two treatment groups. A total of 12 male subjects were planned to be enrolled in one study centre. The study drug [^{14}C]olodaterol was planned to be administered as solution for i.v. administration to a group of 6 subjects (20 µg i.v) and as oral solution to another 6 subjects (40 µg oral). The maximum radioactive dose was 0.096 MBq for i.v. and 0.192 MBq for oral administration. Following intravenous infusion, the total recovery was 95.4 % of the dose (gCV 1.86%). Overall, 42.5% of the dose (gCV 2.81%) was excreted in urine and 53.0% of the dose (gCV 1.63%) was excreted in feces. More than 90% of the dose was excreted within 6 days. Following oral administration, only 9% of the administered radioactivity was recovered in urine, while the major portion was recovered in feces (84%).

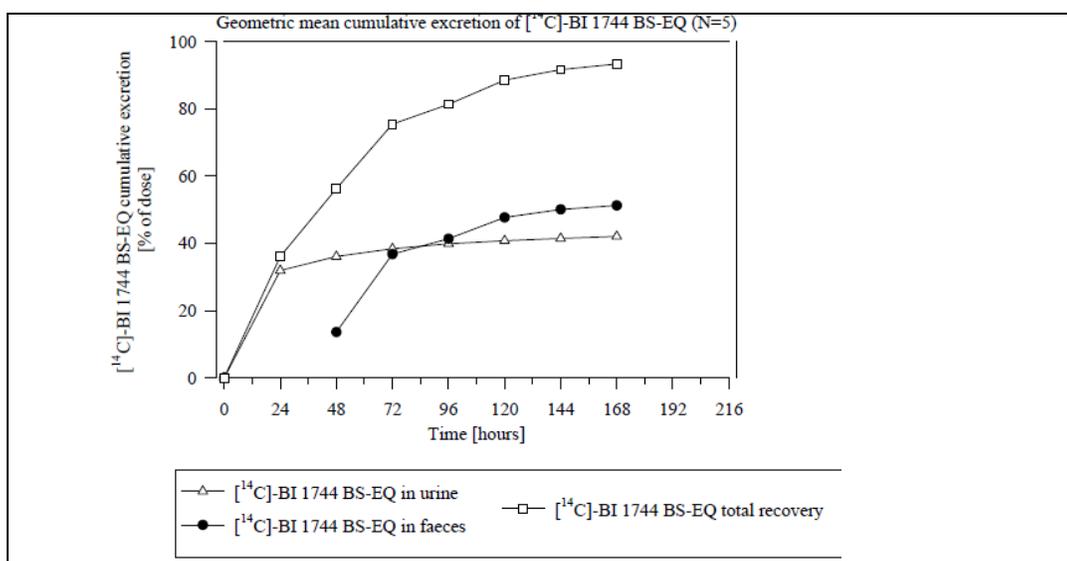


Figure 2.2.3E: Mass balance and total recovery following single intravenous infusion of 20 µg [14C]OLODATEROL over 3 h in healthy subjects

Table 2.2.3E: 1 PK parameter of [14C]olodaterol-EQ, olodaterol, and olodaterol-glucuronide following single i.v. infusion of 20 µg [14C]olodaterol over 3 h in 5 healthy subjects.

	Unit	[¹⁴ C]BI 1744 BS-EQ gMean (gCV [%])	BI 1744 BS gMean (gCV [%])	BI 1744 BS-glucuronide gMean (gCV [%])
C_{max}	[pmol/L]	233 (31.7)	122 (13.6)	32.0 (29.0)
t_{max}	[h]	2.98 (2.98-3.17)	2.98 (2.98-3.07)	3.07 (2.98-3.17)
$AUC_{0-\infty}$	[pmol·h/L]	-	963 (28.3)	199 (38.9)
% $AUC_{tz-\infty}$	[%]	-	21.3 (33.7)	11.6 (58.4)
AUC_{0-tz}	[pmol·h/L]	435 (32.2)	746 (24.9)	173 (39.6)
$AUC_{0-tz, norm}$	[pmol·h/L/µg]	-	38.3 (28.5)	-
t_z^*	[h]	4.00 (3.50-5.00)	48.0 (24.0-48.0)	48.0 (24.0-48.0)
$t_{1/2}$	[h]	-	22.1 (46.8)	16.0 (39.3)
MRT	[h]	-	21.3 (61.5)	13.6 (44.7)
CL	[mL/min]	-	872 (33.5)	-
V_{ss}	[L]	-	1110 (29.5)	-
$CL_{R,0-48}$	[mL/min]	-	173 (30.1)	322 (24.7)
Ae_{0-tz}	[nmol]	21.4 (5.24)	9.52 (13.7)	4.14 (19.3)
fe_{0-tz}	[%]	42.5 (2.81)	18.9 (12.5)	-
$Ae_{faeces,0-tz}$	[nmol]	26.7 (6.59)	-	-
$fe_{faeces,0-tz}$	[%]	53.0 (1.63)	-	-
$RC_{max, Met}$		-	-	0.262 (24.6)
$RAUC_{0-\infty, Met}$		-	-	0.206 (21.3)

* Median and range

f) What are the characteristics of drug metabolism?

Olodaterol is substantially metabolized, with about half of the drug-related material excreted after intravenous administration being metabolites. The metabolic pathways involve direct glucuronidation (CD992) of olodaterol and O-demethylation (SOM1522) at the methoxy moiety followed by glucuronidation (CD11249) or sulfation (CD12656). Of six metabolites identified only the unconjugated demethylation product SOM 1522 exhibits pharmacological activity on the β_2 -receptor, with binding affinity and agonistic potency similar to olodaterol. SOM 1522 however is a minor metabolite, which was not detectable in plasma after chronic inhalation of the planned therapeutic dose or doses of up to 4-fold higher.

CYP2C8 and CYP2C9 mainly contribute to the formation of SOM 1522, while contribution of CYP3A4 is negligible [U06-1439, U08-2268, U09-1129]. Moreover, the UDP-glucuronyl transferases UGT1A1, UGT1A7, UGT1A9, and UGT2B7 were found to be involved in the glucuronidation of olodaterol [U10-1331].

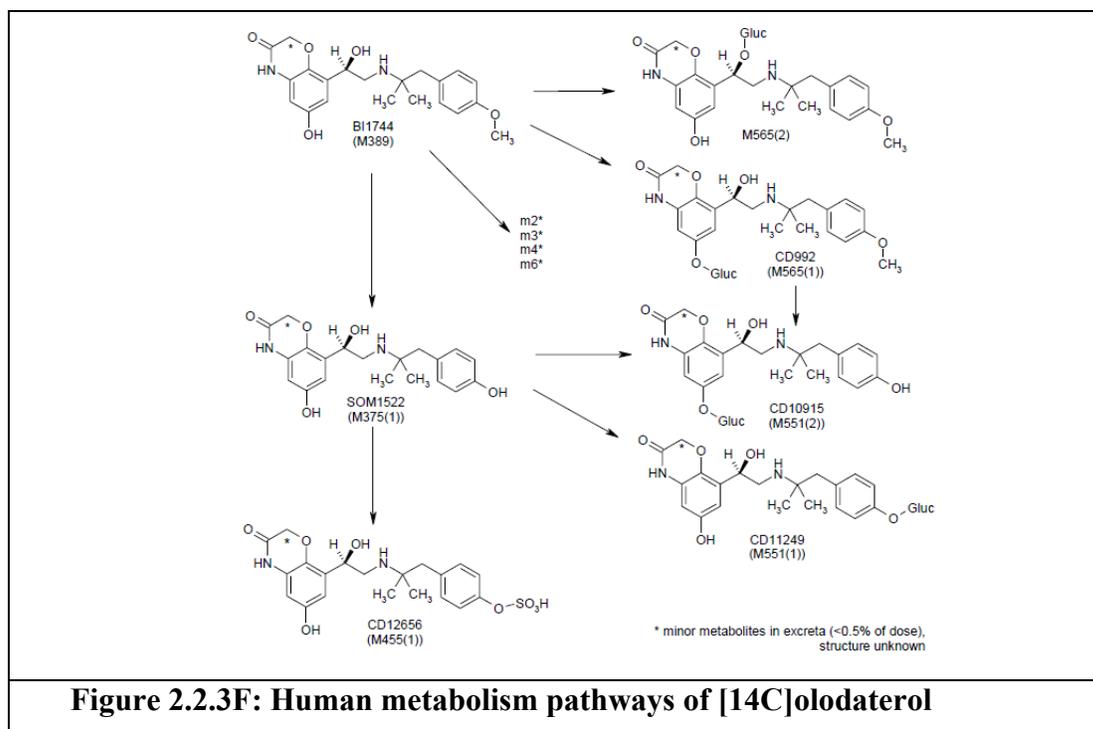


Table 2.2.3F: 1 Metabolite pattern in urine and feces after single intravenous and single oral administration of [¹⁴C]olodaterol to healthy male subjects.

Metabolite	Intravenous administration Dose: 20 µg			Oral administration Dose: 40 µg		
	Urine 0-72 h	Feces 0-216 h	Urine+feces	Urine 0-72 h	Feces 0-168 h	Urine+feces
	% of dose					
Olodaterol (BI 1744)	19.1 [§]	23.5	42.6	0.7	59.7	60.3
CD 992	9.8	n.d.	9.8	3.7	n.d.	3.7
M565(2)	n.d.	n.d.	n.d.	0.2	n.d.	0.2
SOM 1522	0.2	28.4	28.7	0.1	24.0	24.1
CD 10915	5.5	n.d.	5.5	1.9	n.d.	1.9
CD 11249	1.5	n.d.	1.5	0.7	n.d.	0.7
CD 12656	1.6	1.0	2.6	1.2	0.6	1.8
Non extractable	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Others*	0.6	n.d.	0.6	0.6	n.d.	0.6
Sum	38.4 ^{§,§}	52.9 ^{§,§}	91.3 [§]	9.1 ^{§,§}	84.3 ^{§,§}	93.4 [§]

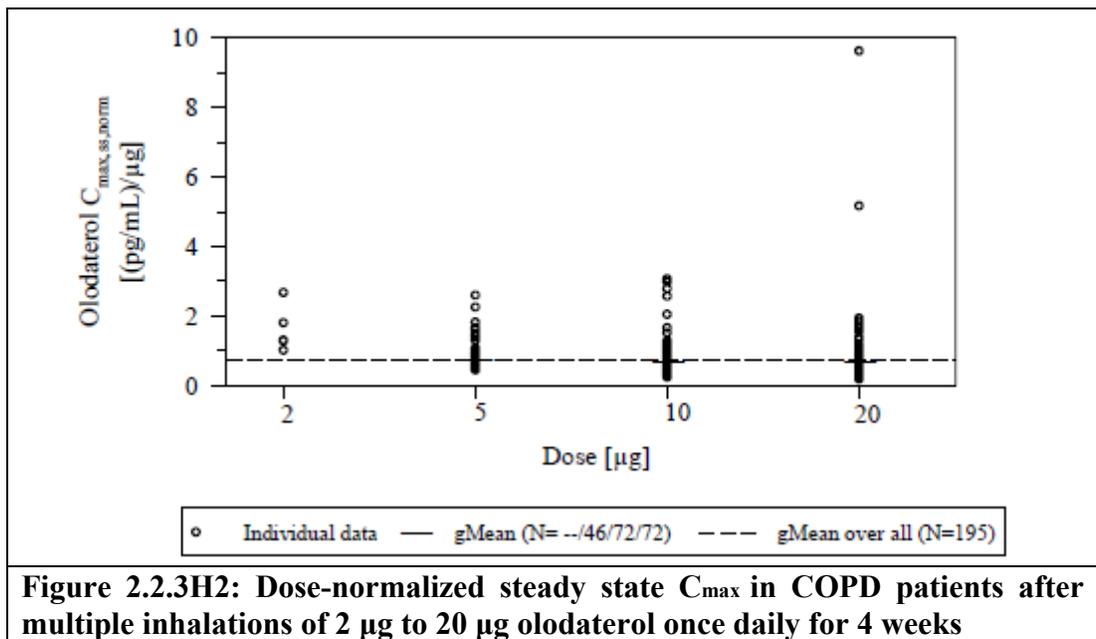
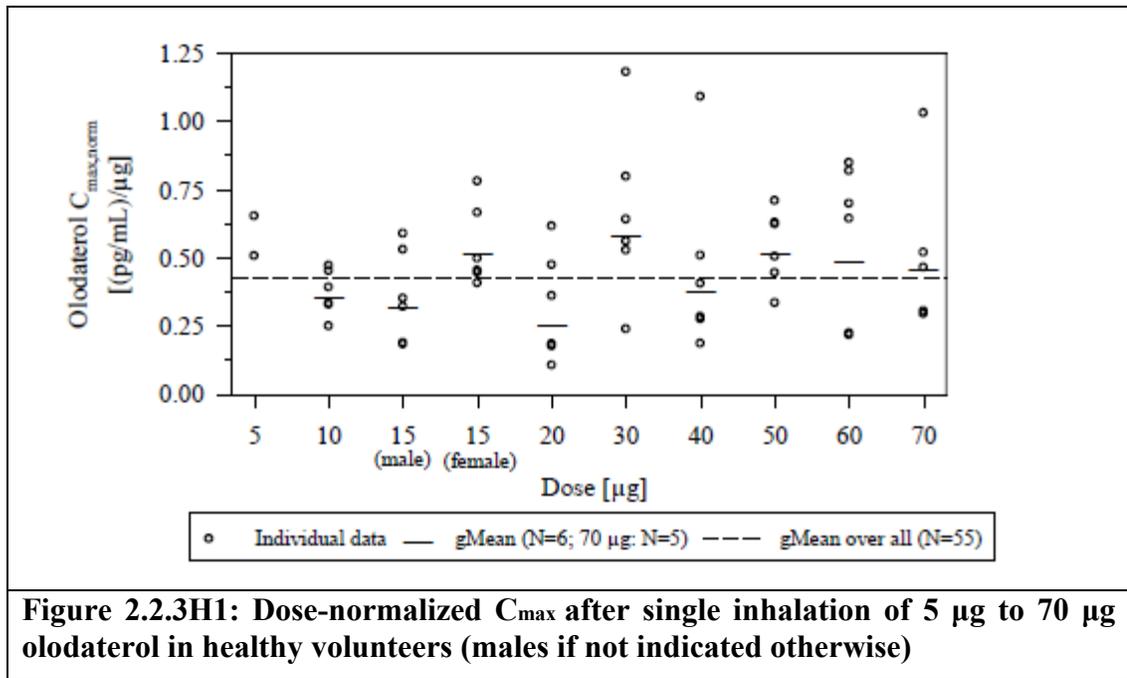
* Structure unknown, individually <0.5% of dose
[§] Arithmetic mean of 5 individuals
[§] Arithmetic mean of 6 individuals
[§] Slight differences between values given in this Table and the data described in the paragraphs "Excretion and mass balance" and "Pharmacokinetics" above are due to different methodology, different sampling intervals considered and the use of arithmetic versus geometric means
n.d. Not detected

g) What are the characteristics of drug excretion?

Total clearance of olodaterol as determined in healthy volunteers following intravenous infusion is 872 mL/min, and renal clearance is 173 mL/min, indicates active secretion in the kidney. The terminal half-life of olodaterol is 16-26 hours after single intravenous dosing in healthy subjects. However, the effective half-life at daily dose of 5 µg calculated from C_{max} from study 1222.5 is about 7.5 hours.

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

Olodaterol showed linear pharmacokinetics, with an overall dose-proportional increase of systemic exposure after single inhaled doses of 5 to 70 µg.



A power model was made to calculate the linearity based on C_{max} from both healthy subjects and COPD patients. For healthy subjects, the exponent of C_{max} was estimated as 1.1 (0.9-1.3) indicating the exposure is linear with dose.

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

The steady state concentration was about 4 pg/mL for 5 µg and 7 pg/mL for 10 µg inhaled olodaterol after chronic dosing as shown in the Phase 3 trials. No change in observation with time was observed.

Table 2.2.3I: The PK exposure of olodaterol in COPD patients			
Study 1222.11			
Treatments (dose, regimen, route)	Test product ID [batch], device [batch]	Subjects completed	Results – Study parameters [unit] Geometric mean (% gCV)
			C _{0.167,ss} [pg/mL]
Olodaterol 5.0 µg, q.d., 48 weeks, inhalation	Olodaterol solution for Respimat 2.5 µg [B072000346], Respimat A5 [B082000007]	173	Day 43: 4.094 (47.767) Day 85: 4.065 (52.336) Day 127: 3.962 (50.585) Overall: 4.044 (49.973)
Olodaterol 10 µg, q.d., 48 weeks, inhalation	Olodaterol solution for Respimat 5 µg [B072000356], Respimat A5 [B072000354]	172	Day 43: 6.693 (64.277) Day 85: 6.798 (63.386) Day 127: 6.392 (69.648) Overall: 6.622 (65.740)
Study 1222.22			
			C _{0.167,ss} [pg/mL]
Olodaterol 5.0 µg, q.d., 48 weeks, inhalation	Olodaterol solution for Respimat 2.5 µg [B072000346], Respimat A5 [B082000007]	185	Day 43: 4.172 (43.726) Day 85: 4.104 (50.416) Day 127: 3.941 (46.553) Overall: 4.072 (46.748)
Olodaterol 10 µg, q.d., 48 weeks, inhalation	Olodaterol solution for Respimat 5 µg [B072000356], Respimat A5 [B072000354]	181	Day 43: 7.516 (64.424) Day 85: 7.593 (66.360) Day 127: 6.950 (66.275) Overall: 7.341 (65.678)

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-individual variability of olodaterol plasma concentrations after inhalation was moderate. After inhalation of the planned therapeutic dose of 5 µg by COPD patients, geometric coefficients of variation for single dose and steady state C_{max} and AUC₀₋₁ values ranged from 26% to 57% (Study 1222.5).

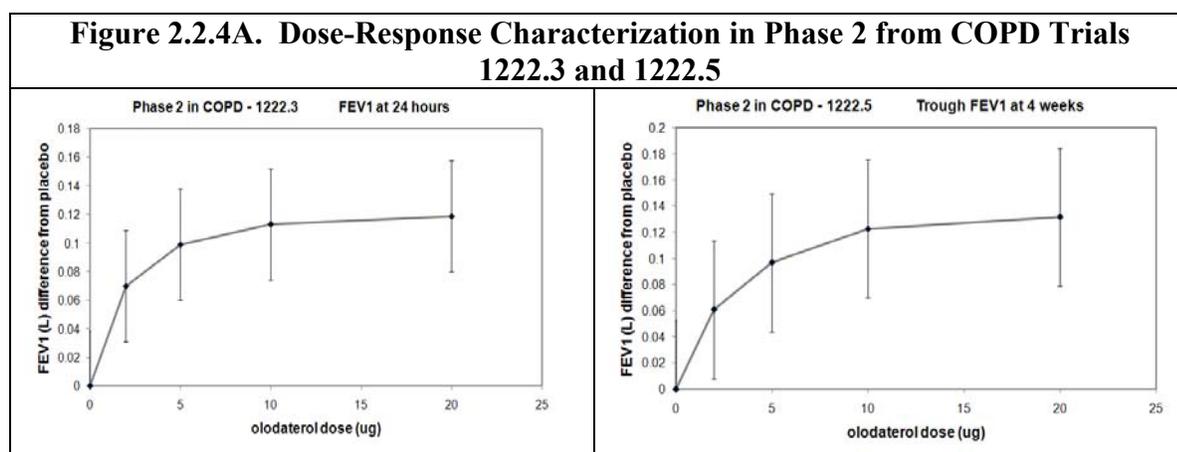
2.2.4 Exposure-response

2.2.4.1 Is there evidence of dose-response relationship for efficacy?

There is evidence of a dose-response relationship with regard to the pertinent pulmonary endpoints. The doses explored in both COPD and asthma patients included 2 µg, 5 µg, 10 µg and 20 µg. A clear dose-response relationship is observed, with an increasing effect with increasing dose, for all endpoints evaluated (see question below).

2.2.4.2 Has the dosing of olodaterol been adequately explored?

The dosing regimen of olodaterol has been adequately explored in Phase 2 trials. The doses explored in both COPD and asthma patients included 2 µg, 5 µg, 10 µg and 20 µg. Moreover, once-daily and twice daily dosing posology was investigated to determine the effectiveness of the different regimens. Based on the gathered Phase 2 data in both COPD and asthma patients, 5 µg and 10 µg doses, given once daily, were appropriate to use in the phase 3 trials. This conclusion is based on the fact that both doses yield a near maximal effect in lung function tests, without undue side effects. The figure below depicts the placebo-corrected dose-response curves for the dose ranging trials in COPD patients. For both trials, all doses resulted in a statistically different improvement over placebo (all p-values <0.01). Moreover, the relative efficacy of olodaterol 5 µg was between the response with 2 µg and 10 µg, such that the position of olodaterol 5 µg on the dose-response curve can only be characterized as intermediate between suboptimal (2 µg) and plateauing in efficacy (10 or 20 µg).



Placebo-corrected, Mean ± 95% CI

With regard to the dosing posology of olodaterol, once-daily vs. twice daily dosing was assessed in both COPD and asthma patients. All olodaterol dose regimens showed a significant increase in FEV1 AUC₀₋₁₂ and FEV1 AUC₁₂₋₂₄ compared with baseline. Moreover, the 24 hr bronchodilatory profile of olodaterol 5 µg once daily was superior to the profile of olodaterol 2 µg twice daily, and olodaterol 10 µg once daily did not induce a greater FEV1 response than olodaterol 5 µg once daily.

Of note, prior to initiation of the Phase 3 program, the decision to further evaluate olodaterol 5 µg and olodaterol 10 µg, once daily, was accepted by the FDA (end-of-Phase II meeting). The results of the Phase 3 study reiterate the appropriateness of the dosing regimen chosen. Based on the efficacy results of the pivotal trials, 5 µg and 10 µg showed comparable, statistically significant effects.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The effect of (b) (4) RESPIMAT on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo- and active (moxifloxacin) controlled study at single doses of 10, 20, 30, and 50 mcg. Dose-dependent QTcF prolongation was observed. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 3.4 (7.1) ms, 5.9 (9.6) ms, 7.4 (10.9) ms and 8.5 (12.4) ms following doses of 10, 20, 30 and 50 mcg, respectively. Please see the QT/IRT review for details.

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) Pediatric patients

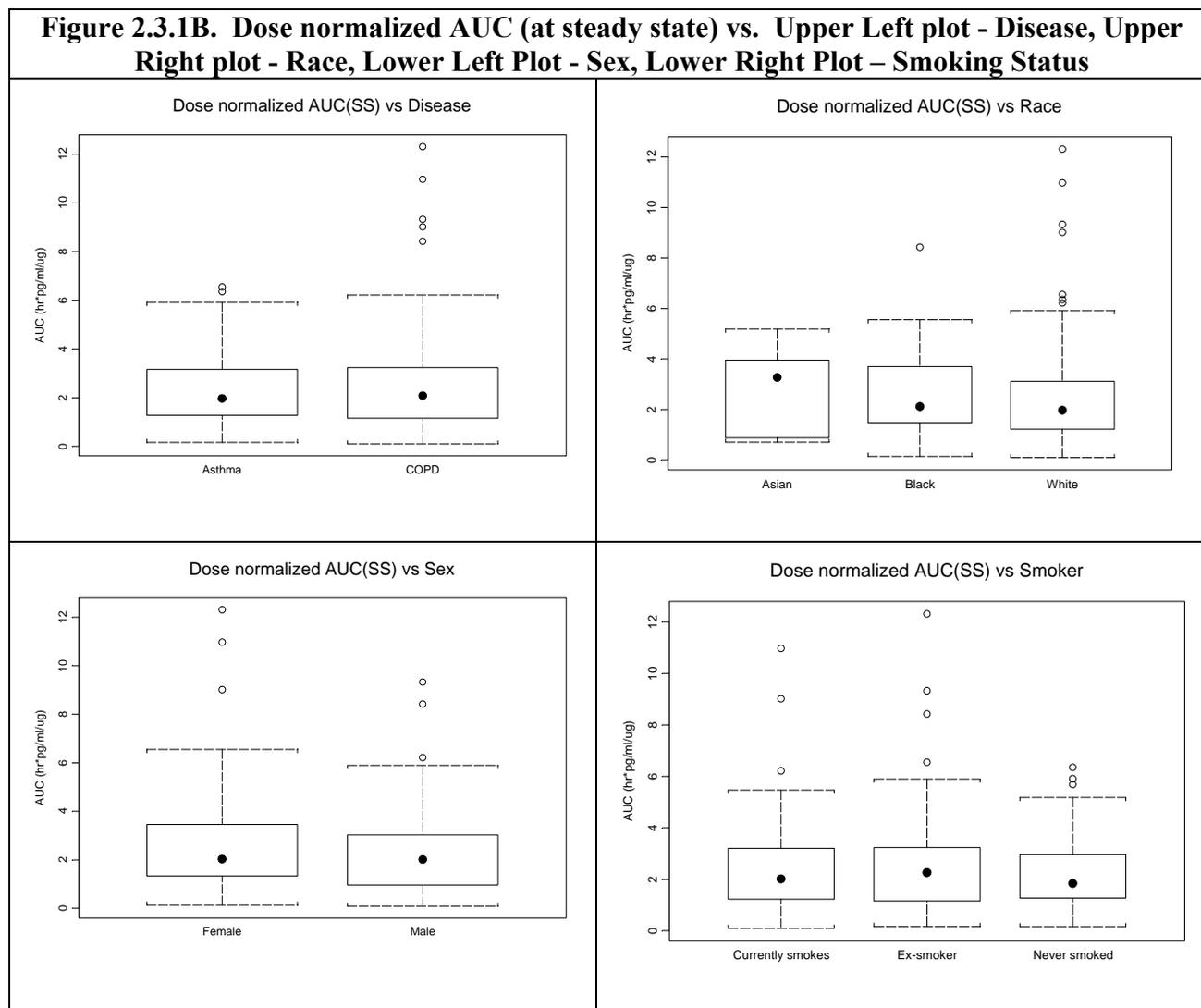
COPD is not a pediatric disease. Safety and effectiveness of olodaterol in children and adolescents below 18 years of age have not been established. Olodaterol is not recommended in this population.

b) Gender, race, disease, smoking status

No categorical covariates were significant in the univariate analysis for the $AUC_{norm,ss}$ exposure metric. Disease status (asthma vs. COPD), race (asian vs. black vs. white), sex (male vs. female), and smoking status did not have influence on steady state exposures. Plots depicting the covariate-exposure relationships are shown in Figure 2.3.1B below.

c) renal impairment

A renal impairment study (1222.20) was conducted to evaluate the effect of severe renal



impairment (n=8) on the PK of olodaterol at single dose of 20 mcg. Olodaterol levels were increased by approximately 40% in subjects with severe renal impairment.

Table 2.3.1C: Inter-individual comparison of pharmacokinetic parameters of olodaterol between subjects with severe renal impairment and matched healthy subjects

Parameter	sRIP		N	HV		Ratio sRIP/HV [%]	2-sided 90% CI	
	N	Adj. gMean		Adj. gMean	Lower Limit (%)		Upper Limit (%)	

C_{max} [pg/mL]	7	11.1	13	8.2	136.6	84.1	222.0
AUC_{0-4} [pg·h/mL]	7	23.4	13	17.3	135.2	93.7	195.0
Ae_{0-tz} [ng]	8	123.2	14	693.5	17.8	8.5	37.3
$CL_{R,0-8}$ [mL/min]	7	35.9	13	178.9	20.1	12.9	31.4

sRIP: subjects with severe renal impairment; HV: healthy subjects

d) hepatic impairment

A hepatic impairment study (1222.35) showed that olodaterol levels were not affected in subjects with hepatic impairment. Olodaterol exposure was comparable between normal and mild & moderate hepatic impairment patients.

Table 2.3.1D: Inter-individual comparison of dose-normalized pharmacokinetic parameters of olodaterol between hepatically impaired and matched healthy subjects

Parameter		LIP		HV		2-sided 90% CI		
						Ratio LIP/HV [%]	Lower Limit (%)	Upper Limit (%)
Mild liver impairment								
$C_{max, norm}$	[pg/mL/ μ g]	8	0.439	15	0.391	112.2	83.6	150.7
$AUC_{0-4, norm}$	[pg·h/mL/ μ g]	8	0.802	15	0.829	96.7	74.6	125.3
fe_{0-tz}	[%]	8	3.31	16	3.61	91.8	56.9	148.1
Moderate liver impairment								
$C_{max, norm}$	[pg/mL/ μ g]	7	0.387	15	0.391	99.0	72.7	134.7
$AUC_{0-4, norm}$	[pg·h/mL/ μ g]	6	0.871	15	0.829	105.1	79.0	140.0
fe_{0-tz}	[%]	7	2.95	16	3.61	81.8	49.6	135.0

LIP: Liver impaired patients, HV: Healthy volunteers

e) genetic polymorphism

The impact of UGT polymorphisms (UGT1A1 *28/36/37, *60, *93, UGT1A7 *2, *3, *4, *12, UGT1A9 *3, UGT2B7 *2) was investigated as potential covariates. *UGT polymorphisms do not have any influence on systemic olodaterol exposure.*

f) 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.

Both 5 µg and 10 µg olodaterol once daily regimen were investigated in the controlled Phase 3 trials and no dose related safety issues were identified. The efficacy was comparable between the two regimens. As the proposed dosing regimen is 5 µg once daily and the PK is linear, increase of systemic exposure up to 2-fold would not lead to clinically meaningful differences in terms of safety. It is of note that the efficacy of olodaterol is not correlated with systemic exposure as the effect site is in the lung. As such, the following factors including elderly, gender, race, renal impairment, hepatic impairment, and genetic polymorphism would not need dose adjustment as the impact on PK is less than 2-fold.

a) Elderly

No dose adjustment is needed for elderly patients.

b) Gender

No dose adjustment is needed for gender.

c) Race

No dose adjustment is needed for race.

d) Renal impairment

No dose adjustment is needed for renal impairment patients.

e) Hepatic impairment

No dose adjustment is needed for renal impairment patients.

f) Genetic polymorphism

No dose adjustment is needed for genetic polymorphic patients.

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?

None.

2.4.2. Drug-Drug Interactions

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

Yes. Olodaterol is the substrate of CYP2C8, 2C9 and P-gp. Olodaterol is a weak inhibitor of P-gp.

When incubating [¹⁴C]olodaterol with human liver microsomes the predominant metabolite was SOM 1522. The reaction leading to SOM 1522 was dependent mostly on the cytochrome P450 enzymes CYP 2C8 and CYP 2C9[U06-1439].

In *Vitro* studies showed olodaterol to be a substrate of the transporter protein P-gp, with concentration dependent efflux ratios of 38.9 (at 10 µM olodaterol) to 9.45 (at 600 µM olodaterol) in the Caco-2 cell system [U08-3378, U08-3424]. In Caco-2 monolayers olodaterol inhibited the P-gp mediated AtoB and BtoA transport of digoxin in a concentration dependent manner. The apparent IC₅₀ mean value of both directions was 365 µM, indicating that olodaterol acts as a weak P-gp inhibitor. This profile of olodaterol as a weak P-gp inhibitor was confirmed in MDR1-expressing cells. Olodaterol did not show a clear inhibitory effect on the digoxin transport at concentrations up to 600 µM. In the intravesicular uptake assay, the BCRP-mediated uptake of estrore 3-sulfate was inhibited by olodaterol. The IC₅₀ was estimated to be in the range from 10 to 100 µM.

b) Is the drug a substrate of CYP enzymes?

Yes. Olodaterol is weak substrate of CYP2C9.

In an open label, fixed sequence drug interaction study, 10 µg of olodaterol oral inhalation was administered alone or in combination with multiple doses of 400 mg qd fluconazole in healthy subjects n=35) (1222.48). Olodaterol exposure when olodaterol was administered with fluconazole was increased by 9% and 13% for C_{max} and AUC₀₋₆, respectively, as compared to when olodaterol was administered alone. However, the upper limit of 90% CI was below the 125%.

Table 2.4.2B: Adjusted by treatment geometric means and relative bioavailability for olodaterol with respect to C_{max,ss}, AUC_{0-1,ss}, and Ae_{0-24,ss} – intraindividual comparison of combined treatment with olodaterol and fluconazole vs. treatment with olodaterol alone (1222.48).

Parameter	Olodaterol + fluconazole		Olodaterol alone		gMean ratio (90%CI) of olodaterol + fluconazole to olodaterol [%]	Intra-individual gCV [%]
	N	Adjusted gMean	N	Adjusted gMean		
Primary endpoints						
C _{max,ss} [pg/mL]	32	5.81	30	5.34	108.8 (101.6, 116.5)	15.5
AUC _{0-6,ss} [pg·h/mL]	28	22.3	24	19.7	113.3 (105.9, 121.2)	13.6
Secondary endpoint						
Ae _{0-24,ss} [ng]	32	647	32	563	114.8 (99.9, 131.9)	33.5

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

No, olodaterol does not have in vivo potential to inhibit/induce the CYP enzymes.

Olodaterol dose not have in vitro inhibition potential up to 100 µM for CYP 1A1/1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 3A4 and 4A11 and it inhibited the CYP2D6 at a K_i of 1.92 µM in an *in vitro* study using pooled human liver microsomes [U06-1043]. The olodaterol glucuronide CD 992 showed a minor mechanism-based inhibition of CYP 2D6 at 100 µM [U09-2417]. Olodaterol and CD992 dose not have induction potential on the activity and mRNA expression of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4 up to 1 nM. As the picomolar plasma concentrations of olodaterol (C_{max,ss}: 4.02 pg/mL, =10.4 pM) and CD 992 (C_{max,ss}: 4.90 pg/mL, =8.71 pM) achieved in COPD patients with the planned therapeutic dose of 5 µg olodaterol [U09-3125], inhibitory or inducing effects on the CYP-mediated metabolism of concomitantly administered other drugs based on these results are considered to be highly unlikely.

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

Yes, olodaterol is a substrate of P-gp.

In an open label, fixed sequence drug interaction study, 10 µg of olodaterol oral inhalation was administered alone or in combination with multiple doses of 400 mg qd ketoconazole in healthy subjects n=32) (1222.47). Olodaterol exposure when olodaterol was administered with fluconazole was increased by 66% and 68% for C_{max} and AUC₀₋₁, respectively, as compared to when olodaterol was administered alone.

Table 2.4.2D: Adjusted by treatment geometric means and relative bioavailability for olodaterol with respect to C_{max,ss}, AUC_{0-1,ss}, and Ae_{0-24,ss} – intraindividual comparison of combined treatment with olodaterol and ketoconazole vs. treatment with olodaterol alone

Parameter	Olodaterol + ketoconazole		Olodaterol alone		gMean ratio of olodaterol + ketoconazole to olodaterol (90% CI) [%]	Intra-individual gCV [%]
	N	Adjusted gMean	N	Adjusted gMean		
Primary endpoints						
C _{max,ss} [pg/mL]	31	5.17	26	3.11	166.1 (153.6, 179.6)	16.8
AUC _{0-1,ss} [pg-h/mL]	31	4.23	24	2.51	168.4 (155.5, 182.4)	16.4
Secondary endpoint						
Ae _{0-24,ss} [ng]	32	618.7	32	429.0	144.2 (133.9, 155.4)	17.8

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

None.

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?

None.

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

No interaction was observed between olodaterol and tiotropium when olodaterol 10 µg and tiotropium 5 µg were coadministered together.

The interaction potential of olodaterol and tiotropium was evaluated in a randomised, double-blind, 3-way crossover study to compare pharmacokinetics and safety of 10 µg BI 1744 CL plus 5 µg tiotropium bromide given as fixed dose combination via the Respimat® Inhaler with the pharmacokinetics and the safety of the single agents, i.e. 10 µg BI 1744 CL and 5 µg tiotropium bromide, delivered via the Respimat® Inhaler following 21 day treatment periods in patients with COPD. Pharmacokinetics of BI 1744 BS and tiotropium after inhalation of the fixed dose combination was not significantly altered in comparison to when each of the two compounds was administered alone.

Table2.4.2G1: Adjusted geometric mean PK parameters of olodaterol, ratios and two-sided 90% confidence intervals following administration of the olodaterol + tiotropium (test) and olodaterol (reference), respectively.

Parameter	Adjusted. gMean		Ratio [%]	Intra-indiv. gCV [%]	2-sided 90% CI	
	Test BI 1744 + tio	Reference BI 1744			Lower Limit (%)	Upper Limit (%)
$C_{max,ss}$ (pg/mL)	5.87	5.28	111	27.17	101	122
$AUC_{0-1,ss}$ (pg·h/mL)	4.67	4.15	112	32.15	99	127
$AUC_{0-2,ss}$ (pg·h/mL)	8.52	8.36	102	21.33	93	112
$Ae_{0-24,ss}$ (ng)	360.98	344.17	105	19.85	98	113
$AUC_{0-tz,ss}$ (pg·h/mL)	12.20	9.25	132	96.12	98	177

Table2.4.2G2: Adjusted geometric mean PK parameters of tiotropium, ratios and two-sided 90% confidence intervals following administration of the olodaterol + tiotropium (test) and tiotropium (reference), respectively

Parameter	Adjusted. gMean		Ratio [%]	Intra-indiv. gCV [%]	2-sided 90% CI	
	Test BI 1744 + tio	Reference tiotropium			Lower Limit (%)	Upper Limit (%)
$Ae_{0-24,ss}$ (ng)	900.57	918.63	98	20.43	91	106
$C_{max,ss}$ (pg/mL)	15.55	16.15	96	29.92	87	107
$AUC_{0-4,ss}$ (pg·h/mL)	21.92	24.00	91	22.61	84	100
$AUC_{0-6,ss}$ (pg·h/mL)	29.97	33.24	90	19.81	83	98
$AUC_{0-tz,ss}$ (pg·h/mL)	32.67	32.91	99	72.08	79	125

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

None.

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.

For the same reason addressed in section 2.3.2, no dose adjustment is needed in terms of smoking and drug-drug interaction.

a) *Smoking*

No dose adjustment is needed.

b) *Drug-drug interaction*

No dose adjustment is needed when coadministered olodaterol with tiotropium, fluconazole and ketoconazole.

2.5 General Biopharmaceutics

2.5.1. What is the *in vivo* relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

No BA/BE studies were conducted as the formulation used in the clinical trial and the final commercial formulation is the same.

The RESPIMAT inhalation device used in the very first clinical trial (1222.1) was RESPIMAT A4, whereas in all other clinical studies the to-be-marketed inhaler RESPIMAT A5 was employed. The two RESPIMAT versions are identical in their performance parameters and properties in terms of duration of spray, spray velocity, particle size distribution and delivered volume. The only difference between the two versions is that the RESPIMAT A5 is equipped with a locking mechanism that prevents the use of olodaterol RESPIMAT beyond the labeled number of doses.

As there were no formulation changes and no relevant device changes during the clinical development of olodaterol RESPIMAT solution for inhalation, no relative BA or BE studies were conducted.

2.5.2. 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?

The interaction study between inhaled olodaterol and food was not conducted. It is not likely that inhaled olodaterol PK is changed by food.

2.6 Analytical Section

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

Specific and highly sensitive HPLC-MS/MS (high performance liquid chromatography coupled to tandem mass spectrometry) methods for olodaterol were developed and validated using human plasma and human urine samples.

Plasma (500 µL) or urine (300 µL) was mixed with the internal standard [D3]olodaterol. The samples were subjected to solid phase extraction (SPE) in the 96-well plate format and subsequently submitted for HPLC-MS/MS analysis. Chromatography was achieved on an analytical RP 18 HPLC column under gradient elution. Olodaterol was detected and quantified using a tandem mass spectrometer in the positive ionization mode. The ion masses monitored were 387.3/163.2 for olodaterol and 390.3/166.2 for the internal standard.

2.6.2 Which metabolites have been selected for analysis and why?

SOM1522 was selected for analysis as it is the active metabolite in plasma.

2.6.3 How was the assay performed for olodaterol?

The analytical methods performed for olodaterol and its metabolite were validated.

Table 2.6.3A: Characteristics of most important analytical methods used in clinical studies for the determination of olodaterol concentrations in plasma and urine.

Plasma

Range	LLOQ	QC low	QC mid	QC high
2.00 - 2000 pg/mL	2.00 pg/mL	5.00 pg/mL	100 pg/mL	1600 pg/mL
Method 01 (automated SPE)				
Deviation (%)	10.2	7.5	4.7	5.2
CV (%)	17.1	8.6	4.2	3.2
N	23	11	12	12
Method 01 (manual SPE)				
Deviation (%)	12.8 (2.7)*	5.3	0.7	0.5
CV (%)	22.5 (6.2)*	11.5	1.2	0.2
N	6 (5)*	2	2	2
Range	LLOQ	QC low	QC mid	QC high
2.00 - 200 pg/mL	2.00 pg/mL	5.00 pg/mL	25.0 pg/mL	160 pg/mL
Method 1.2				
Deviation (%)	5.3	6.7	10.1	10.7
CV (%)	7.7	1.0	4.1	3.7
N	12	2	2	2
Method 1.3				
Deviation (%)	-1.8	2.7	4.5	2.3
CV (%)	5.7	4.0	5.8	5.6
N	6	6	6	6

* data excluding one statistical outlier is given in brackets

a

Urine

	LLOQ	QC low	QC mid	QC high
	10.0 pg/mL	25.0 pg/mL	500 pg/mL	8000 pg/mL
Method 01 (automated SPE)				
Deviation (%)	1.2	-2.0	-3.0	0.0
CV (%)	8.7	4.7	1.6	2.5
N	23	12	12	12
Method 01 (manual SPE)				
Deviation (%)	4.2	5.6	-2.5	-2.2
CV (%)	5.0	5.2	1.8	4.0
N	6	2	2	2
Method 1.2 and 1.3				
Deviation (%)	-3.1	8.2	4.8	3.2
CV (%)	4.4	4.8	2.5	1.6
N	6	6	6	6
Method 1.4				
Deviation (%)	-5.1	-6.0	-11.3	-7.8
CV (%)	6.2	8.0	5.2	9.1
N	6	6	6	6

Table 2.6.3B: Validation data for SOM 1522 in human plasma and urine.

Human plasma	LLOQ 10.0 pg/mL	QC low 25.0 pg/mL	QC mid 90.0 pg/mL	QC high 160 pg/mL
Method 01 (automated SPE*)				
Deviation (%)	12.0	5.3	6.9	8.4
CV (%)	5.1	4.7	12.0	9.0
N	18	10	10	10
Method 1.1				
Deviation (%)	3.7	6.0	-0.3	2.2
CV (%)	3.7	4.6	5.5	5.4
N	12	4	4	4
Method 1.2				
Deviation (%)	15.6	1.6	1.9	1.5
CV (%)	3.0	3.7	2.0	2.5
N	6	8	8	8
Human urine	LLOQ 100 pg/mL	QC low 25.0 pg/mL	QC mid 90.0 pg/mL	QC high 160 pg/mL
Method 1.1 (automated SPE)				
Deviation (%)	-1.5	-3.9	-8.0	-3.7
CV (%)	13.6	4.8	7.6	2.3
N	18	10	10	10
Method 1.1 (manual SPE)				
Deviation (%)	6.5	-3.8	-5.2	-1.8
CV (%)	5.8	3.4	1.7	0.6
N	6	2	2	2
Method 1.2				
Deviation (%)	6.0	0.1	1.3	0.0
CV (%)	3.7	2.4	3.5	2.6
N	6	8	8	8
* for manual sample extraction, the highest deviation/CV at all levels was = 4.7% / 6.3% with N = 6 for plasma and = 6.6% / 5.8% with N = 4 - 6 for urine.				

The lower and upper limits of quantification for undiluted plasma were 2.00 pg/mL and 2000 pg/mL (method version 01 and 1.1) and 2.00 pg/mL and 200 pg/mL (method version 1.2 and higher) for BI 1744 BS. Olodaterol in spiked plasma samples was stable during 3 freeze/thaw cycles, 137 h at room temperature, and up to 615 days in a freezer at -20°C. Incurred samples containing olodaterol were stable during 4 freeze/thaw cycles, 25 h at room temperature and 777 days in a freezer at -20°C. Olodaterol was also stable for 129 h in sample extracts and for 4 h at ambient temperature in whole blood [U05-1910] and [U10-2355].

3. Detailed Labeling Recommendations

7 DRUG INTERACTIONS

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of (b) (4) RESPIMAT may be potentiated [see *Warnings and Precautions* (5.3, 5.5, 5.6, 5.7)].

7.2 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of (b) (4) RESPIMAT [see *Warnings and Precautions* (5.7)].

7.3 Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics.

7.4 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

(b) (4) RESPIMAT, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

7.5 Beta-Blockers

(b) (4)
Therefore (b) (4) RESPIMAT should only be given together with beta-adrenergic blockers (b) (4) if there are compelling reasons for their use. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.6 Inhibitors of Cytochrome P450 and P-gp Efflux Transporter

In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of maximum plasma concentrations and AUC was observed [see *Pharmacokinetics* (12.3)]. No safety concerns were identified in clinical studies of up to one year with (b) (4) RESPIMAT at doses up to twice the recommended therapeutic dose. No dose adjustment is necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies with (b) (4) RESPIMAT in pregnant women. (b) (4) RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of (b) (4) RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of (b) (4) RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

(b) (4)

8.4 Pediatric Use

(b) (4) RESPIMAT is not indicated for use in children. The safety and effectiveness of (b) (4) RESPIMAT in the pediatric population have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of (b) (4) RESPIMAT dosage in geriatric patients is necessary.

Of the 876 patients who received (b) (4) RESPIMAT at the recommended dose of 5 mcg once daily in the clinical studies from the pooled 1-year database 485 were less than or equal to 65 years of age and 391 (44.6%) were greater than 65 years of age.

No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall.

8.6 Hepatic Impairment

Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

8.7 Renal Impairment

Subjects with severe renal impairment showed no clinically relevant changes in C_{max} or AUC compared to their healthy controls.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Beta-adrenoceptors are divided into three subtypes: beta₁-adrenoceptors predominantly expressed on cardiac smooth muscle, beta₂-adrenoceptors predominantly expressed on airway smooth muscle, and beta₃-adrenoceptors predominantly expressed on adipose tissue. Beta₂-agonists cause bronchodilation. Although the beta₂-adrenoceptor is the predominant adrenergic receptor in the airway smooth muscle, it is also present on the surface of a variety of other cells, including lung epithelial and endothelial cells and in the heart. The precise function of beta₂-receptors in the heart is not known, but their presence raises the possibility that even highly selective beta₂-agonists may have cardiac effects.

12.2 Pharmacodynamics

Systemic Safety

The major adverse effects of inhaled beta₂-adrenergic agonists occur as a result of excessive activation of systemic beta-adrenergic receptors. The most common adverse effects in adults include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium, and increases in plasma glucose.

Changes in serum potassium were evaluated in COPD patients in double-blind phase 3 studies. In pooled data, at the recommended 5 mcg dose there was no clinically relevant change compared to placebo in serum potassium.

Electrophysiology

[REDACTED] (b) (4)

The effect of [REDACTED] (b) (4) RESPIMAT on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo- and active (moxifloxacin) controlled study at single doses of 10, 20, 30, and 50 mcg. Dose-dependent QTcF prolongation was observed. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was [REDACTED] (b) (4) following doses of 10, 20, 30 and 50 mcg, respectively.

The effect of 5 mcg and 10 mcg [REDACTED] (b) (4) RESPIMAT on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 772

patients in the 48-week, placebo-controlled phase 3 trials. There were no dose- or time-related trends or patterns observed for the magnitudes of mean changes in heart rate or premature beats. Shifts from baseline to the end of treatment in premature beats did not indicate meaningful differences between (b) (4) RESPIMAT 5 mcg, 10 mcg, and placebo.

12.3 Pharmacokinetics

Olodaterol showed linear pharmacokinetics (b) (4)

On repeated once daily inhalation steady-state of olodaterol plasma concentrations was achieved after 8 days, and the extent of exposure was increased up to 1.8-fold as compared to a single dose.

Absorption

Maximum plasma concentrations are generally reached within 10 to 20 minutes following drug inhalation. In healthy volunteers the absolute bioavailability of olodaterol following inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was below 1% when given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is mainly determined by lung absorption, while any swallowed portion of the dose only negligibly contributes to systemic exposure.

Distribution

Olodaterol exhibits multi-compartmental disposition kinetics after inhalation as well as after intravenous administration. The volume of distribution is high (1110 L), suggesting extensive distribution into tissue. *In vitro* binding of [¹⁴C] olodaterol to human plasma proteins is independent of concentration and is approximately 60%.

Metabolism

Olodaterol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety followed by conjugation. Of the six metabolites identified, only the unconjugated demethylation product binds to beta₂-receptors. This metabolite, however, is not detectable in plasma after chronic inhalation of the recommended therapeutic dose (b) (4)

Cytochrome P450 isozymes CYP2C9 and CYP2C8, with negligible contribution of CYP3A4, are involved in the O-demethylation of olodaterol, while uridine diphosphate glycosyl transferase isoforms UGT2B7, UGT1A1, 1A7, and 1A9 were shown to be involved in the formation of olodaterol glucuronides.

Elimination

Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min. The terminal half-life following intravenous administration is 22 hours. The terminal half-life following inhalation in contrast is about 45 hours, indicating that the latter is determined by absorption rather than by elimination processes. However, the effective halflife at daily dose of 5 µg calculated from Cmax from COPD patients is 7.5 hours.

Following intravenous administration of [¹⁴C]-labeled olodaterol, 38% of the radioactive dose was recovered in the urine and 53% was recovered in feces. The amount of unchanged olodaterol recovered in the urine after intravenous administration was 19%. Following oral administration, only 9% of the radioactivity was recovered in urine, while the major portion was recovered in feces (84%). More than 90% of the dose was excreted within 6 and 5 days following intravenous and oral administration, respectively. Following inhalation, excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5% to 7% of the dose.

Special Populations

A pharmacokinetic meta-analysis was performed utilizing data from 2 controlled clinical trials that included 405 patients with COPD and 296 patients with asthma who received treatment with (b) (4) RESPIMAT.

The analysis showed that no dose adjustment is necessary based on the effect of age, gender and weight on systemic exposure in COPD patients after inhalation of (b) (4) RESPIMAT.

Renal Impairment

(b) (4)
olodaterol levels were increased by approximately 40% in subjects with severe renal impairment.

Hepatic Impairment

Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

Drug-Drug Interactions

Drug-drug interaction studies were carried out using fluconazole as a model inhibitor of CYP 2C9 and ketoconazole as a potent P-gp (and CYP3A4, 2C8, 2C9) inhibitor.

Fluconazole: Co-administration of 400 mg fluconazole once a day for 14 days had no relevant effect on systemic exposure to olodaterol.

Ketoconazole: Co-administration of 400 mg ketoconazole once a day for 14 days increased olodaterol C_{max} by 66% and AUC₀₋₁ by 68%.

Tiotropium: Co-administration of tiotropium bromide, delivered as fixed-dose combination with olodaterol, for 21 days had no relevant effect on systemic exposure to olodaterol, and vice versa.

4. Appendixes

4.1 Pharmacometrics Review

Office of Clinical Pharmacology Pharmacometric Review

NDA Number	203018
Brand Name	STRIVERDI RESPIMAT
Drug Components	Olodaterol Respimat®
Pharmacometrics Reviewer	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Sponsor	Boehringer Ingelheim International GmbH

1 SUMMARY OF FINDINGS

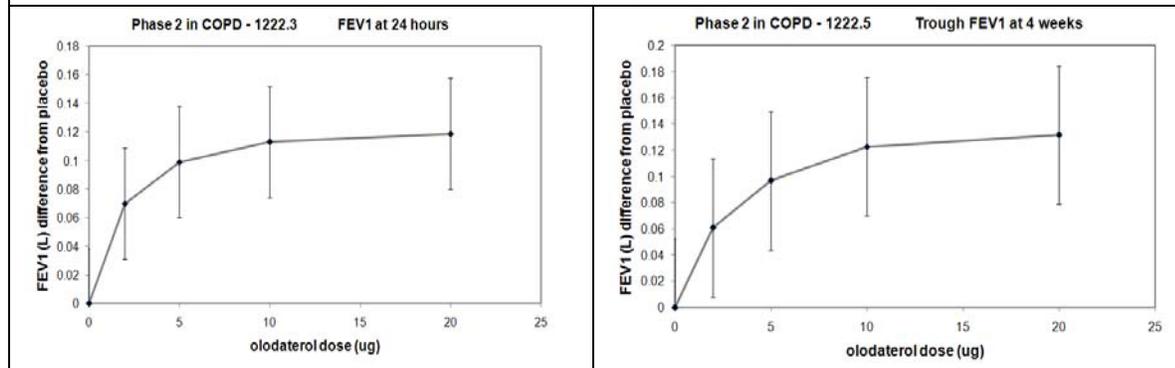
1.1 Key Review Questions

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

1.1.1 Has the dosing of olodaterol been adequately explored?

The dosing regimen of olodaterol has been adequately explored in Phase 2 trials. The doses explored in both COPD and asthma patients included 2 µg, 5 µg, 10 µg and 20 µg. Moreover, once-daily and twice daily dosing posology was investigated to determine the effectiveness of the different regimens. Based on the gathered Phase 2 data in both COPD and asthma patients, 5 µg and 10 µg doses, given once daily, were appropriate to use in the phase 3 trials. This conclusion is based on the fact that both doses yield a near maximal effect in lung function tests, without undue side effects (Figure 1).

Figure 1. Dose-Response Characterization in Phase 2 from COPD Trials 1222.3 and 1222.5



Placebo-corrected, Mean ± 95% CI

Of note, prior to initiation of the Phase 3 program, the decision to further evaluate olodaterol 5 µg and olodaterol 10 µg was accepted by the FDA (end-of-Phase II meeting). The results of the Phase 3 study reiterate the appropriateness of the dosing regimen chosen.

1.1.2 Are there any covariates that influence the systemic exposure of olodaterol?

Baseline FEV1, weight, height and age were found to be the most significant covariates that influence systemic olodaterol exposure. Specifically, using multivariate regression model estimates for olodaterol steady-state maximum concentrations (C_{max,ss}), a ~24% higher olodaterol maximum plasma concentration is predicted for a COPD patient of 42 kg weight compared to a typical COPD patient of 78 kg weight. A patient of 200 cm height is expected to have a ~40% higher systemic exposure than a typical patient of 170 cm. A patient with a pre-treatment baseline FEV1 of 0.46 L is expected to have a ~22% higher exposure than a typical patient with a pre-treatment baseline FEV1 of 1.12 L. For a patient of 43 years systemic exposure is predicted to be 15% higher than for a typical patient of 64 years. Calculations for a “worst case” condition, (a 43 year old COPD patient that is 200 cm tall, weighing 42 kg, having a low baseline FEV1, with moderate renal impairment) showed a 2-fold maximum increase of olodaterol exposure as compared to a typical COPD patient.

1.2 Recommendations

The Pharmacometrics reviewer finds the application acceptable.

1.2 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.

12.3 Pharmacokinetics

Special Populations

A pharmacokinetic meta-analysis

(b) (4)

showed that no dose adjustment is necessary based on the effect of age, gender and weight on systemic exposure in COPD patients after inhalation of STRIVERDI RESPIMAT.

2 PERTINENT REGULATORY BACKGROUND

Olodaterol is a selective β₂-adrenoceptor agonist developed for oral inhalation. The drug product is formulated for use with the RESPIMAT, a hand-held, pocket-sized, multi-dose, oral inhalation device. An IND application was submitted to the US FDA for olodaterol (IND 76,362) on January 26, 2007 and became effective on February 28, 2007. A number of interactions have

occurred between the Division of Pulmonary and Allergy Drug Products and the Sponsor regarding clinical, non-clinical and CMC aspects of the development of olodaterol.

The End-of-Phase 2 meeting was held on July 17, 2008 to discuss the design of the Phase 3 clinical trials, the adequacy of the proposed clinical pharmacology and non-clinical data packages, as well as the clinical safety exposure planned to be available at time of NDA submission. The FDA agreed with the Sponsor's proposal to evaluate olodaterol 5 µg once daily and olodaterol 10 µg once daily in the Phase 3 clinical program. However, the FDA recommended an evaluation of different dosing frequencies for olodaterol to support the proposed dosing regimen.

The clinical program for olodaterol comprised twelve Phase 1 trials (eleven in healthy volunteers, and one in patients with chronic obstructive pulmonary disease (COPD)), four Phase 2 trials in COPD, and ten Phase 3 trials in COPD. In addition, four Phase 2 trials in asthma were conducted. Overall, 4376 patients with COPD (47 patients in Phase 1; 488 patients in Phase 2; 3841 patients in Phase 3) and 731 patients with asthma (all in Phase 2) were included in the olodaterol clinical program. Olodaterol is proposed as a long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

The proposed recommended therapeutic dose of olodaterol is 5 µg (2 inhalations of 2.5 µg) once daily.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Overall Efficacy results

Efficacy of olodaterol 5 µg once daily and olodaterol 10 µg once daily in COPD was evaluated by 2 sets of replicate, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trials, each with a 48-week treatment duration. One set of replicate trials was placebo-controlled (1222.11, 1222.12), while the other set was placebo- and active-controlled (1222.13, 1222.14). Supportive evidence that characterizes the bronchodilating profile of olodaterol over a continuous 24-hr dosing interval is provided from 2 sets of replicate, randomized, double-blind, placebo- and active-controlled, cross-over trials with a 6 week treatment duration (1222.24, 1222.25; 1222.39, 1222.40).

In the pivotal trials (1222.11, 1222.12; 1222.13, 1222.14), treatment was continued up to 48 weeks to provide sufficient exposure for a rigorous evaluation of the long-term safety of olodaterol 5 µg once daily and olodaterol 10 µg once daily compared to placebo and active comparator. All Phase 3 trials included olodaterol 5 µg (two actuations of 2.5 µg) and olodaterol 10 µg (two actuations of 5 µg) administered once daily. In each of the pivotal studies, the co-primary lung function endpoints were FEV1 AUC0-3 and trough FEV1. The results for the pivotal Phase 3 olodaterol trials are shown in Figure 2 and Figure 3 below. Based on the

sponsors conclusions, for all trials, both olodaterol 5 µg once daily and olodaterol 10 µg once daily were significantly different compared to placebo at 12 weeks and 24 weeks. Further assessments of olodaterol’s efficacy from the pivotal trials are reviewed in the medical and statistical reviews (Dr. Robert Lim and Dr. Robert Abugov).

Figure 2. Difference from Placebo (mean ± 95%CI) in Trough FEV1 at 12 and 24 weeks for Pivotal Trials 1222.11, 1222.12, 1222.13, 1222.14

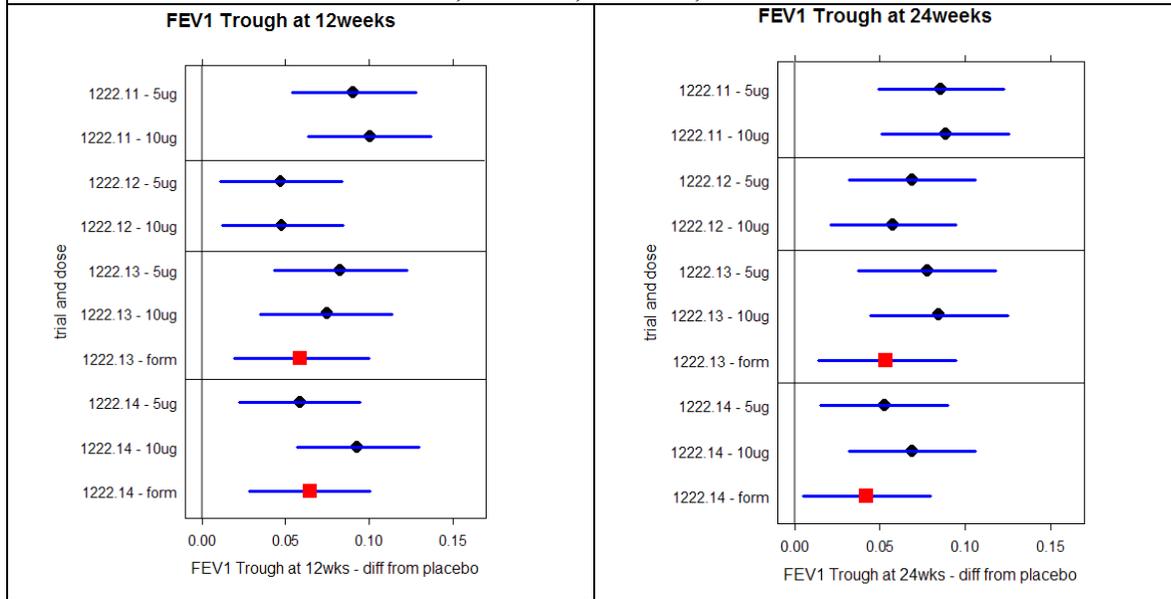
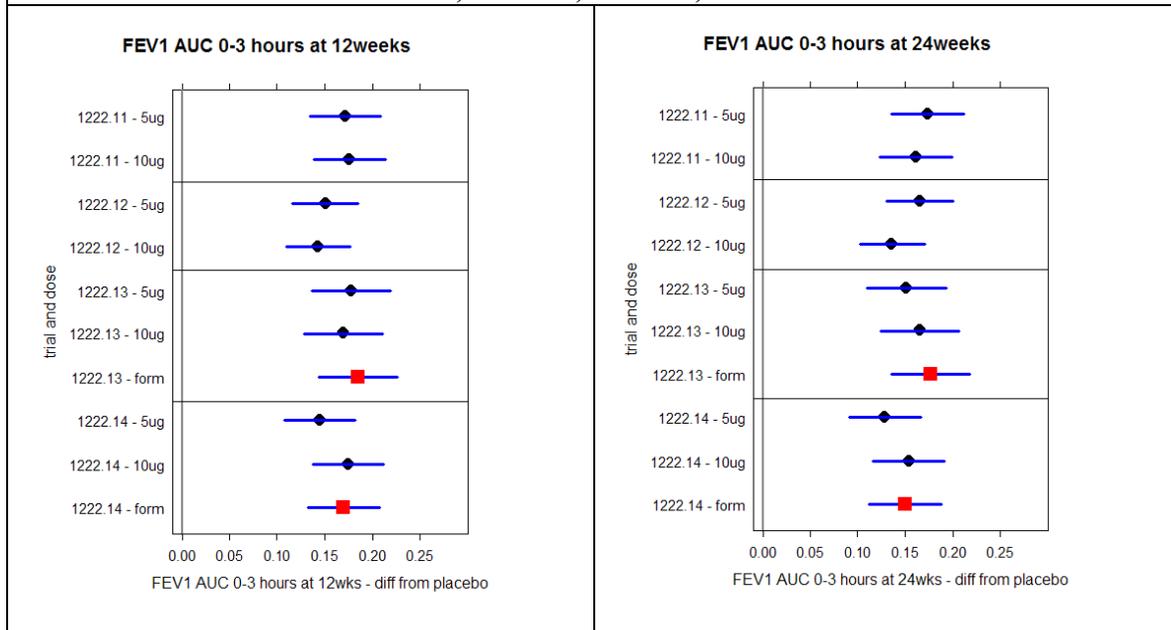


Figure 3. Difference from Placebo (mean ± 95%CI) in FEV1 AUC_{0-3hrs} at 12 and 24 weeks for Pivotal Trials 1222.11, 1222.12, 1222.13, 1222.14



3.2 Dose selection

In order to support the dosing selection for Phase 3 investigation, a total of seven Phase 2 trials were conducted in both COPD and asthma patients. Three Phase 2 trials in patients with COPD were conducted:

- 1222.3 Single-dose, placebo-controlled, cross-over study to provide clinical evidence that the bronchodilating effect of olodaterol was maintained up to 24 hours post-dose (n=36).
- 1222.5 Four-week parallel group, placebo-controlled study evaluating the dose response of olodaterol in patients with COPD. Selection of doses to be taken forward into Phase 3 program (n=405).
- 1222.26 Three-week cross-over study in patients with COPD. Evaluation of the 24-hour forced expiratory volume in one second (FEV1)-time profile of olodaterol when administered once daily vs. twice daily. To support once daily posology of olodaterol (n=47).

Four Phase 2 trials in patients with asthma were conducted:

- 1222.4 Single dose, placebo-controlled, cross-over study to provide clinical evidence that the broncho-protective effect of olodaterol against methacholine-induced bronchoconstriction maintained for at least 24 hours post-dose (n=29).
- 1222.6 Four-week, placebo-controlled, parallel group study evaluating the dose response of olodaterol in patients with asthma (n=296).
- 1222.27 Four-week, cross-over, active-control study in patients with persistent asthma. Further evidence that bronchodilating effect of olodaterol is maintained up to 24 hours post-dose after chronic, once daily administration. Evaluation of dose response of olodaterol in patients with asthma (n=198). Formoterol 12 µg BID used as active comparator.
- 1222.29 Three-week, cross-over, active-control study in patients with persistent asthma. Evaluation of the 24-hour FEV1-time profile of olodaterol when administered once daily (n=206). Formoterol 12 µg BID used as active comparator.

Specifically, the dose selection for the Phase 3 clinical development program for olodaterol was based on the efficacy (FEV1) dose-response relationship of olodaterol observed in studies 1222.3 and 1222.5. For both studies, a range of once-daily doses of 2 µg, 5 µg, 10 µg and 20 µg olodaterol were investigated. Based on the gathered efficacy and safety information from the Phase 2 studies, the sponsor selected both 5 µg and 10 µg, given once daily, as the dosage

regimens to be tested in the pivotal trials. The Pharmacometrics reviewer independently assesses the appropriateness of the regimen in Section 4.

3.3 Covariate analysis on Systemic Exposure of Olodaterol

3.3.1 Methods

The objective of this analysis was to explore the influence of intrinsic and extrinsic factors on olodaterol and olodaterol glucuronide systemic exposure. The data used for the analysis included PK and demographic information gathered from two Phase 2 dose ranging trials: Study 1222.5 in 405 COPD patients and Study 1222.6 in 296 asthma patients. The attributes of each trial are described in Table 1 below.

Table 1. Study Designs for Study 1222.5 and 1222.6		
<i>Study Number and Design</i>	<i>Doses (N)</i>	<i>PK Sampling Schedule</i>
1222.5: Randomized, double-blind, placebo-controlled, parallel group study in COPD patients. Olodaterol administered over 4 weeks.	Placebo, 2 µg, 5 µg, 10 µg and 20 µg (N = 79-86 per group)	On Days 1 and 29, serial PK blood samples were taken up to 3 and 6 hours after the inhalation, respectively. Additional pre-dose and 10 min post-dose blood samples were taken on Days 8 and 15 to confirm attainment of steady state.
1222.6: Randomized, double-blind, placebo-controlled, parallel group study in Asthma patients. Olodaterol administered over 4 weeks.	Placebo, 2 µg, 5 µg, 10 µg and 20 µg (N = 54-61 per group)	On Days 1 and 29, serial PK blood samples were taken up to 3 and 6 hours after the inhalation, respectively. Additional pre-dose and 10 min post-dose blood samples were taken on Days 8 and 15 to confirm attainment of steady state.

Exposure metrics (AUC, C_{max}) that were assessed include those listed in Table 2 and Table 3 for olodaterol and olodaterol glucuronide, respectively.

Table 2. Exposure metrics for Olodaterol PK Covariate Analysis

PK endpoint	Variable name	Description	Day
$C_{max, norm}$	Cmax_D	Dose-normalized maximum plasma concentration after a single dose	1
$C_{max, ss, norm}$	Cmax_ss_D	Dose-normalized maximum plasma concentration at steady state	29
$AUC_{0-1, norm}$	AUC0_1_D	Dose-normalized area under the plasma concentration-time curve from 0 up to 1 hour after a single dose	1
$AUC_{0-1, ss, norm}$	AUC0_1_ss_D	Dose-normalized area under the plasma concentration-time curve from 0 up to 1 hour at steady state	29
$AUC_{0-3, norm}$	AUC0_3_D	Dose-normalized area under the plasma concentration-time curve from 0 up to 3 hours after a single dose	1
$AUC_{0-3, ss, norm}$	AUC0_3_ss_D	Dose-normalized area under the plasma concentration-time curve from 0 up to 3 hours at steady state	29
$AUC_{0-6, ss, norm}$	AUC0_6_ss_D	Dose-normalized area under the plasma concentration-time curve from 0 up to 6 hours at steady state	29
$AUC_{0-24, ss, norm}$	AUC0_24_ss_D	Dose-normalized area under the plasma concentration-time curve from 0 up to 24 hours at steady state	29
$AUC_{0-tz, norm}$	AUClast_D	Dose-normalized area under the plasma concentration-time curve from 0 up to time of the last quantifiable plasma concentration after a single dose	1
$AUC_{0-tz, ss, norm}$	AUClast_ss_D	Dose-normalized area under the plasma concentration-time curve from 0 up to time of the last quantifiable plasma concentration at steady state	29

Source: 1222-9956pk-metaanalysis-report.pdf, pg 21

Table 3. Exposure metrics for Olodaterol Glucuronide PK Covariate Analysis

PK endpoint	Variable name	Description	Day
$C_{max, ss}$	Cmax_ss	Maximum plasma concentration at steady state	29
$AUC_{0-6, ss}$	AUC0_6_ss	Area under the plasma concentration-time curve from 0 up to 6 hours at steady state	29
$AUC_{0-tz, ss}$	AUClast_ss	Area under the plasma concentration-time curve from 0 up to time of the last quantifiable plasma concentration at steady state	29

Source: 1222-9956pk-metaanalysis-report.pdf, pg 22

Covariates listed in Table 4 were investigated for potential influence on olodaterol exposure. Moreover, the impact of UGT polymorphisms (UGT1A1 *28/36/37, *60, *93, UGT1A7 *2, *3, *4, *12, UGT1A9 *3, UGT2B7 *2) was investigated as potential covariates.

Table 4. Covariates analyzed for potential influence on systemic exposure

Covariate	Unit / Categories	Comments
Indication (syn. Disease)	COPD, asthma	---
Dose of olodaterol administered	µg	5, 10, 20 µg Analysis was done on logarithm to base 2
Gender	Male, Female	To make interpretation of regression coefficient easier, original variable is recoded to Male=0, Female=1
Age at screening	years	---
Weight at screening	kg	---
Height	cm	---
Creatinine clearance	mL/min	---
Smoking history as captured at screening	Non-smoker, ex-smoker, current smoker	Implemented through the dummy variables SMOK1 and SMOK2: Non-smoker (SMOK1=0, SMOK2=1); ex-smoker (SMOK1=0, SMOK2=0); current smoker (SMOK1=1, SMOK2=0)
Alcohol history as captured at screening	Non-drinker, normal consumption, excessive consumption	For the general covariate analysis two patients with excessive consumption were dropped
Pre-treatment baseline FEV ₁ (syn. 'trough FEV ₁ on day 1')	L	Mean of the FEV ₁ values measured 1 hour and 10 minutes prior to drug administration on the first day of study medication

Source: 1222-9956pk-metaanalysis-report.pdf, pg 23

Any covariates which were highly correlated were not included together in the final statistical model. The relationship between the covariates and the PK parameters was explored using multiple linear regression. Multivariate linear regression analyses were performed for each PK parameter of olodaterol and olodaterol glucuronide based on the individual datasets (1222.5, 1222.6) and the combined analysis dataset. Both the PK parameters and the covariate for dose were analyzed on a logarithmic scale. For the PK parameters the natural logarithm was used. For dose, logarithm to base 2 was used so that regression coefficients can be interpreted as doubling doses of olodaterol. The variable selection was done using a stepwise approach, allowing for both addition and removal of variables from the model based on a pre-defined significance level. The alpha level for both addition and removal of variables was set to 0.10.

3.3.2 Results

3.3.2.1 Olodaterol

Relevant patient characteristics of all patients providing a dose-normalized maximum olodaterol plasma concentration after single dose ($C_{max, norm}$) or at steady-state ($C_{max, ss, norm}$) to the general covariate analysis are summarized in Table 5.

Patient characteristics in the two individual trials 1222.5 and 1222.6 were comparable with regard to all parameters except for “indication” (COPD or asthma) and the indication-related variables ‘smoking’, ‘age’ and ‘pre-treatment baseline FEV1’.

Table 5. Patient characteristics of patients providing dose normalized C_{max} (after single dose and steady state)

		Single dose PK ($C_{max, norm}$)			Steady-state PK ($C_{max, ss, norm}$)		
		1222.5	1222.6	Combined	1222.5	1222.6	Combined
Total no. of patients [N]		179	123	302	189	140	329
Gender [N, (%)]	Male	111 (62.0)	58 (47.2)	169 (56.0)	120 (63.5)	69 (49.3)	189 (57.4)
	Female	68 (38.0)	65 (52.8)	133 (44.0)	69 (36.5)	71 (50.7)	140 (42.6)
Indication [N, (%)]	COPD	179 (100)	0	179 (59.3)	189 (100)	0	189 (57.4)
	Asthma	0	123 (100)	123 (40.7)	0	140 (100)	140 (42.6)
Olodaterol dose [μ g]	Mean (SD)	12.74 (6.07)	13.86 (6.07)	13.20 (6.08)	12.59 (6.14)	12.61 (6.36)	12.60 (6.22)
	Median (Range)	10.0 (5-20)	10.0 (5-20)	10.0 (5-20)	10.0 (5-20)	10.0 (5-20)	10.0 (5-20)
Smoking [N, (%)]	Never smoked	0	92 (74.8)	92 (30.5)	0	98 (70.0)	98 (29.8)
	Ex-smoker	91 (50.8)	27 (22.0)	118 (39.1)	97 (51.3)	37 (26.4)	134 (40.7)
	Currently smokes	88 (49.2)	4 (3.3)	92 (30.5)	92 (48.7)	5 (3.6)	97 (29.5)
Alcohol history [N, (%)]	Non-drinker	75 (41.9)	61 (49.6)	136 (45.0)	74 (39.2)	69 (49.3)	143 (43.5)
	Average consumption	104 (58.1)	62 (50.4)	166 (55.0)	115 (60.8)	71 (50.7)	186 (56.5)
Race [N, (%)]	White	167 (93.3)	105 (85.4)	272 (90.1)	174 (92.1)	121 (86.4)	295 (89.7)
	Black	11 (6.1)	13 (10.6)	24 (7.9)	14 (7.4)	13 (9.3)	27 (8.2)
	Asian	1 (0.6)	5 (4.1)	6 (2.0)	1 (0.5)	6 (4.3)	7 (2.1)
Age [y]	Mean (SD)	63.75 (8.32)	45.18 (13.30)	56.19 (14.01)	63.66 (8.41)	46.74 (13.73)	56.46 (13.81)
	Median (Range)	64.0 (43-86)	45.0 (18-79)	58.5 (18-86)	64.0 (43-86)	47.5 (18-79)	59.0 (18-86)

		Single dose PK ($C_{max,ss,dose}$)			Steady-state PK ($C_{max,ss,dose}$)		
		1222.5	1222.6	Combined	1222.5	1222.6	Combined
Weight [kg]	Mean (SD)	78.83 (17.07)	78.37 (17.29)	78.64 (17.14)	80.28 (17.67)	77.04 (16.69)	78.90 (17.31)
	Median (Range)	76.00 (42.0-142.0)	78.00 (43.0-135.2)	76.20 (42.0-142.0)	78.00 (42.0-157.0)	76.40 (43.0-135.2)	77.30 (42.0-157.0)
Height [cm]	Mean (SD)	169.66 (9.17)	168.46 (9.08)	169.17 (9.14)	169.50 (8.99)	168.28 (9.24)	168.98 (9.10)
	Median (Range)	170.0 (150-200)	169.0 (147-189)	169.0 (147-200)	170.0 (150-200)	168.5 (147-189)	169.0 (147-200)
Creatinine clearance [mL/min]	Mean (SD)	82.41 (26.04)	106.50 (29.92)	92.17 (30.06)	85.03 (30.28)	101.37 (28.65)	91.92 (30.65)
	Median (Range)	78.815 (39.07-156.80)	105.316 (53.92-211.71)	86.660 (39.07-211.71)	80.197 (39.07-270.98)	98.699 (49.78-201.76)	86.660 (39.07-270.98)
Pre-treatment baseline FEV ₁ [L]	Mean (SD)	1.27 (0.51)	2.35 (0.61)	1.71 (0.77)	1.25 (0.49)	2.31 (0.64)	1.70 (0.77)
	Median (Range)	1.120 (0.46-3.05)	2.320 (1.05-3.82)	1.573 (0.46-3.82)	1.120 (0.46-3.05)	2.245 (1.05-3.82)	1.555 (0.46-3.82)

Source: 1222-9956pk-metaanalysis-report.pdf, pg 36 and 37

A summary of regression coefficients is given in Table 6. The following covariates remained at least once in a model for olodaterol PK parameters during multivariate linear regression analysis: olodaterol dose, pre-treatment baseline FEV₁, weight, height, alcohol history, smoking status, age, and creatinine clearance. Gender and disease were not significant covariates for any olodaterol PK parameter.

Table 6. Regression coefficients for olodaterol

	Intercept	Log2 Dose	FEV ₁	Weight	Height	Age	SMOK1	Alcohol hist.	CrCL
Study 1222.5 analysis dataset (COPD patients)									
C _{max, norm}	-0.12860	---	-0.29215	---	---	---	---	---	---
AUC _{0-1, norm}	2.93613	-0.25755	-0.20825	---	-0.01397	---	---	-0.15775	---
AUC _{0-3, norm}	5.15050	-0.39391	---	---	-0.02047	---	---	---	---
AUC _{0-tz, norm}	0.15275	0.23837	-0.29156	-0.00961	---	---	-0.28583	-0.24479	---
C _{max, ss, norm}	-1.31857	---	-0.28190	-0.00639	0.01105	---	---	---	---
AUC _{0-1, ss, norm}	-0.28764	---	-0.20785	---	---	---	---	---	---
AUC _{0-3, ss, norm}	1.34943	-0.17597	-0.22284	---	---	---	---	---	---
AUC _{0-6, ss, norm}	2.80569	-0.31987	-0.16597	-0.00507	---	---	---	---	---
AUC _{0-24, ss, norm}	4.30746	-0.40549	---	-0.00751	---	---	---	---	---
AUC _{0-tz, ss, norm}	0.01742	0.33991	---	-0.00834	---	---	---	---	---
Combined analysis dataset (studies 1222.5 and 1222.6)									
C _{max, norm}	0.22552	-0.13387	-0.20776	---	---	---	---	---	---
AUC _{0-1, norm}	0.53210	-0.26917	-0.22493	---	---	---	---	---	---
AUC _{0-3, norm}	1.71910	-0.34875	-0.15934	---	---	---	---	---	---
AUC _{0-tz, norm}	-0.65093	0.19713	-0.25258	---	---	---	-0.25959	---	---
C _{max, ss, norm}	-1.06755	---	-0.29519	-0.00546	0.01171	-0.00684	---	---	---
AUC _{0-1, ss, norm}	-0.67142	-0.09394	-0.27683	-0.00475	0.00981	-0.00758	---	---	---
AUC _{0-3, ss, norm}	1.96499	-0.16842	-0.19839	---	---	-0.00786	---	---	-0.00218
AUC _{0-6, ss, norm}	2.37494	-0.25360	-0.10730	-0.00358	---	---	---	---	---
AUC _{0-24, ss, norm}	3.74772	-0.33742	---	---	---	---	---	---	-0.00351
AUC _{0-tz, ss, norm}	0.21659	0.28843	---	-0.00890	---	---	---	---	---
Study 1222.6 analysis dataset (asthma patients)									
C _{max, norm}	0.13177	-0.24509	---	---	---	---	---	---	---
AUC _{0-1, norm}	0.28112	-0.34181	---	---	---	---	---	---	---
AUC _{0-3, norm}	1.38453	-0.37717	---	---	---	---	---	0.17382	---
AUC _{0-tz, norm}	---	---	---	---	---	---	---	---	---
C _{max, ss, norm}	-0.25956	---	---	-0.00494	---	---	---	0.19011	---
AUC _{0-1, ss, norm}	-0.38953	---	---	-0.00560	---	---	---	0.18615	---
AUC _{0-3, ss, norm}	1.13938	-0.17211	-0.13121	---	---	---	---	0.18072	---
AUC _{0-6, ss, norm}	1.95067	-0.21552	-0.13849	---	---	---	---	0.18107	---
AUC _{0-24, ss, norm}	3.07483	-0.18720	-0.17635	---	---	---	---	0.19005	---
AUC _{0-tz, ss, norm}	0.44817	0.22363	---	-0.00943	---	---	---	---	---

Source: 1222-9956pk-metaanalysis-report.pdf, pg 40

With regard to dose, most of the dose-normalized PK parameters were found to be lower with increasing dose. In the combined analysis dataset, 122-133% of the initial value was predicted for AUC_{0-tz, norm} and AUC_{0-tz, ss, norm}, with doubling the dose, and 71-91% for the other dose-normalized PK parameters.

Pre-treatment baseline FEV₁ (was selected for most of the olodaterol PK parameters during regression analysis on the combined analysis dataset. Regression coefficients indicated higher systemic exposure with lower FEV₁ values. In the combined analysis dataset 74-90% of the initial PK parameter value was predicted.

Weight was selected as a significant covariate mostly on steady-state PK parameters during regression analysis. Estimated regression coefficients always indicated a negative relationship of systemic exposure with weight. However, the absolute predicted effect of weight remained relatively small as the final models of all affected PK parameters predicted only a 4% to 9% decrease in PK parameter values per 10 kilograms increase in weight. For the combined analysis dataset, C_{max, ss, norm} and AUC_{0-1, ss, norm} were found to be 12% and 10% higher, respectively, with an increase in height by 10 centimeters.

Based on the combined dataset, alcohol history not identified as a significant predictor of any PK parameter by regression analysis. The observed effects of alcohol history were inconsistent between studies and the predicted magnitude of the effect was small.

Smoking status was identified as a significant covariate only for $AUC_{0-tz, norm}$ based on the COPD dataset and the combined analysis dataset. A mild effect was predicted, with 25% and 23% lower $AUC_{0-tz, norm}$, in current smokers compared to non- and ex-smokers.

Age was detected as a significant covariate for $AUC_{0-1, ss, norm}$ and $C_{max, ss, norm}$ in the regression analysis based on the combined analysis dataset, where the largest age range was available. The predicted effect of age on these two PK parameters was modest with 7% decrease in PK parameter values per 10 years of age.

Creatinine clearance was only detected as a statistically significant covariate for $AUC_{0-24, ss, norm}$ and $AUC_{0-3, ss, norm}$ in the regression analysis of the combined analysis dataset, and an increase of 4% and 2%, respectively, was predicted per 10 mL/min decrease in creatinine clearance.

No evidence for a pronounced effect of UGT polymorphisms on the olodaterol systemic exposure parameters was noted.

3.3.2.2. Olodaterol glucuronide

For olodaterol glucuronide, the regression coefficients obtained from the multivariate analysis is included in Table 7 below.

Table 7. Regression coefficients for olodaterol glucuronide (non dose-normalized exposure metrics)								
	Intercept	Log2 dose	Pre-treatment baseline FEV ₁	Weight	Age	SMOK2	Gender	CrCL
Study 1222.5 analysis dataset (COPD patients)								
$C_{max, ss}$	0.81759	0.41105	-0.23052	---	---	---	---	---
$AUC_{0-6, ss}$	1.93410	0.43671	---	---	---	---	---	---
$AUC_{0-tz, ss}$	1.76765	0.54324	-0.24124	---	---	---	---	---
Combined analysis dataset								
$C_{max, ss}$	0.72392	0.40554	-0.13654	---	---	---	---	---
$AUC_{0-6, ss}$	3.47971	0.38874	-0.27707	---	-0.01222	---	---	-0.00332
$AUC_{0-tz, ss}$	2.88279	0.50769	-0.23907	0.00687	-0.01491	---	---	-0.00717
Study 1222.6 analysis dataset (asthma patients)								
$C_{max, ss}$	1.29452	0.38942	---	---	-0.00612	---	---	-0.00527
$AUC_{0-6, ss}$	2.33974	0.29862	---	---	---	0.21274	0.36145	-0.00457
$AUC_{0-tz, ss}$	2.60991	0.47939	---	---	-0.00888	---	---	-0.00662

Source: 1222-9956pk-metaanalysis-report.pdf, pg 45

Non-dose normalized PK parameters of olodaterol glucuronide were found to increase with dose during regression analysis. When doubling the dose, PK parameters increased by 47- 66% based on the combined analysis dataset.

Pre-treatment baseline FEV₁ was selected as significant covariate for most of the olodaterol glucuronide PK parameters during regression analysis on the COPD dataset and based on the combined analysis dataset. In the combined analysis dataset, 76-87% of the initial PK parameter value was predicted. Thus, the effect of pre-treatment baseline FEV₁ on systemic exposure of olodaterol glucuronide is the same as observed for olodaterol and appears modest.

In the combined dataset a negative correlation was seen between age and some PK parameters evaluated. Per 10 years increase in age systemic exposure was predicted to be 12-14% lower based on the combined dataset.

Creatinine clearance was detected as a significant covariate for most PK parameters in the regression analysis of the combined analysis dataset. A 3-7% increase in systemic exposure to olodaterol glucuronide was predicted per 10 mL/min decrease in creatinine clearance.

Weight was only detected once as a significant covariate for AUC_{0-tz,ss} in the regression analysis of the combined analysis dataset, and 7% higher values were predicted per 10 kg increase in weight.

Smoking and gender were detected as significant covariates for AUC_{0-6,ss} during regression analysis of the asthma dataset only. Based on the model estimates, a 24% higher AUC_{0-6,ss} value is predicted in non-smokers compared to ex-smokers and a 44% higher AUC_{0-6,ss} value is predicted in females compared to males.

No evidence for a pronounced effect of UGT polymorphisms on olodaterol glucuronide systemic exposure parameters was noted.

3.3.2.3 Impact of Individual Covariates

The impact of the individual covariates (i.e., height, weight, pre-treatment baseline FEV₁ and age on maximum plasma concentrations for COPD patients after chronic inhalation of olodaterol was assessed by comparing predicted C_{max,ss,norm} values of “typical” and “extreme” COPD patients. The characteristics of the COPD patients selected for prediction of olodaterol exposure are included in Table 8. A comparison of the estimated “typical” and “worst case” C_{max,ss,norm} and AUC_{0-24,ss,norm} values is given in Table 9.

Table 8. COPD patient characteristics selected for prediction of systemic exposure parameters.

	Extreme value ¹	Median value ²
Age [y]	43	64
Height [cm]	200*	170
Weight [kg]	42*	78
Creatinine clearance [mL/min]	39	80
Pre-treatment baseline FEV ₁ [L]	0.46	1.12

- 1 maximum value for height and minimum values for age, weight, creatinine clearance and pre-treatment baseline FEV₁ of COPD patients that provided C_{max,ss, norm} values for olodaterol
 2 median values of COPD patients that provided C_{max,ss, norm} values for olodaterol
 * Since a patient of 200 cm height and 42 kg body weight is not plausible, “worst case” calculations were performed with 42 kg/163 cm and 63.6 kg/200 cm. Both variants represent the minimum observed BMI of 15.9 kg/m².

Source: 1222-9956pk-metaanalysis-report.pdf, pg 47

Table 9. Comparison of predicted “typical” and “worst case” dose-normalized olodaterol PK parameters.

PK Parameter	Typical	Worst case (42kg/163cm)	Ratio worst/typical	Worst case (63.6kg/200cm)	Ratio worst/typical
Calculation A (using model estimates from COPD data set)					
C _{max,ss, norm} [pg/mL/μg]	0.776	1.09	1.40	1.43	1.84
AUC _{0-24,ss, norm} [pg·h/mL/μg]	16.1	21.1	1.31	18.0	1.12
Calculation B (using model estimates from combined data set)					
C _{max,ss, norm} [pg/mL/μg]	0.762	1.20	1.57	1.64	2.16
AUC _{0-24,ss, norm} [pg·h/mL/μg]	14.6	16.9	1.15	16.9	1.15

Source: 1222-9956pk-metaanalysis-report.pdf, pg 48

Using the model estimates for C_{max,ss, norm} of olodaterol derived from the analysis of the COPD patient data set (for ‘weight’, ‘height’, ‘pre-treatment baseline FEV₁’) and the combined data set (additionally for ‘age’), a 22-26% higher olodaterol maximum plasma concentration is predicted for a COPD patient of 42 kg weight compared to a typical COPD patient of 78 kg weight. A patient of 200 cm height is expected to have a 39-42% higher C_{max,ss, norm} value than a typical patient of 170 cm. A patient with a pre-treatment baseline FEV₁ of 0.46 L is expected to have a 20-22% higher C_{max,ss, norm} value than a typical patient with a pre-treatment baseline FEV₁ of 1.12 L. For a patient of 43 years C_{max,ss, norm} is predicted to be 15% higher than for a typical patient of 64 years. Calculations for worst case conditions, i.e. plausible combinations of the extremes for weight, height, lung function and age, revealed a maximum increase of C_{max,ss, norm} by a factor of 1.8 to 2.2 as compared to a typical COPD patient.

3.3.3 Sponsor's Conclusions

There was no pronounced effect of any of the investigated covariates on olodaterol or olodaterol glucuronide systemic exposure in COPD patients. A 'worst case' patient after chronic inhalation of olodaterol is predicted to have about 2-fold higher plasma concentrations than an average COPD patient.

***Reviewer's comments:** A rigorous exploratory analysis of the covariate effects on olodaterol exposure was performed using multivariate regression. The sponsor evaluated several exposure metrics to guide the selection of important covariates and made appropriate interpretation of the resulting analyses. Residual diagnostics based on the sponsor's analyses showed that the model fitted the data reasonably well. The reviewer reproduced a similar analysis, specifically focusing on three exposure metrics to select the important covariates, $C_{max, norm}$, $C_{max,ss, norm}$ and $AUC_{0-24,ss, norm}$ for the combined dataset (COPD and asthma patients). With regard to the covariates chosen, the analysis concluded similar results with similar parameter estimates. Therefore, the reviewer concludes the analysis, and the corresponding conclusions and interpretations, presented by the sponsor is reasonable.*

4 REVIEWER'S ANALYSIS

4.1 Objectives

Analysis objectives are:

1. To determine if an adequate dosing regimen of olodaterol was explored.
2. To determine if there are any covariates that influences the systemic exposure of olodaterol.

4.2 Methods

Efficacy results from the Phase 2 dose-ranging studies were evaluated for the assessment of olodaterol dosing. Graphical analysis of dose-response curves were evaluated using the primary endpoint measures for the Phase 2 trial results (for both asthma and COPD patients).

The reviewer produced a similar analysis using the same multivariate regression technique as the sponsor. Prior to multivariate regression, univariate graphical analysis was performed to evaluate trends in the covariate-exposure relationships. Specifically, the following dose-normalized exposure parameters were assessed for the covariate analysis: $C_{max, norm}$, $C_{max,ss, norm}$, and $AUC_{0-24,ss, norm}$. The same covariates and similar criteria for covariate selection was chosen for the backward and forward stepwise covariate modeling (p-value <0.1 deemed to be a significant covariate). Regression parameters were compared to the sponsor's results.

4.2.1 Data Sets

Data sets used are summarized in Table 10.

Table 10. Analysis Data Sets

Study Number(s)	Name	Link to EDR
1222.3, 1222.5, 1222.26, 1222.4, 1222.6, 1222.27, 1222.29	pftsum.xpt (for each trial)	\\cdsesub1\evsprod\NDA203108\0013\m5\datasets\

4.2.2. Software

TIBCO Spotfire S-PLUS 8.0 was used for data organization, as well as graphical and statistical analysis.

4.3 Results

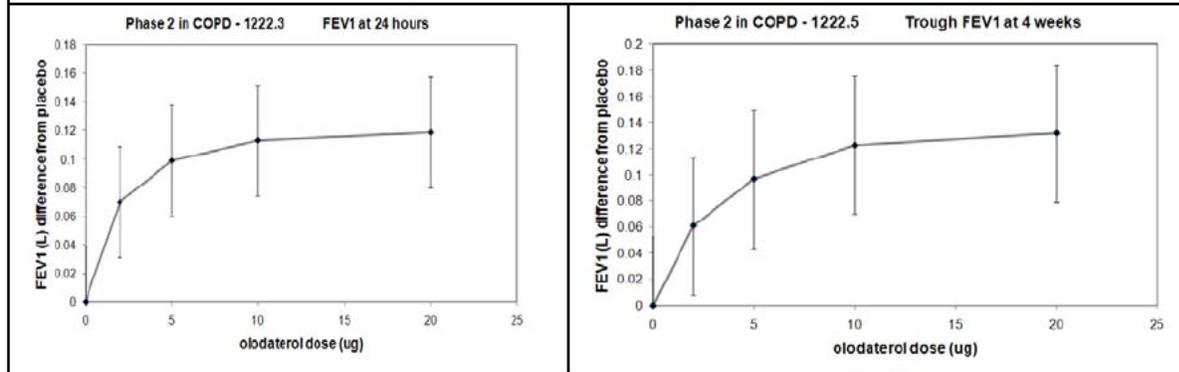
4.3.1. Adequacy of Olodaterol Dosing

For the Phase 2 studies, a range of once-daily doses of 2 µg, 5 µg, 10 µg and 20 µg olodaterol were investigated. Effects of olodaterol on systemic pharmacodynamic parameters that are known to be sensitive to β₂- agonists were used to support an appropriate dose selection for Phase 3. Figure 4 depicts the placebo-corrected dose-response curves for the dose ranging trials in COPD patients. For both trials, all doses resulted in a statistically different improvement over placebo (all p-values <0.01).

In trial 1222.3 (single-dose olodaterol), FEV₁ at 24 hours showed increasing improvement with increasing dose. Near maximal effect was observed with a dose of 10 µg, which showed similar response to the highest dose tested of 20 µg. The 2 µg dose yielded a response on the steepest portion of the dose-response curve. The relative efficacy of olodaterol 5 µg was between the response with 2 µg and 10 µg, such that the position of olodaterol 5 µg on the dose-response curve can only be characterized as intermediate between suboptimal (2 µg) and plateauing in efficacy (10 or 20 µg). The FEV₁ vs. time profile in Figure 5 shows that the FEV₁ 24-hour effect is maintained over placebo, in a dose-response fashion (i.e., increasing FEV₁ 24-hour effect with increasing dose).

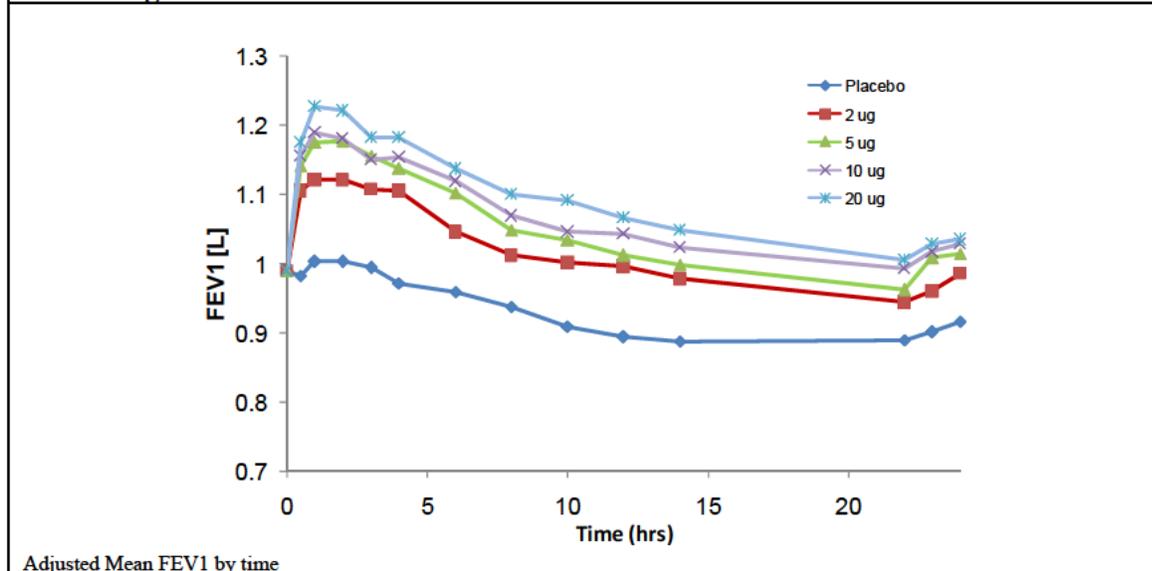
In trial 1222.5 (4-week daily dosing of olodaterol), Trough FEV₁ at 4 weeks showed a similar dose-response relationship to that found in trial 1222.3 (i.e., increasing improvement with increasing dose). Near maximal effect was observed with a dose of 10 µg, which showed similar response to the highest dose tested of 20 µg. The 2 µg dose yielded a response on the steepest portion of the dose-response curve.

Figure 4. Dose-Response Characterization in Phase 2 from COPD Trials 1222.3 and 1222.5



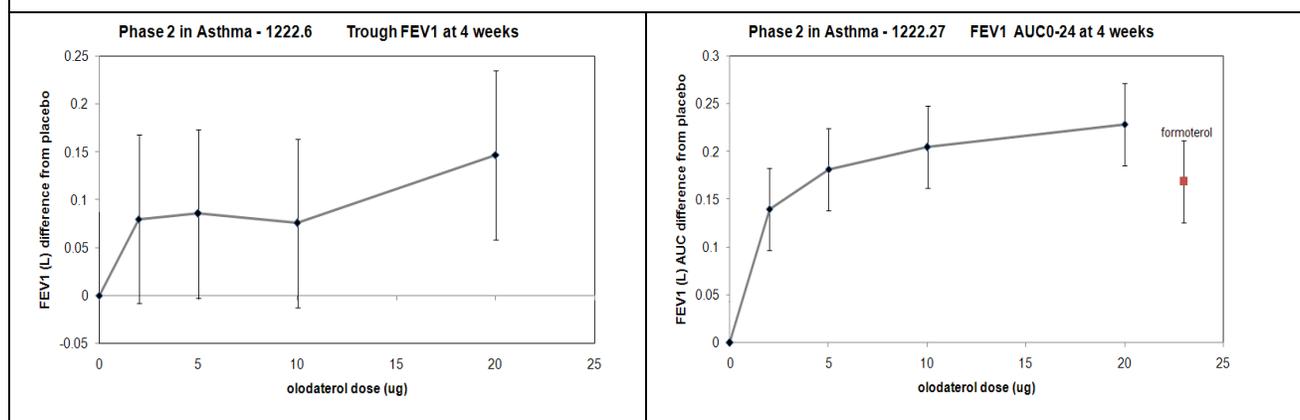
Placebo-corrected, Mean \pm 95% CI

Figure 5. FEV1 vs. time for the different doses in COPD Trial 1222.3



The Phase 2 studies in asthma provided additional information on the dose-response characteristics of olodaterol in a bronchodilator responsive population (see Figure 6).

Figure 6. Dose-Response Characterization in Phase 2 from Asthma Trials 1222.6 and 1222.27



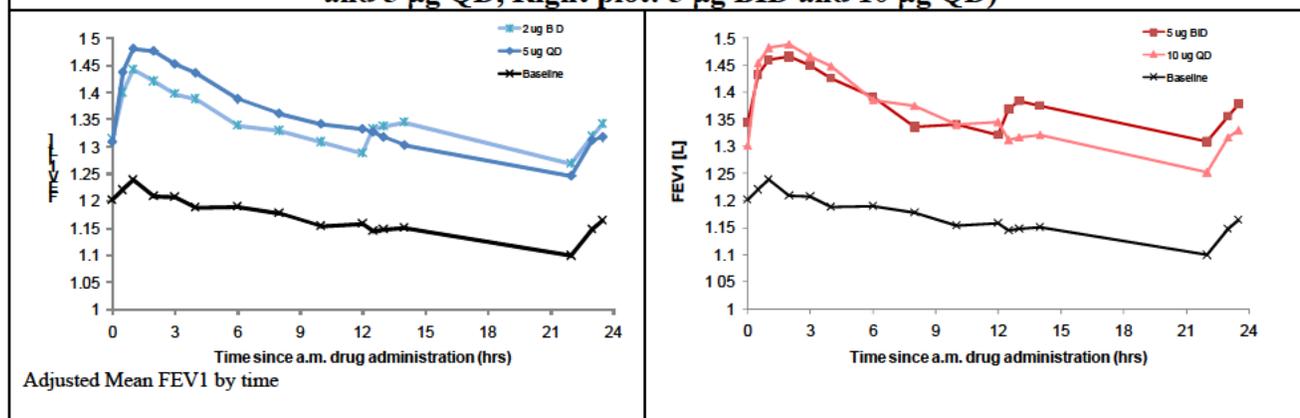
Placebo-corrected, Mean \pm 95% CI

In the 4-week once daily dosing studies (1222.6, 1222.27), there was a larger dose-response range compared to the studies in COPD. In the asthma trials, there is evidence of an incremental benefit in bronchodilation with olodaterol 20 μg compared to olodaterol 10 μg . In 1222.27, the average bronchodilatory effect over 24 hrs for olodaterol 5 μg once daily was comparable to formoterol 12 μg twice daily. Of note, in the first COPD study (1222.3), which also included patients with an increased responsiveness to β_2 -agonists, there was also evidence of a slight incremental benefit with olodaterol 20 μg compared to olodaterol 10 μg . Importantly, all Phase 2 studies (COPD and asthma) provided consistent evidence that olodaterol 2 μg is on the steep part of the dose-response curve.

In trial 1222.26, lung function in patients with COPD was compared after once daily and twice daily dosing of olodaterol. A number of once daily doses (olodaterol 5 μg , olodaterol 10 μg) and twice daily doses (olodaterol 2 μg , olodaterol 5 μg) of olodaterol were included. A lower dose of 2 μg twice daily was included, since at the time of the study the 2.5 μg dose was not available.

All olodaterol dose regimens showed a significant increase in FEV1 AUC0-12 and FEV1 AUC12-24 compared with baseline. The FEV1-time profiles for olodaterol 10 μg QD and olodaterol 5 μg QD were almost identical, with no differences in FEV1 AUC0-12 and FEV1 AUC12-24 responses. This suggests that a near maximal effect may be observed at the 5 μg QD dose. FEV1 AUC0-12 and FEV1 AUC12-24 responses for olodaterol 5 μg BID were significantly increased compared with olodaterol 2 μg BID.

Figure 7. FEV1 vs. time in COPD Trials 1222.26 QD vs. BID assessment (Left plot: 2 µg BID and 5 µg QD, Right plot: 5 µg BID and 10 µg QD)



FEV1 AUC₀₋₁₂ response for olodaterol 5 µg QD was significantly increased compared with olodaterol 2 µg BID, but there was no major difference in FEV1 AUC₁₂₋₂₄ response between olodaterol 5 µg QD and olodaterol 2 µg BID. Compared to 5 µg QD, 10 µg QD did not show any increased efficacy. A second dose of 5 µg in the evening provided additional bronchodilation compared with both 5 µg QD and 10 µg QD.

Based on the gathered Phase 2 data in both COPD and asthma patients, 5 µg and 10 µg doses, given once daily, were appropriate to use in the phase 3 trials. This conclusion is based on the fact that both doses yield a near maximal effect in lung function tests, with no undue side effects. With regard to the dosing posology, the 24 hr bronchodilatory profile of olodaterol 5 µg once daily was superior to the profile of olodaterol 2 µg twice daily, and olodaterol 10 µg once daily did not induce a greater FEV1 response than olodaterol 5 µg once daily.

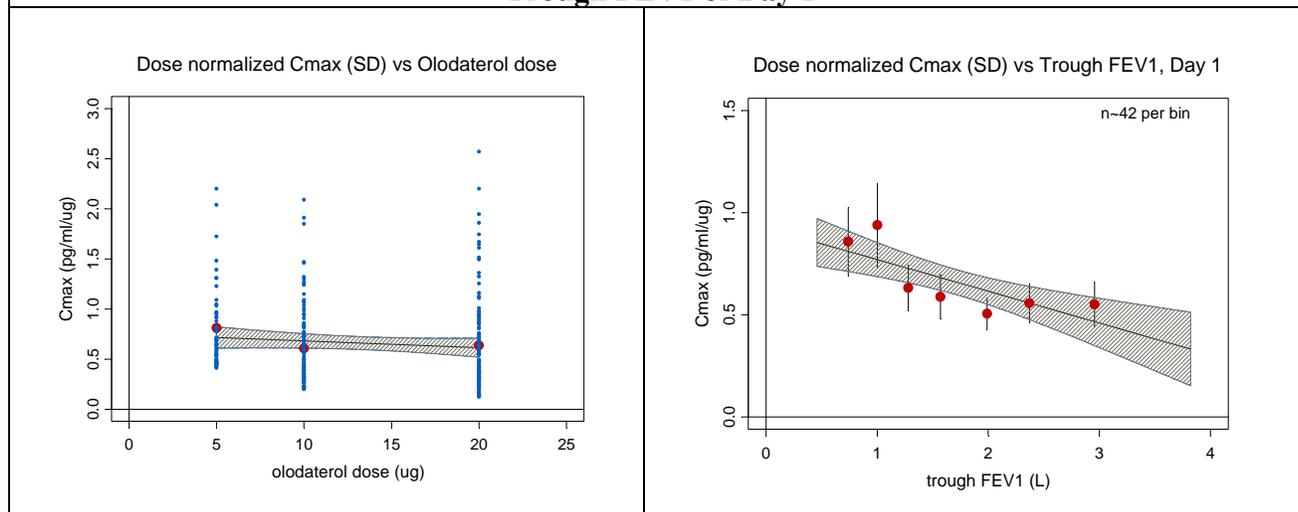
Of note, prior to initiation of the Phase 3 program, the decision to further evaluate olodaterol 5 µg and olodaterol 10 µg was accepted by the FDA (end-of-Phase II meeting). The results of the Phase 3 study reiterate the appropriateness of the dosing regimen chosen.

4.3.2 Covariate analysis for Olodaterol Systemic Exposure

Univariate assessment of the combined asthma and COPD data yielded trends in the covariate-exposure analysis. Specifically, the following dose-normalized exposure parameters were assessed for the covariate analysis: $C_{max, norm}$, $C_{max, ss, norm}$, and $AUC_{0-24, ss, norm}$. Of note, there were no significant pharmacogenomic covariates that influenced olodaterol exposure.

With regard to $C_{max, norm}$ (dose normalized C_{max} after single dose), a significant trend was not observed with olodaterol dose. The only significant covariate observed was trough FEV1 on day 1 (p-value <0.001). For every 1 liter increase in trough FEV1, dose normalized C_{max} decreases -0.155 pg/ml/µg. Plots depicting the covariate-exposure relationships are in Figure 8 below.

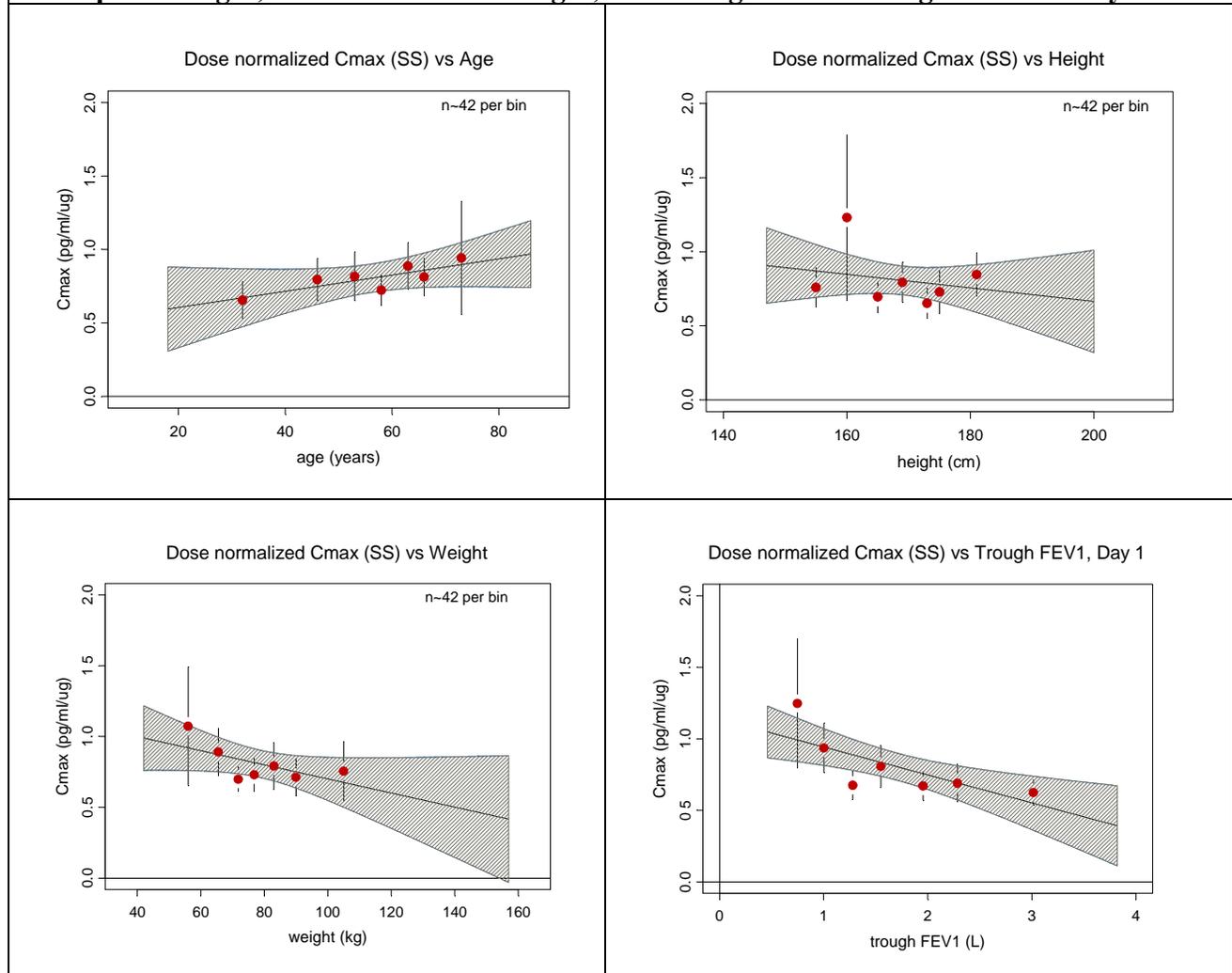
Figure 8. Dose normalized C_{max} (single dose) vs. Left plot: Olodaterol dose, Right plot: Trough FEV1 of Day 1



Note: For covariate-exposure relationships, solid symbols and bars represent the mean and 95% confidence interval of C_{max} for each x-axis quantile. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval (shaded region).

With respect to C_{max, norm, ss} (dose normalized C_{max} at steady state), a shallow trend was observed with age (not statistically significant, p>0.05). The only significant covariates were weight (p-value<0.03) and trough FEV1 on day 1 (p-value <0.001). With regard to weight, for every 10 kg increase, dose normalized C_{max} decreases -0.05 pg/ml/μg. For every 1 liter increase in trough FEV1, dose normalized C_{max} decreases -0.195 pg/ml/μg. Plots depicting the covariate-exposure relationships are in Figure 9 below.

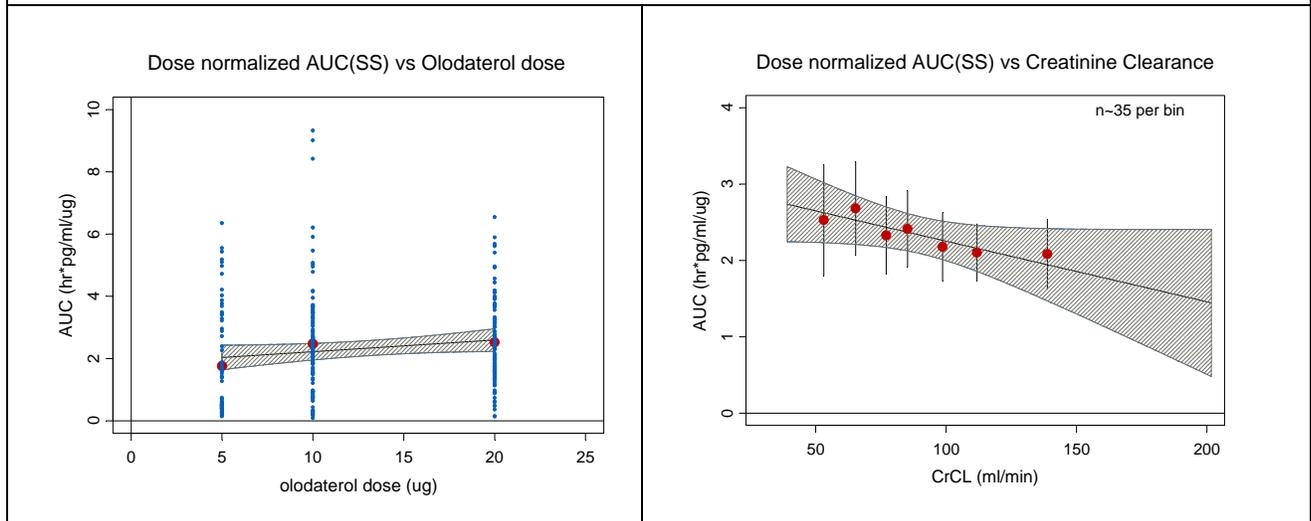
Figure 9. Dose normalized C_{max} (at steady state) vs. Upper Left plot - Age, Upper Right plot - Height, Lower Left Plot - Weight, Lower Right Plot - Trough FEV₁ of Day 1



Note: For covariate-exposure relationships, solid symbols and bars represent the mean and 95% confidence interval of C_{max} for each x-axis quantile. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval (shaded region).

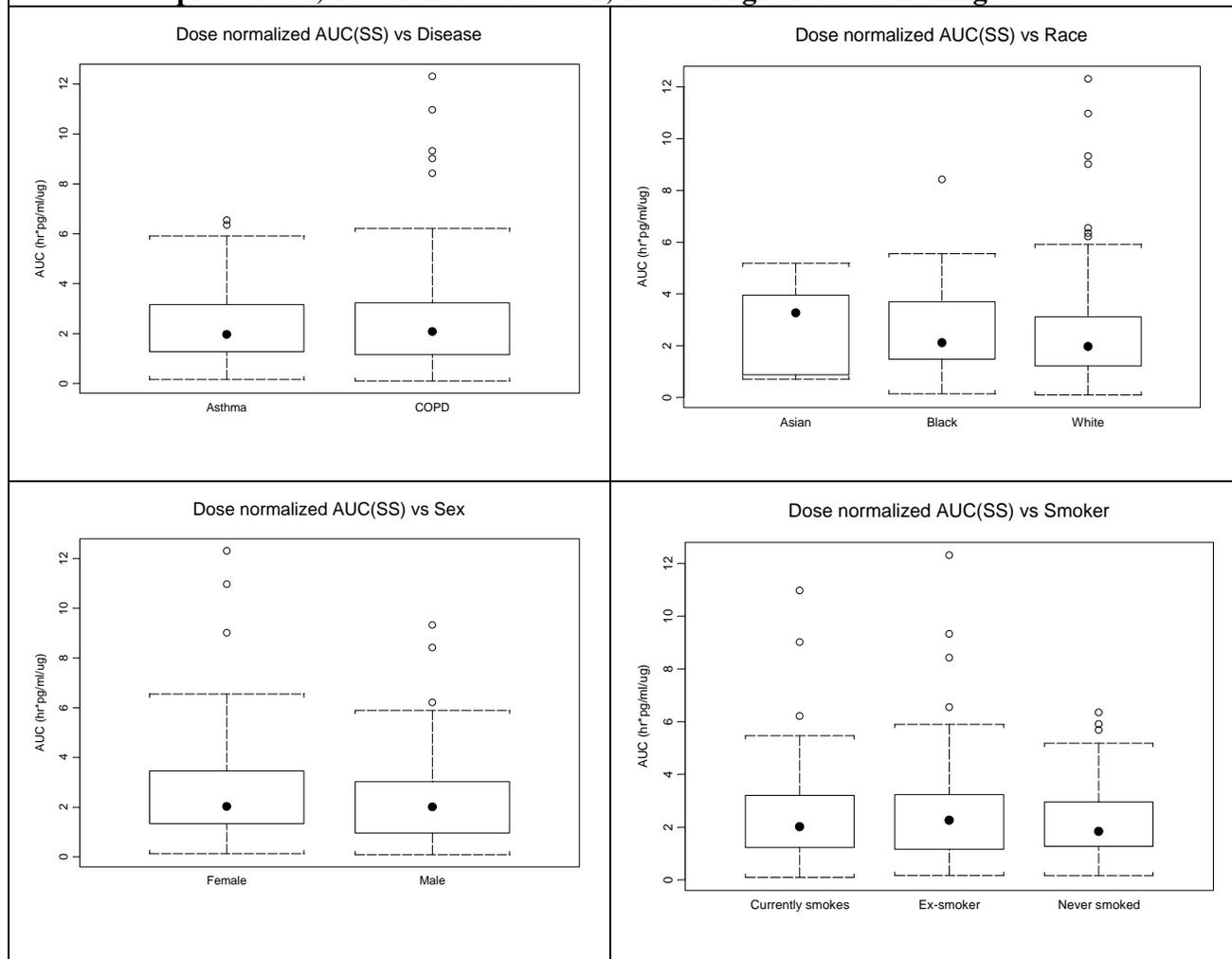
With respect to AUC_{norm,ss} (dose normalized AUC at steady state), a significant trend was observed with dose (p-value = 0.02) and creatinine clearance (p-value = 0.02). With regard to dose, for every 1 µg increase, dose normalized AUC increases 0.037 hr*pg/ml/µg. For every 10 ml/min decrease in creatinine clearance, dose normalized AUC increases 0.08 hr*pg/ml/µg. Plots depicting the covariate-exposure relationships are in Figure 10 below.

Figure 10. Dose normalized AUC (at steady state) vs. Left plot - Dose, Right plot – creatinine clearance



No categorical covariates were significant in the univariate analysis for the $AUC_{norm,ss}$ exposure metric. Disease status (asthma vs. COPD), race (asian vs. black vs. white), sex (male vs. female), and smoking status did not have influence on steady state exposures. Plots depicting the covariate-exposure relationships are in Figure 11 below.

Figure 11. Dose normalized AUC (at steady state) vs. Upper Left plot - Disease, Upper Right plot - Race, Lower Left Plot - Sex, Lower Right Plot – Smoking Status



For the multivariate regression analysis, the same covariates and similar criteria for covariate selection was chosen for the backward and forward stepwise covariate modeling (sponsor used p-value <0.1 deemed to be a significant covariate). Regression parameters were compared to the sponsor's results. The significant covariates, along with the regression parameter estimate, for each of the PK exposure parameters are presented in Table 11 below.

Table 11. Selected covariates and regression parameter estimates for dose-normalized olodaterol exposure parameters.

Model terms	Estimate	S.E.	p-value	90% CI
<i>C_{max, norm}</i> (pg/mL/μg)- after single dose				
Intercept	0.226	0.174	0.1954	(-0.06, 0.512)
Olodaterol dose (μg)	-0.134	0.045	0.0029	(-0.021, -0.06)
Trough FEV1 on Day 1 (L)	-0.208	0.044	<0.0001	(-0.28, -0.14)
<i>C_{max,ss, norm}</i> (pg/mL/μg)- at steady state				
Intercept	-1.067	0.614	0.0829	(-2.08, -0.06)
Age (years)	-0.007	0.0033	0.0373	(-0.01, -0.0001)
Height (cm)	0.012	0.0042	0.0052	(0.005, 0.019)
Weight (kg)	-0.0054	0.0019	0.0052	(-0.01, -0.0001)
Trough FEV1 on Day 1 (L)	-0.295	0.0636	<0.0001	(-0.4, -0.19)
<i>AUC_{0-24,ss, norm}</i> (hr*pg/mL/μg)- at steady state				
Intercept	3.74	0.249	<0.0001	(3.34, 4.16)
Olodaterol dose (μg)	-0.337	0.0012	0.0031	(-0.01, -0.0001)
Creatinine clearance (ml/min)	-0.0035	0.0576	<0.0001	(-0.43, -0.24)

As similar covariates were obtained from the multivariate regression, calculations for worst case conditions (i.e., combinations of the extremes for weight, height, lung function and age), were similar to the sponsor. Based on these covariates, a maximum increase of $C_{max,ss, norm}$ and $AUC_{0-24,ss, norm}$ by a factor of less than 2.0 is expected as compared to a typical COPD patient.

4.2 Genomics Group Review

The Pharmacometrics reviewer concluded that UGT polymorphisms do not have influence on olodaterol exposure. A Genomics Group review, therefore, is not included in this document.

4.3 Individual Study Review

Study No. 8222052

In vitro binding to human plasma proteins in subjects with renal or hepatic impairment and healthy volunteers

Objectives: determine the *in vitro* plasma protein binding of [³H]BI 1744 using pre-dose plasma samples taken from healthy volunteers and patients with renal or hepatic impairment.

Methods: Plasma protein binding of BI 1744 was assessed in pre-dose plasma samples after spiking of [³H]BI 1744 at the target concentration of 10 pmol/L and using equilibrium dialysis. Radioactivity was quantified using liquid scintillation counting.

Results:

Summary Table: Mean and SD of the plasma protein bound fraction (f_B) of [³H]BI 1744 related radioactivity in pre-dose plasma samples of healthy volunteers and patients with liver and renal impairment.

BI Study No.	Study Group	N	Mean % protein bound f_B	Mean % protein bound (f_B) for each study group	Overall Mean % protein bound f_B
1222.20	HV	16	59.8 ± 4.5	59.7 ± 6.4	60.4 ± 5.6
	miLIP	8	62.8 ± 8.9		
	moLIP	8	56.6 ± 6.2		
1222.35	HV	14	60.1 ± 3.8	61.4 ± 4.0	
	sRIP	8	63.7 ± 3.6		

Where; HV – healthy volunteer, miLIP – mild liver impairment, moLIP – moderate liver impairment and sRIP – severe renal impairment

Conclusions: Plasma protein binding of [³H]BI 1744 was comparable across all subjects from both studies with a mean protein binding of 60.4 ± 5.6%.

Name: A180/05LU

Objective: To investigate the contribution of human cytochrome P450 enzymes involved in the in vitro metabolism of [14C]olodaterol and to investigate the metabolism of [14C]olodaterol in human hepatocytes, lung microsomes.

Method: Human liver microsomes, human lung microsomes, expressed CYP enzymes and human hepatocytes were used for experiments. Formation of [14C]BI 1744 CL metabolites was investigated using HPLC with radioactivity detection and metabolites were identified by HPLC-MS/MS measurement.

Results: In vitro metabolism of [14C]BI 1744 CL by human liver microsomes was dependent on NADPH and resulted in the formation of one predominant metabolite U3, that was identified as O-demethylated product of [14C]BI 1744 CL (SOM 1522). In some incubations formation of low amounts of up to four (U1, U2, U4 and U5, all of unknown structures) additional metabolites was observed. The amounts of these metabolites were usually below the linear detection range and close to background radioactivity. U6 (unknown structure) was also present in parent compound solutions and in incubations without NADPH and was assumed to be a degradation product of [14C]BI 1744 CL.

There was no metabolism by human lung microsomes.

Incubations with human hepatocytes were performed with freshly prepared hepatocytes of three individual liver donors in suspension cultures. Formation of various metabolites was observed that were identified by HPLC-MS/MS measurement. The predominant metabolites formed in human hepatocytes were: O-desmethyl BI 1744 CL-glucuronide (SOM 1522-glucuronide), O-desmethyl BI 1744 CL (SOM 1522) and BI 1744 CLglucuronide (CD 992).

Study Name: a031-09os

In vitro cytochrome P450 enzyme induction in primary human hepatocytes

Method: The in vitro induction potential of BI 1744 CL on six human cytochrome P450 enzymes was assessed in sandwich cultured primary human hepatocytes from three different donors. Six concentrations of BI 1744 CL ranging from 0.5 - 1000 pM in culture medium were tested.

This concentration range was selected with regard to the very low circulating plasma concentrations of BI 1744 and its metabolites. In situ enzyme activities were assessed using selective test substrates and mRNA levels were determined by semi-quantitative real-time PCR for CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4 after 48 h of treatment. The results for BI 1744 CL were compared to vehicle control and prototypical CYP-inducers that served as negative and positive control, respectively. Activities of P450 isoenzymes were determined using validated probe substrate assays with HPLC-MS/MS quantification. Relative gene expression was investigated using validated TaqMan real-time PCR assays.

Results: No relevant induction of in vitro enzyme activity was found for any of the P450 enzymes tested following treatment with up to 1000 pM of BI 1744 CL for 48 h. No relevant induction of mRNA expression levels was observed for the respective enzymes upon treatment with BI 1744 CL.

Concentrations of the phenol-glucuronide metabolite of BI 1744 (CD 992) in cell culture supernatants after two consecutive 24 h incubations were measured using a semi-quantitative HPLC-MS/MS method. Hereby, the glucuronide metabolite CD 992 was determined indirectly via quantification of BI 1744 in cell culture supernatants before and after glucuronidase treatment. In situ formation of CD 992 increased with increasing concentrations of test compound and CD 992 was quantifiable for the 50, 200, and 1000 pM treatment groups for all three donors used in the study. In these samples, the relative amount of CD 992 in the 24 h supernatants was 7% - 24% referred to the initial BI 1744 input. Thus, substantial intracellular exposure of primary hepatocyte cultures to BI 1744 and the metabolite CD 992 can be concluded.

Conclusions: Based on the results from this study, metabolic drug-drug interactions resulting from induction of cytochrome P450 enzymes are not expected for BI 1744 and its glucuronide metabolite CD 992.

Study Name: A282/08TE

In vitro phase II metabolism characterization of olodaterol

Method: The in vitro glucuronidation of olodaterol and the in vitro sulphation of its O-demethylated metabolite SOM 1522 was investigated by using pooled human liver, lung, kidney and intestinal microsomes (glucuronidation of olodaterol) and pooled human lung, liver and intestinal cytosol and tissue S9000 homogenate (sulphation of SOM 1522). In addition, the involved enzymes were identified by using expressed UGT (glucuronidation) and SULT (sulphation) enzymes.

Results: Glucuronidation of olodaterol:

Only negligible glucuronidation was observed with pooled human lung microsomes. Therefore, enzyme kinetics were assessed for human liver, kidney and intestinal microsomes and standard hyperbolic enzyme kinetics (Michaelis-Menten type) were observed. A higher glucuronidation clearance was observed in liver and kidney microsomes compared to intestinal microsomes and it can be concluded that olodaterol is effectively glucuronidated in liver, kidney and intestine but not in lung. Olodaterol was also incubated with expressed human UGT enzymes. Six UGTs were identified that were able to glucuronidate olodaterol. The highest glucuronidation activity was observed for UGT2B7, UGT1A1, UGT1A7 and UGT1A9 (UGT1A3 and UGT1A8 showed only minor activity). Glucuronidation by expressed UGTs followed a hyperbolic Michaelis-Menten enzyme kinetics. The UGTs identified are expressed in the intestine (UGT1A7, UGT1A1), liver (UGT1A1, UGT1A9, UGT2B7) and kidney (UGT1A9).

Sulphation of SOM 1522:

Human intestine exhibited the highest sulphation activity with an intrinsic clearance more than 20-fold higher than that in liver. Comparable rates of sulphation of SOM 1522 were observed for human liver and lung whereas kidney exhibited a lower sulphation activity.

Enzyme kinetics were assessed for human liver, lung and intestinal cytosol / S9000 homogenate and for expressed SULT1A1 and SULT1A3, both exhibiting a high sulphation activity. Standard hyperbolic enzyme kinetics (Michaelis-Menten type) were observed and results indicate that the intestine is the major site for sulphation of SOM 1522. As SULT1A1 and 1A3 are both expressed in the intestine it is concluded that both are most likely the major catalysts for this metabolic pathway.

Conclusions: inhaled olodaterol will most likely undergo only minimal, if any, metabolic conjugation by UGT-catalysed glucuronidation. In marked contrast, swallowed olodaterol will be extensively glucuronidated in intestine and liver and SOM 1522, after formed by oxidative O-demethylation of olodaterol, will be very rapidly and effectively sulphated, in particular in the intestine.

Study Name: A167-04LU

In vitro inhibition studies on cytochrome P450 dependent metabolic reactions

Method: Inhibition of cytochrome P450-catalysed test reactions by BI 1744 CL was investigated in liver microsomes of humans. The extent of inhibition of BI 1744 CL was assessed at concentrations of 0.1, 1, 10 and 100 μ M.

The following 13 test reactions were used because they are generally accepted as selective markers of the enzymatic activity of a single or two closely related cytochrome P450 isoenzymes that are relevant for drug metabolism in humans.

- phenacetin O-deethylation test for cytochrome P450 1A1 and 1A2
- coumarin 7-hydroxylation test for cytochrome P450 2A6
- bupropion hydroxylation test for cytochrome P450 2B6
- paclitaxel 6 α -hydroxylation test for cytochrome P450 2C8
- tolbutamide hydroxylation test for cytochrome P450 2C9
- S-mephenytoin 4'-hydroxylation test for cytochrome P450 2C19
- bufuralol 1'-hydroxylation test for cytochrome P450 2D6
- lauric acid 11-hydroxylation test for cytochrome P450 2E1
- nifedipine oxidation test for cytochrome P450 3A4
- testosterone 6 β -hydroxylation test for cytochrome P450 3A4
- midazolam 1'-hydroxylation test for cytochrome P450 3A4
- erythromycin N-demethylation test for cytochrome P450 3A4
- lauric acid 12-hydroxylation test for cytochrome P450 4A11

The test substrates were incubated with human liver microsomes in the presence of β -nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) and the formation of the respective metabolites was quantified using sensitive and selective analytical techniques. BI

1744 CL was added to the incubation experiments and its effect on the formation of the respective metabolites was evaluated.

Results: BI 1744 CL inhibited CYP 2D6 catalysed bufuralol 1'-hydroxylation with a K_i of 1.92 μM . There was no inhibition of other CYP isoenzymes under investigation. There was no indication of irreversible CYP 3A4 inhibition by BI 1744 CL. With the assumption of therapeutic BI 1744 CL plasma concentrations below 1 μM (a geometric mean C_{max} of about 0.0000138 μM was measured after single inhalation of 20 μg to males in BI Trial no. 1222.0001), the I/K_i ratio [P03-04490] results in a value of 7.19 x 10⁻⁶.

Conclusions: Therefore, an inhibition of CYP 2D6 by BI 1744 CL seems to be highly unlikely. Inhibition of other CYP enzymes is even more unlikely because no relevant inhibition was observed at BI 1744 CL concentrations of up to 100 μM .

Study Name: A258-09lu

BI 1744-Glucuronide (CD 992): In vitro inhibition studies on cytochrome P450 dependent metabolic reactions

Methods: Inhibition of cytochrome P450-catalysed test reactions by BI 1744-glucuronide (CD 992) was investigated in liver microsomes of humans. The extent of inhibition of CD 992 was assessed at concentrations of 0.1, 1, 10 and 100 μM .

The following 10 test reactions were used because they are generally accepted as selective markers of the enzymatic activity of a single or two closely related cytochrome P450 isoenzymes that are relevant for drug metabolism in humans.

phenacetin O-deethylation test for cytochrome P450 1A1 and 1A2

bupropion hydroxylation test for cytochrome P450 2B6

amodiaquine N-deethylation test for cytochrome P450 2C8

diclofenac 4'-hydroxylation test for cytochrome P450 2C9

S-mephenytoin 4'-hydroxylation test for cytochrome P450 2C19

dextromethorphan O-demethylation test for cytochrome P450 2D6

lauric acid 11-hydroxylation test for cytochrome P450 2E1

nifedipine oxidation test for cytochrome P450 3A4

testosterone 6 β -hydroxylation test for cytochrome P450 3A4

midazolam 1'-hydroxylation test for cytochrome P450 3A4

The test substrates were incubated with human liver microsomes in the presence of β -nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) and the formation of the respective metabolites was quantified using sensitive and selective analytical techniques. CD 992 was added to the incubation experiments and its effect on the formation of the respective metabolites was evaluated.

Results: There was no reversible inhibition of cytochrome P450 (CYP) enzymes under investigation at CD 992 concentrations of up to 100 μM . Minor mechanism-based inhibition of CYP 2D6 was observed at a CD 992 concentration of 100 μM .

Investigations based solely on the determination of (reversible) IC_{50} or K_i values may yield misleading information in the presence of mechanism-based inactivation (R02-2329) because the mechanism-based inactivation exponentially increases inhibitory potency as a function of exposure time.

CD 992 was a very poor mechanism-based inactivator of CYP 2D6 with K_i and kinact values for the inhibition of dextromethorphan O-demethylation in human liver microsomes were 99.0 μM and 0.044 min^{-1} .

With the assumption of therapeutic CD 992 plasma concentrations below 1 μM ($\text{C}_{\text{max,ss}}$ of about 0.01 nM was measured after inhalation of 10 μg to asthma patients in BI Trial No. 1222.5), the fractional decrease of intrinsic clearance resulted in the value of 1.

Conclusions: Therefore, an inhibition of CYP 2D6 by CD 992 seems to be highly unlikely. Inhibition of other CYP enzymes is even more unlikely because no relevant inhibition was observed at CD 992 concentrations of up to 100 μM .

Study Name: A206-06lu

Effect of BI 1744 CL on the oxidative in vitro metabolism of [^{14}C]tiotropium

Methods: In this study the effect of BI 1744 CL on the oxidative in vitro metabolism of [^{14}C]tiotropium was investigated in human liver microsomes. Additionally, the metabolism of [^{14}C]tiotropium in pooled human lung homogenate was investigated. Incubations were performed with pooled human liver microsomes and with lung homogenate of 1 male and 3 female donors. The pool contained lung tissue of 2 smokers. Radiolabelled [^{14}C]tiotropium was used for incubation experiments. The metabolism of [^{14}C]tiotropium was assessed using high performance liquid chromatography (HPLC) with radioactivity detection.

Results: Turnover of [^{14}C]tiotropium by human liver microsomes was low and close to background radioactivity. Apart from predominant non-enzymatic cleavage (formation of dithienylglycolic acid), only very small amounts of a fraction designated as “other metabolites” were formed. Formation of metabolites by human liver microsomes was comparable to the results described in [U99-1348 and U03-1745].

The effect of BI 1744 CL on the oxidative in vitro metabolism of [^{14}C]tiotropium was assessed at concentrations of 1, 10 and 100 μM . At concentrations above 10 μM , BI 1744 CL weakly inhibited the formation of the fraction of “other metabolites” compared to control experiments without BI 1744 CL. Addition of BI 1744 CL had no effect on the formation of dithienylglycolic acid. Because of therapeutic BI 1744 CL plasma concentrations will be far below 1 μM (a geometric mean C_{max} of about 13.8 pM was measured after single inhalation of 20 μg to males in BI Trial no. 1222.0001), a metabolic drug-drug interaction of [^{14}C]tiotropium and BI 1744 CL based on inhibition of CYP by BI 1744 CL is considered to be very unlikely to occur.

Conclusions: In human lung homogenate, most probably non-enzymatic ester hydrolysis of [¹⁴C]tiotropium under formation of dithienylglycolic acid dominated the degradation of tiotropium. No formation of “polar metabolites” or of “other metabolites” which are considered to be the result of enzymatic metabolism was detected. It was concluded that human lung does not exhibit P450-dependent oxidative metabolism of tiotropium.

Study Name: A212_07LU

Effect of BI 1744 CL on the oxidative in vitro metabolism of [¹⁴C] BI 54903 XX

Methods: Aim of this study was to investigate the effect of BI 1744 CL on the oxidative in vitro metabolism of [¹⁴C]BI 54903 XX (ciclesonide isobutyrate). As [¹⁴C]BI 54903 XX is rapidly cleaved by ester hydrolysis under formation of the active principle CD 1857 XX (the desisobutyl derivative), experiments were performed with both compounds [¹⁴C]BI 54903 XX and [¹⁴C]CD 1857 XX.

The metabolism of [¹⁴C]BI 54903 XX and [¹⁴C]CD 1857 XX was assessed using HPLC with radioactivity detection. The effect of BI 1744 CL on the oxidative in vitro metabolism of [¹⁴C]BI 54903 XX and [¹⁴C]CD 1857 XX was investigated in samples of pooled liver microsomes of humans and human liver homogenate and was assessed at concentrations of 0.1, 1, 10 and 100 µM.

Results: In human liver microsomes, [¹⁴C]BI 54903 XX was rapidly cleaved to CD 1857 XX. This ester cleavage was not dependent on the presence of the cosubstrate NADPH and was therefore not catalyzed by monooxygenase enzymes (cytochrome P450). With the cosubstrate NADPH several other polar metabolites were formed in minor amounts. In human lung homogenate, ester cleavage of [¹⁴C]BI 54903 XX resulting in the formation of CD 1857 XX was observed. There was only marginal formation of other metabolites. These findings were in accordance with the results described in [R07-2082]. In concentrations up to 100 µM, BI 1744 CL neither affected ester cleavage nor the formation of other metabolites of [¹⁴C]BI 54903 XX and [¹⁴C]CD 1857 XX, respectively.

Conclusion: A metabolic drug-drug interaction of [¹⁴C]BI 54903 XX based on inhibition of CYP by BI 1744 CL is therefore considered as unlikely to occur.

Study Name: A180_05LU

Effect of tiotropium bromide on the oxidative in vitro metabolism of [¹⁴C]BI 1744 CL

Method: Aim of this study was to investigate the effect tiotropium bromide on the oxidative in vitro metabolism of [¹⁴C]BI 1744 CL.

Radiolabelled [¹⁴C]BI 1744 CL was used for incubation experiments. The metabolism of [¹⁴C]BI 1744 CL was assessed using HPLC with radioactivity detection. Inhibition of the

oxidative in vitro metabolism of [¹⁴C]BI 1744 CL was investigated in liver microsomes of humans. The extent of inhibition was assessed at concentrations of 0.01, 0.1, 1, 10 and 100 μM.

Results: Incubation of [¹⁴C]BI 1744 CL for 15 min (0.5 mg protein/mL) resulted in the formation of U3, the O-desmethyl metabolite of BI 1744 CL, as the principal metabolite. Tiotropium bromide neither inhibited U3 formation nor the metabolic depletion of [¹⁴C]BI 1744 CL.

Conclusion: Therefore, inhibition was not observed of the oxidative [¹⁴C]BI 1744 CL in vitro metabolism by tiotropium bromide.

Study Name: A180_05LU

Effect of BI 54903 XX (ciclesonide) on the oxidative in vitro metabolism of [¹⁴C]BI 1744 CL

Method: Aim of this study was to investigate the effect of BI 54903 XX (ciclesonide isobutyrate) on the oxidative in vitro metabolism of [¹⁴C]BI 1744 CL. Radiolabelled [¹⁴C]BI 1744 CL was used for incubation experiments. The metabolism of [¹⁴C]BI 1744 CL was assessed using HPLC with radioactivity detection. The effect of BI 54903 XX on the oxidative in vitro metabolism of [¹⁴C]BI 1744 CL was investigated in liver microsomes of humans and was assessed at concentrations of 0.01, 0.1, 1, 10 and 100 μM.

Results: Incubation of [¹⁴C]BI 1744 CL for 15 min (0.5 mg protein/mL) resulted in the formation of U3, the O-desmethyl metabolite of BI 1744 CL, as the principal metabolite. BI 54903 XX (ciclesonide isobutyrate) had no effect neither on U3 formation nor on the metabolic depletion of [¹⁴C]BI 1744 CL.

Conclusion: BI 54903 XX (ciclesonide isobutyrate) had no effect on the oxidative [¹⁴C]BI 1744 CL in vitro metabolism.

Study Name: PK0720T

Investigation in the permeability of BI 1744 CL and its interaction with P glycoprotein using the Caco-2 cell in vitro absorption model

Method: The aim of this study was to assess the in vitro membrane permeability of BI 1744 CL, a selective partial agonist of the human α_2 -adrenoceptor, and to determine whether BI 1744 CL interacts with the drug efflux transporter P-glycoprotein (P-gp). These questions were addressed by means of in vitro bi-directional transport studies in monolayers of the human colon carcinoma-derived cell line Caco-2, a well-established in vitro model of the intestinal epithelium.

Results: The suitability of the Caco-2 cell monolayers to assess passive permeability and P-gp-mediated transport was monitored in a series of apical-to-basal (AtoB; absorptive) and basalto-

apical (BtoA; secretory) bi-directional transport experiments with three reference compounds for low to high permeability, i.e., mannitol, atenolol and propranolol, and the two P-gp substrates WEB 2086 BS and digoxin throughout the study period (passage number from 45 to 51). Higher B toA than A to B permeability of the P-gp substrates WEB 2086 BS (efflux ratio: 9.51, N=3) and digoxin (efflux ratio: 6.40, N=3) was observed. In addition, the apically directed vectorial transport of digoxin was completely abolished in the presence of the P-gp inhibitors cyclosporin A (CsA, efflux ratio: 0.634, N=3) and verapamil (VP, efflux ratio: 0.942, N=3). These findings indicate the functional expression of P-gp in the present Caco-2 cell system.

The apically directed vectorial transport of BI 1744 CL showed concentration-dependency. At low drug concentration (10 μM), the B to A apparent permeability coefficient (P_{app} : 10.2×10^{-6} cm/s, N=3) was 38.9-fold higher than the AtoB P_{app} (0.264×10^{-6} cm/s, N=3). The vectorial transport approached symmetric transport with an increase of BI 1744 CL concentration, although it was still asymmetric even at 600 μM (efflux ratio: 9.45, N=3), indicating the presence of an active, saturable efflux mechanism. Moreover, the vectorial transport observed at 10 μM BI 1744 CL (efflux ratio: 43.5, N=3) was completely abolished in the presence of the P-gp inhibitors CsA (efflux ratio: 0.966, N=3) and VP (efflux ratio: 1.76, N=3), but was hardly inhibited by the MRP inhibitor MK-571 (efflux ratio: 36.7, N=3).

The concentration-dependent permeability and the inhibition by P-gp inhibitors indicate that BI 1744 CL is a substrate of P-gp. The apparent K_m values were determined to be 439 μM in the AtoB direction and 245 μM in the BtoA direction, with a mean K_m value of 342 μM . These K_m values suggest that BI 1744 CL is a substrate for P-gp with low affinity. The P_m (passive permeability) values were 0.598×10^{-6} cm/s in the AtoB direction and 2.25×10^{-6} cm/s in the BtoA direction, which were similar to the permeability coefficients in the presence of a fully inhibitory concentration of P-gp inhibitors (1.45×10^{-6} cm/s, N=12), and ranged between those of the low permeability references, mannitol and atenolol, and those of the high permeability reference propranolol.

In the interaction experiments, BI 1744 CL inhibited the P-gp-mediated AtoB and BtoA transport of digoxin across the Caco-2 monolayers in a concentration-dependent manner. The apparent IC_{50} values for digoxin transport estimated from the fitting analysis were determined to be 427 μM for the AtoB direction, 303 μM for the BtoA transport direction (mean value of both directions: 365 μM), indicating that BI 1744 CL is a weak inhibitor of P-gp.

Conclusions: BI 1744 CL is suggested to have low potential to interact with P-gp substrates in vivo unless the in vivo concentration of BI 1744 CL approaches or exceeds this IC_{50} value.

Study Name: PK0724T

In vitro evaluation of the transport and the interaction of BI 1744 CL with human P glycoprotein (P-gp / MDR1)

Methods: The aim of this study was to investigate whether BI 1744 CL is a substrate and/or an inhibitor of P-glycoprotein (P-gp; gene *ABCB1* or MDR1). This question was addressed by

means of transcellular transport studies using human MDR1-expressing and parental LLC-PK1 cells

Results: To investigate whether BI 1744 CL is a substrate for human P-gp, BtoA transport and AtoB transport of [¹⁴C]BI 1744 CL in MDR1-expressing LLC-PK1 cells were compared with those in the parental cells. Though the BtoA transport was higher than the AtoB transport in MDR1-expressing cells, such vectorial transport of BI 1744 CL was not observed in parental cells (ER MDR1/parent: 16.4). The apically directed BI 1744 CL transport in MDR1-expressing cells disappeared in the presence of fully inhibitory concentrations of the P-gp inhibitors cyclosporin A (CsA) and zosuquidar (ZSQ) (ERMDR1/parent: 0.927 and 0.672, respectively). These results indicate that BI 1744 CL is a substrate of P-gp. Saturation of bi-directional transport of BI 1744 CL was not observed up to 600 μM, and therefore the Km value of BI 1744 CL was considered to be more than 600 μM for both directions. Taking into consideration the high ERMDR1/parent, the lack of saturation of the transport, and the inhibition profile by P-gp inhibitors, BI 1744 CL is suggested to be a low-affinity substrate of P-gp though it is efficiently recognized by P-gp. These results indicate that P-gp is likely to be involved in the transport of BI 1744 CL in organs where P-gp is expressed.

To determine the potential of BI 1744 CL to inhibit P-gp activity, bi-directional transcellular transport studies using digoxin as a probe P-gp substrate were performed in the absence or presence of BI 1744 CL. BI 1744 CL did not show a clear inhibitory effect on the MDR1-mediated digoxin transport at concentrations up to 600 μM. This finding indicates that BI 1744 CL is not an inhibitor of P-gp at concentrations up to 600 μM. Consequently, the likelihood that BI 1744 CL would affect the P-gp dependent absorption, biliary excretion, tissue distribution or urinary secretion of co-administered drugs that are substrates of P-gp is considered to be low.

Conclusions: This finding indicates that BI 1744 CL is not an inhibitor of P-gp at concentrations up to 600 μM. Consequently, the likelihood that BI 1744 CL would affect the P-gp dependent absorption, biliary excretion, tissue distribution or urinary secretion of co-administered drugs that are substrates of P-gp is considered to be low.

Study Name: A452/05BC, A646/05BC, A465/05BC, A467/06BC, A468/06BC, A470/06BC, A475/06BC, A476/06BC, A473/06BC

Investigation of in vitro metabolism of olodaterol

Methods: Investigation on the *in vitro* metabolite pattern after incubation of human and rat hepatocytes with [¹⁴C]olodaterol. In addition, the mechanism of metabolic activation was investigated.

Results:

Tabulated results:

Compound code	Human hepatocytes	Rat hepatocytes
Olodaterol	61.4	64.7
CD 992	10.1	12.1
SOM 1522	5.8	1.1
CD 11249	2.8	15.1
CD 10915	12.3	0.5
CD 12656	5.4	+
M389(2)	+	+
M405(6)	+	0.4
M581(2)	-	0.6
M448(1)	0.9	+
M462(1)	1.3	0.8
M478(1)	+	1.0
M565(2)	-	1.0
M583(1)	-	0.5
M581(1)	-	1.8
M595(1)	-	
m0	-	
sum	100.0	100.0

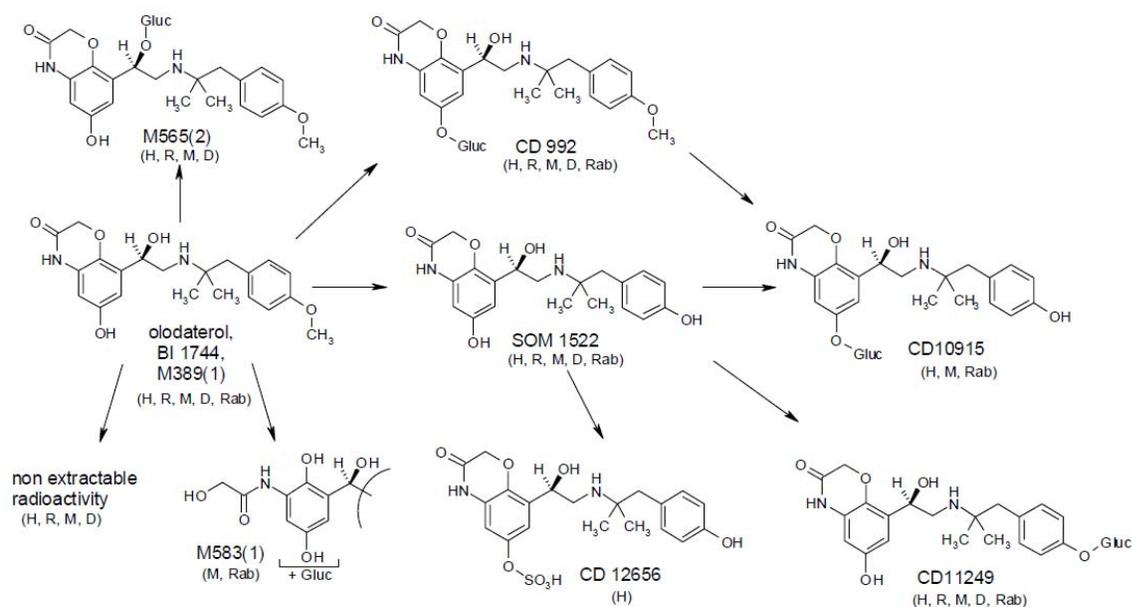
- not detected

+ mass spectrometry detection only, no radioactivity signal

Main metabolic reactions of [14C]olodaterol with human and rat hepatocytes were identical. The pathways were the glucuronidation of the 6-hydroxybenzoxazine-moiety of olodaterol to CD 992, the demethylation of the methoxyphenyl-moiety of olodaterol to SOM 1522 and the glucuronidation of SOM 1522 to CD 11249 and CD 10915. CD 11249 was predominantly formed by rat hepatocytes; CD10915 was the dominant glucuronide of SOM 1522 in incubations with human hepatocytes. The metabolite CD 12656 was identified as phase II sulphate of SOM 1522. It was predominantly observed in human hepatocytes. In rat hepatocytes CD 12656 was only detected in trace amounts. The metabolite M389(2) with 3,5-dihydroxy-2,3-dihydrobenzopyrrol structure was detected by mass spectrometry methods in incubations with human and rat hepatocytes. The formation of M389(2) was proposed to occur via an initial metabolic activation by oxidation of the methylene unit of the benzoxazine moiety of olodaterol. Subsequently, an intramolecular cyclization results in the formation of a quinonimine-system that is finally reduced to yield M389(2). Indirect evidence for the chemical reactive quinonimine intermediate was given by the structures of two adducts with glutathione M694(1) and M694(2). The metabolites M389(2), M694(1) and M694(2) were isolated from incubations of dexamethasone induced rat liver microsomes in the presence and without glutathione. The structures of these three metabolites were elucidated by NMR-spectroscopy and mass spectrometry experiments. Due to its reactivity, the quinonimine-intermediate was supposed to be involved in the formation of not extractable covalently bound radioactivity to plasma proteins, that was observed in the in vivo metabolism studies including rats (U06-1514, Module 4.2.2.4) dogs (U08-1057, Module 4.2.2.4), mice (U06-1516, Module 4.2.2.4) and humans (U09-1129, Module 5.3.3.2). M583(1), a metabolite with hydroquinone structure which was stabilized by glucuronidation was only identified in vitro in incubations with rat hepatocytes and in vivo in urine of mice and rabbits and plasma of rabbits after administration of [14C]olodaterol (U06-1516, U08-1317, Module 4.2.2.4). Additional metabolites with unknown structures were identified by radioactivity and

mass spectrometry detection in low amounts (< 1.4% of sample radioactivity) in incubations with human and rat hepatocytes. Further trace amounts of in vitro metabolites with isomeric structures formed by the combination of oxidation, demethylation and glucuronidation at several positions could be identified by mass spectrometry investigations. The concentrations were below the detection limit of the HPLC/radioactivity detection system. Minute amounts of metabolites of human hepatocytes with unknown structure (M373(1), M391(4), M551(3), M551(4)) which were only identified by mass spectrometry investigations were not detected in incubations with rat hepatocytes. Other minute amounts of metabolites were only identified in incubations with rat hepatocytes.

Conclusions: The proposed pathways for the metabolism are shown below:



* H: Human, R: Rat, M: Mouse, D: Dog, Rab: Rabbit

Trial 1222.3

Study Title: Randomised, double-blind, placebo-controlled, 5-way cross-over trial to assess the efficacy and safety of a single dose of orally inhaled olodaterol (2 µg, 5 µg, 10 µg, 20 µg, 40 µg) in COPD patients followed by open label olodaterol (40 µg)

Objectives: The objectives of the main trial were to investigate the efficacy, safety, and exploratory pharmacokinetics (PK) of single doses of olodaterol in patients with COPD. The objectives of the extension were to investigate the PK, safety, and tolerability of a single dose of 40 µg olodaterol in a subset of patients with COPD who participated in the PK substudy.

Study Design: Randomized, double-blind, placebo-controlled, 5-way cross-over design with an open-label one-way extension. In the main part of the study, 36 COPD patients received

single doses of 2, 5, 10, 20 µg olodaterol, and placebo inhaled via the RESPIMAT inhaler in a randomized sequence. In the extension, 14 patients received a dose of 40 µg olodaterol in addition. In each treatment period, from a subgroup of 18 patients in the main study, and from all 14 patients in the extension study pharmacokinetic blood samples were taken up to 4 hours (main study) or 24 hours (extension study), and urine samples were collected up to 24 hours after dosing. Blood samples for determination of potassium were taken from all patients up to 4 hours (main study) or 8 hours (extension study) after dosing. Serial ECG and vital sign measurements were performed up to 24 hours after dosing.

Pharmacokinetic Results: Maximum plasma concentrations were measured at about 10 minutes after drug inhalation. Inspection of dose-normalized AUC₀₋₁ and C_{max} values and of urinary excretion data pointed to proportional increase of systemic exposure to olodaterol within the dose range of 2 to 40 µg.

Pharmacokinetic analysis of the olodaterol metabolites SOM 1522 and olodaterol glucuronide was performed for the 40 µg dose group. SOM 1522 was detectable in plasma of only one patient at 10 and 20 minutes after the inhalation of olodaterol, and in the urine of 7 out of 14 patients. Where quantifiable, the ratio between molar amounts of SOM 1522 and olodaterol excreted in urine within the dosing interval (RA_{e0-24, Met}) varied between 0.239 and 0.785.

Maximum plasma concentrations of olodaterol glucuronide were generally observed 2 hours after inhalation of olodaterol. The geometric mean molar ratio between olodaterol glucuronide and olodaterol was 0.374 (gCV 62.2%) for AUC_{0-∞} and 0.725 (gCV 37.6%) for the amounts excreted in urine within the dosing interval.

Pharmacokinetic Conclusions: Systemic exposure in COPD patients after single inhalation of olodaterol increased about proportionally with increasing doses of 2 µg to 40 µg. The metabolite SOM 1522 was present in plasma only at low concentrations around or below the lower limit of quantification

(10 pg/mL) even after a dose of 40 µg olodaterol. Systemic exposure to olodaterol glucuronide as assessed by AUC_{0-∞} amounted to about 40% of the olodaterol systemic exposure, while the molar amounts of olodaterol glucuronide excreted via urine within 24 hours after dosing amounted to about 70% of those for olodaterol.

Trial 1222.5

Study Title: Randomised, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of four weeks of once daily treatment of orally inhaled olodaterol (2 µg, 5 µg, 10 µg, 20 µg) delivered by the RESPIMAT Inhaler in patients with COPD

Objectives: to determine the optimum dose of olodaterol inhalation solution delivered by the RESPIMAT inhaler once daily for four weeks in patients with COPD.

Study Design: Randomized, double-blind, placebo-controlled, parallel group design comparing five groups over four weeks

Pharmacokinetic Results: In the 2 µg dose group, olodaterol plasma concentrations were mostly below the lower limit of quantification (2 pg/mL). In the 5 µg group, plasma concentrations could be quantified up to 20 minutes (Day 1) and 40 minutes (Day 29) post-dose, and in the 10 and 20 µg groups, plasma concentrations could be quantified over the whole sampling period, i.e. up to 3 hours (Day 1) and 6 hours (Day 29), respectively, in at least 1/3 of the patients. Maximum olodaterol plasma concentrations after single inhalation as well as at steady state (shown to be reached by Day 8) were measured 10 to 12 minutes after drug inhalation. Accumulation accounted for a factor of 1.12 to 1.34 based on C_{max}, and 1.37 based on AUC₀₋₃. C_{max,ss} and AUC_{0-1,ss} values of olodaterol increased proportionally within the dose range 2–20 µg.

Olodaterol glucuronide maximum plasma concentrations were observed 3 hours after a single inhalation as well as at steady state. Similar to olodaterol, steady state of olodaterol glucuronide was shown to be reached by Day 8, and accumulation based on C_{max} values accounted for a factor of 1.04 to 1.13. The molar ratio between olodaterol glucuronide and olodaterol was 0.592 to 0.697 for AUC_{0-6,ss}. The metabolite SOM 1522 was not detectable in all but two plasma samples (LLOQ: 10 pg/mL).

Pharmacokinetic Conclusions: Steady state of olodaterol and of olodaterol glucuronide on once daily inhalation of olodaterol in COPD patients was reached by Day 8. Accumulation of both analytes was low and in the same range. C_{max,ss} and AUC_{0-1,ss} values of olodaterol increased proportionally within the dose range 2–20 µg.

Trial 1222.26

Study Title: Randomised, double-blind, 4-way cross-over study to determine the 24-hour FEV₁-time profile of orally inhaled BI 1744 CL, delivered with the Respimat® inhaler, after 3 weeks of once daily (5 µg [2 actuations of 2.5 µg], 10 µg [2 actuations of 5 µg]) or twice daily (2 µg [2 actuations of 1 µg], 5 µg [2 actuations of 2.5 µg]) administration in patients with Chronic Obstructive Pulmonary Disease (COPD)

Objectives: The objective of the trial was to determine the 24-hour FEV₁-time profile of BI 1744 CL inhalation solution administered once daily (5 µg and 10 µg) or twice daily (2 µg and 5 µg) using the Respimat® Inhaler after 3-week treatment periods.

Study Design: Randomized, double-blind, placebo-controlled, parallel group design comparing five groups over four weeks

Evaluation:

Efficacy / clinical pharmacology:

Primary: FEV₁ AUC₀₋₁₂ response and FEV₁ AUC₁₂₋₂₄ response after 3 weeks of

Treatment

Secondary: FEV1 AUC0-24, peak FEV1 and trough FEV1 after 3 weeks of treatment. Individual FEV1 and FVC measurements at each time point over 24 hours after 3 weeks of treatment. FVC AUC0-12, FVC AUC12-24, FVC AUC0-24, peak FVC and trough FVC after 3 weeks treatment.

Safety: Vital signs (blood pressure, pulse rate), 12-lead ECG, clinical laboratory tests, adverse events (AEs).

Pharmacokinetic Results:

After 3 weeks inhalation of 2 µg bid and 5 µg qd BI 1744 CL, trough plasma concentrations of OLODATEROL were mostly below the limit of quantification (LOQ: 2.0 pg/mL); hence (geometric) mean C_{pre,ss} was not calculated. After inhalation of 5 µg bid and 10 µg qd, respectively, trough plasma concentrations were quantifiable in at least 1/3 of the patients and geometric mean values were comparable between both treatments (gMean 2.92 pg/mL, gCV: 24.3%, N=24 and gMean 2.97 pg/mL, gCV: 23.2%, N=19, respectively).

OLODATEROL concentrations at 10 minutes post dosing (C_{0.167,ss}) after inhalation of 2 µg bid were mostly below the LOQ. Geometric mean C_{0.167,ss} values in the 5 µg qd, 5 µg bid and 10 µg qd groups were 3.52 pg/mL (gCV: 35.9%, N=25), 4.28 pg/mL (gCV: 42.0%, N=36) and 5.78 pg/mL (gCV: 62.1%, N=41), respectively.

The fraction of the dose excreted via the urine within the dosing interval was similar in all dose groups (3.27–3.61%), suggesting dose-linear PK.

Pharmacokinetic Conclusions: Total daily systemic exposure to olodaterol based on urine data was proportional to the dose, and was comparable if the dose was given as a single daily dose, or split into a bid regimen.

Trial 1222.4

Study Title: Randomised, double-blind, placebo-controlled, 5-way cross-over study to assess the efficacy (Bronchoprotection) and safety of a single dose of orally inhaled BI 1744 CL (2 µg, 5 µg, 10 µg, 20 µg) in patients with intermittent asthma

Objectives: To investigate duration of action, efficacy (bronchoprotection), safety, and exploratory PK of BI 1744 CL

Study Design: Randomised, double-blind, placebo-controlled, 5-way cross-over design

Study Population: Outpatients of either sex (including females of child bearing potential using highly effective birth control), age 18-65 years, with a diagnosis of intermittent asthma (GINA), FEV1 PC20 \leq 8 mg/ml, FEV1 > 80% predicted (Morris), non-smokers or ex-smokers. A total of 25 subjects entered the study.

Pharmacokinetic Results: Maximum drug plasma concentrations were observed 13 to 21 minutes following inhalation. The variability of plasma concentrations for the individual sampling time-points was low to moderate.

Urinary excretion of OLODATEROL accounted for approximately 3% within 24 hours after inhalation. The variability of urinary excretion of OLODATEROL was moderate.

Evaluation of dose-normalized AUC₀₋₁ values suggested a dose proportional increase in drug plasma concentrations for the doses 10 and 20 μ g BI 1744 CL. C_{max} values showed dose proportionality for the dose range 5–20 μ g BI 1744 CL. Daily urinary excretion of OLODATEROL suggested dose proportionality for the dose range 2–20 μ g BI 1744 CL.

Similar drug plasma concentrations and similar daily urinary excretion of OLODATEROL were observed in male and female patients.

Pharmacokinetic Conclusions: Systemic exposure to olodaterol in asthma patients after a single inhalation of olodaterol increased dose-proportionally throughout the dose range of 2 to 20 μ g, without any difference between males and females. Slight effects on blood potassium concentrations and systolic blood pressure suggest that the threshold for systemic pharmacodynamic activity in patients with asthma is reached at inhaled doses of about 10–20 μ g olodaterol.

Trial 1222.6

Study Title: Randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy (bronchodilation) and safety of 4 weeks of once daily treatment of orally inhaled BI 1744 CL (2 μ g, 5 μ g, 10 μ g, 20 μ g) delivered by the Respimat® inhaler in patients with asthma

Objectives: To determine the optimum dose of BI 1744 CL inhalation solution delivered by the Respimat® inhaler once daily for 4 weeks in patients with asthma.

Study Design: Study 1222.6 and 1222.27 both were randomized, double-blind, placebo-controlled studies in asthma patients. In Study 1222.6, five parallel groups (54-61 patients per group) received once daily doses of either placebo, or 2, 5, 10 or 20 μ g olodaterol via the RESPIMAT inhaler over a period of 4 weeks. Serial pharmacokinetic blood samples were taken up to 3 and 6 hours after the inhalation on Day 1 and Day 29, respectively, and urine was collected up to 3 hours after the inhalation on both days. Additional pre-dose and 10 min post dose blood samples were taken on Days 8 and 15 to confirm attainment of steady state. Blood samples for determination of potassium were taken on Days 1, 8, 15 and 29 at 1 and 3 hours after the inhalation. Serial measurements of vital signs and ECG were performed up to 3 h post dose on Days 1, 8, 15 and 29.

Study 1222.27 included formoterol as an active control and was designed as double-dummy 4-period incomplete block crossover study with 6 possible treatments. These were the 4 doses of olodaterol (2, 5, 10 or 20 µg) delivered via the RESPIMAT inhaler once daily in the evening (pm), 12 µg formoterol twice daily delivered via the Aerolizer® inhaler, and placebo. Patients were scheduled to receive each treatment for 4 weeks without intermittent washout periods between treatments. A total number of 198 patients entered into the study, which due to the incomplete crossover design resulted in 121–130 patients per treatment. As the PK characteristics of olodaterol in asthma patients had already been established within Study 1222.6, only a limited number of pharmacokinetic blood samples (20 min, 1 h and 3 h post-dose) were taken on the last day of each treatment period in order to assess olodaterol plasma concentrations. Blood samples for determination of potassium (pre-dose, 1 h and 3 h post dose) were taken on the last day of each treatment period. Serial measurements of vital signs and ECG were performed up to 3 h post dose on Day 29.

Evaluation:

Efficacy: FEV₁, peak expiratory flow rate (PEF) in the morning (am) and in the evening (pm), forced vital capacity (FVC), area under the curve (AUC), peak response, rescue medication use, asthma control questionnaire (ACQ)

Pharmacokinetics: Plasma and urine concentrations of OLODATEROL and its metabolites SOM 1522 BS and OLODATEROL - glucuronide.

Safety: Adverse events (AEs), laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical examinations.

Pharmacokinetic Results: In the 2 µg dose group, olodaterol plasma concentrations were mostly below the limit of quantification. In the 5 µg group, plasma concentrations on Day 29 could be quantified only up to 1 hour post-dose in at least 1/3 of the patients. In the 10 µg and 20 µg groups, plasma concentrations could be quantified over the whole sampling period, i.e. up to 3 hours (Day 1) and 6 hours (Day 29), respectively, in at least 1/3 of the patients. Maximum olodaterol plasma concentrations after single inhalation as well as at steady state (shown to be reached by Day 8) were measured 11 to 20 minutes after drug inhalation. Accumulation accounted for a factor of 1.13 to 1.48 based on C_{max}, and 1.46 based on AUC₀₋₃. C_{max,ss} and AUC_{0-1,ss} values of olodaterol increased proportionally within the dose range 5–20 µg. Olodaterol glucuronide maximum plasma concentrations after a single dose as well as at steady state were observed 3 hours after the inhalation of olodaterol. Similar to olodaterol, steady state of olodaterol glucuronide was shown to be reached by Day 8. Accumulation of olodaterol glucuronide based on C_{max} values accounted for a factor of 0.966 to 1.29. The molar ratio between olodaterol glucuronide and olodaterol was 0.630 for AUC_{0-6,ss}. The metabolite SOM 1522 was not detectable in the majority of plasma and urine samples (LLOQ: 10 and 100 pg/mL, respectively).

Pharmacokinetic Conclusions: Pharmacokinetic results for olodaterol and olodaterol glucuronide obtained in asthma patients were comparable to those obtained in COPD patients. In the higher dose groups (10 and 20 µg olodaterol) slight effects of olodaterol on systemic pharmacodynamic parameters in the asthma patients became apparent.

Trial 1222.20

Study Title: Pharmacokinetics, safety and tolerability of a single dose of BI 1744 CL (20 µg administered with the RespimatR Inhaler) in patients with mild and moderate hepatic impairment (Child Pugh classifications A and B) in comparison to a single dose of BI 1744 CL (30 µg administered with the RespimatR Inhaler) in subjects with normal hepatic function in a monocentric, open label, parallel group Phase 1 trial.

Objectives: To investigate the influence of mild and moderate liver impairment on the pharmacokinetics, safety and selected pharmacodynamic parameters of olodaterol in comparison to a control group with normal hepatic function after single orally inhaled administration of olodaterol with the RESPIMAT inhaler.

Study Design: In this single-centre, open-label, parallel group study, 8 subjects with mildly impaired hepatic function (Child Pugh score 5 to 6 points), 8 subjects with moderately impaired hepatic function (Child Pugh score 7 to 9 points) and 16 healthy subjects (control group) with normal hepatic function received single doses of olodaterol via the RESPIMAT inhaler. The subjects of the control group were matched to the hepatically impaired patients with respect to gender, age and weight. The doses administered were 20 µg for the hepatically impaired patients, and 30 µg for the control group. Prior to drug administration blood was collected for determination of olodaterol plasma protein binding. Serial plasma and urine samples for analysis of olodaterol and SOM 1522 concentrations were collected up to 72 hours after the inhalation.

Results:

Pharmacokinetics: Statistical comparison of systemic exposure between patients with liver impairment and healthy volunteers by ANOVA was primarily based on dose-normalized C_{max} and AUC₀₋₄. The urinary excretion (fe_{0-tz}) of olodaterol was evaluated as supportive parameter. Based on adjusted gMean ratios of 82 to 112%, the systemic exposure to olodaterol and the urinary excretion of unchanged drug in patients with mild or moderate liver impairment was similar as compared to healthy volunteers.

The metabolite SOM 1522 was not detectable in plasma of any subject and detected only sporadically in urine throughout all three treatment groups. Plasma protein binding of olodaterol in the patients with liver impairment was unchanged as compared to the subjects with normal liver function

Table. Inter-individual comparison of dose-normalized pharmacokinetic parameters of olodaterol between hepatically impaired and matched healthy subjects

Parameter	N	LIP		HV		2-sided 90% CI	
		Adjusted gMean	N	Adjusted gMean	Ratio LIP/HV [%]	Lower Limit (%)	Upper Limit (%)
Mild liver impairment							
C _{max,norm} [pg/mL/μg]	8	0.439	15	0.391	112.2	83.6	150.7
AUC _{0-4,norm} [pg·h/mL/μg]	8	0.802	15	0.829	96.7	74.6	125.3
fe _{0-tz} [%]	8	3.31	16	3.61	91.8	56.9	148.1
Moderate liver impairment							
C _{max,norm} [pg/mL/μg]	7	0.387	15	0.391	99.0	72.7	134.7
AUC _{0-4,norm} [pg·h/mL/μg]	6	0.871	15	0.829	105.1	79.0	140.0
fe _{0-tz} [%]	7	2.95	16	3.61	81.8	49.6	135.0

LIP: Liver impaired patients, HV: Healthy volunteers

Source data: [U10-2864, Table 11.5.2.1.4: 1]

Conclusions: Mild and moderate impairment of liver function did not translate into a significant change of systemic exposure to olodaterol as compared to normal liver function. There was no indication for a pronounced increase of systemic exposure to the only pharmacologically active metabolite SOM 1522 in case of liver impairment.

Trial 1222.35

Study Title: Pharmacokinetics, safety and tolerability of single dose of BI 1744 CL (30 μg administered with the Respimat® Inhaler) in patients with severe renal impairment in comparison to subjects with normal renal function in a monocentric, open label, parallel group Phase 1 trial

Objectives: To assess the influence of severe renal impairment on the pharmacokinetics (PK), safety, and selected PD parameters of olodaterol (30 μg administered by inhalation with the RESPIMAT inhaler).

Study Design: In this single-centre, open-label, parallel group study, 8 subjects with severe renal impairment (creatinine clearance 18.6-29.8 mL/min) and 14 healthy subjects (control group) with normal renal function (creatinine clearance 81.2-117 mL/min) received single doses of 30 μg olodaterol via the RESPIMAT inhaler. The subjects of the control group were matched to the renally impaired patients with respect to gender, age and weight. Prior to drug administration, blood was collected for the determination of olodaterol plasma protein binding. Serial plasma and urine samples for analysis of olodaterol and SOM 1522 concentrations were collected up to 72 hours after the inhalation.

Pharmacokinetics Results: Statistical comparison of systemic exposure between patients with severe renal impairment and healthy volunteers by ANOVA was primarily based on C_{max} and

AUC₀₋₄ values. The urinary excretion (Ae_{0-tz}) and renal clearance (CLR₀₋₈) of olodaterol were evaluated as supportive parameters. The adjusted gMean ratios and 90% confidence intervals (CI) for C_{max}, AUC₀₋₄, Ae_{0-tz} and CLR₀₋₈ of the renally impaired patients and healthy subjects are summarized. Based on adjusted gMean ratios of 137% for C_{max} (CI: 84-222%) and of 135% for AUC₀₋₄ (CI: 94-195%), systemic exposure in subjects with severe renal impairment was about 1.4-fold higher, while urinary excretion and renal clearance were 5-6 times lower (adjusted gMean ratio: 17.8%, CI: 8.5-37.3% for Ae_{0-tz} and 20.1%, CI: 12.9-31.4% for CLR₀₋₈) as compared to subjects with normal renal function.

The active metabolite SOM 1522 was neither detectable in the plasma of the healthy subjects nor in the plasma of subjects with severe renal impairment. SOM 1522 was detected in a few urine samples of the healthy subjects and in none of the urine samples from the subjects with severe renal impairment.

Plasma protein binding of olodaterol in the patients with renal impairment was unchanged as compared to the subjects with normal renal function.

Table: Inter-individual comparison of pharmacokinetic parameters of olodaterol between subjects with severe renal impairment and matched healthy subjects

Parameter	sRIP		HV		Ratio sRIP/HV [%]	2-sided 90% CI	
	N	Adj. gMean	N	Adj. gMean		Lower Limit (%)	Upper Limit (%)
C _{max} [pg/mL]	7	11.1	13	8.2	136.6	84.1	222.0
AUC ₀₋₄ [pg·h/mL]	7	23.4	13	17.3	135.2	93.7	195.0
Ae _{0-tz} [ng]	8	123.2	14	693.5	17.8	8.5	37.3
CL _{R,0-8} [mL/min]	7	35.9	13	178.9	20.1	12.9	31.4

sRIP: subjects with severe renal impairment; HV: healthy subjects

Source data: [U10-2081, Table 11.5.2.1.4: 1]

Conclusions: On average, systemic exposure to olodaterol was 1.4-fold higher in subjects with severe renal impairment compared with healthy subjects; the maximum effect of renal impairment based on the upper CI limits was an about 2-fold increase. Thus, the effect of severe renal impairment on the PK of olodaterol appears to be moderate. There was no indication for a pronounced increase of systemic exposure to the only pharmacologically active metabolite SOM 1522 in case of renal impairment.

Trial 1222.9

Study Title: Investigation of the metabolism and pharmacokinetics of 20 µg (calculated as free base) [¹⁴C]BI 1744 CL administered as a 3-hour infusion and 40 µg (calculated as free base) [¹⁴C]BI 1744 CL administered as an oral solution

Objectives: Primary objective was to determine the basic pharmacokinetics of olodaterol, its metabolite olodaterol glucuronide and [14C]-radioactivity including excretion mass balance, excretion pathways and metabolism following intravenous and oral administration of [14C]olodaterol.

Secondary objective was to determine safety and tolerability following intravenous and oral administration of [14C]olodaterol in healthy male subjects.

Study Design: In this open-label, single-dose, parallel-group design study, a group of five healthy male subjects received 20 µg [14C]olodaterol (0.096 MBq) as intravenous infusion over 3 hours, and a group of six healthy male subjects received a single oral administration of 40 µg [14C]olodaterol (0.192 MBq) as drinking solution. Serial pharmacokinetic blood samples were collected up to 96 hours for determination of olodaterol, olodaterol glucuronide and total radioactivity. Urine and feces were collected up to 216 hours after the administration for determination of total radioactivity and (in urine only) olodaterol and olodaterol glucuronide. For the purpose of metabolite profiling and structure elucidation, additional blood samples were taken at 1, 2 and 4 hours after the oral administration, and at 10 min, 1 h and 3 h after the end of the 3-hours intravenous infusion (i.e. at 3.17, 4 and 6 h after the start of infusion), respectively. Individual blood samples within the treatment groups were pooled per time point prior to the metabolite analyses. Urine samples pooled by group and sampling interval up to 72 hours, feces samples of the intravenous group pooled by sampling interval up to 216 h and of the oral group pooled by sampling interval up to 168 h were also analysed for metabolites..

Pharmacokinetics Results: After intravenous infusion, C_{max} of olodaterol was observed at the end of the infusion. Thereafter, plasma concentrations declined multi-exponentially with a terminal half-life of 22.1 h. The volume of distribution at steady state (V_{ss}) was 1110 L, and total clearance was 872 mL/min. Excretion of olodaterol in urine (fe_{0-tz}) accounted for 18.9% of the dose. Plasma concentrations of olodaterol glucuronide were detected from 0.5 h onwards and reached their maximum also at the end of the infusion. Elimination of olodaterol glucuronide appeared to proceed in parallel with olodaterol. The molar ratio between olodaterol glucuronide and olodaterol (based on AUC_{0-∞}) was 0.206.

After oral administration, C_{max} of olodaterol was observed 1 hour after the administration. Plasma concentrations were low, so that they could maximally be quantified up to 4 hours after the administration. Plasma concentrations of olodaterol glucuronide could be quantified from 0.5 h onwards and reached their maximum around 2 h post-dose, thus, not largely delayed compared to the parent compound. The molar ratios between olodaterol glucuronide and olodaterol were 6.48 for C_{max} and 18.3 for AUC_{0-tz}.

The absolute bioavailability (F) following oral administration of [14C]olodaterol was below 1% based on comparison of geometric mean dose-normalized AUC_{0-tz} values between the oral and the iv group.

Excretion and mass balance: After intravenous administration of [14C]olodaterol, 42.5% of the total radioactive dose was recovered in urine and 53.0% in feces. More than 90% of the administered dose was excreted within the first 6 days.

Following oral administration, only 8.90% of the radioactive dose was excreted in urine, while the major portion of total radioactivity was recovered in feces (84.4%). More than

90% of the dose was excreted within 5 days.

Metabolism: Six metabolites of olodaterol were identified after intravenous as well as after oral administration of [¹⁴C]olodaterol: CD 992 and M565(2) were glucuronides of olodaterol, SOM 1522 was generated by oxidative demethylation of the methoxy moiety of olodaterol, CD 10915 and CD 11249 were glucuronides of SOM 1522, and CD 12656 was a sulfate SOM 1522. Structures of these metabolites are shown in [Figure 3.2.2: 1](#).

Following intravenous administration unchanged olodaterol was the dominant compound in plasma and urine, followed by CD 992 and CD 10915. After oral administration, predominantly CD 992 was found in plasma and urine, followed by CD 10915 ([Table 3.2.2: 1](#) and [Table 2.1.5: 1](#)). In feces, after both administration routes virtually the entire radioactivity was assigned to olodaterol and SOM 1522, while – presumably due to enzymatic cleavage by the intestinal flora – no glucuronides were found.

Table 2.1.5: 1 Metabolite pattern in urine and feces after single intravenous and single oral administration of [¹⁴C]olodaterol to healthy male subjects

Metabolite	Intravenous administration Dose: 20 µg			Oral administration Dose: 40 µg		
	Urine 0–72 h	Feces 0–216 h	Urine+feces	Urine 0–72 h	Feces 0–168 h	Urine+feces
	% of dose					
Olodaterol (BI 1744)	19.1 [§]	23.5	42.6	0.7	59.7	60.3
CD 992	9.8	n.d.	9.8	3.7	n.d.	3.7
M565(2)	n.d.	n.d.	n.d.	0.2	n.d.	0.2
SOM 1522	0.2	28.4	28.7	0.1	24.0	24.1
CD 10915	5.5	n.d.	5.5	1.9	n.d.	1.9
CD 11249	1.5	n.d.	1.5	0.7	n.d.	0.7
CD 12656	1.6	1.0	2.6	1.2	0.6	1.8
Non extractable	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Others*	0.6	n.d.	0.6	0.6	n.d.	0.6
Sum	38.4 ^{§,§}	52.9 ^{§,§}	91.3 [§]	9.1 ^{&,&}	84.3 ^{&,&}	93.4 [§]

* Structure unknown, individually <0.5% of dose

§ Arithmetic mean of 5 individuals

& Arithmetic mean of 6 individuals

§ Slight differences between values given in this Table and the data described in the paragraphs "Excretion and mass balance" and "Pharmacokinetics" above are due to different methodology, different sampling intervals considered and the use of arithmetic versus geometric means

n.d. Not detected

Conclusions: After intravenous administration, both, urinary and biliary excretion contributed relevantly to the elimination of olodaterol and its metabolites from the body. Major metabolites were the olodaterol glucuronide CD 992 and the SOM 1522 glucuronide CD 10915. Oral absorption of olodaterol calculated solely based on the drug-related material excreted in the urine amounted to at least 9%. However, parts of the drug-related material recovered in the feces after

oral administration may also have been absorbed and excreted via the bile. When assuming a similar relative contribution of urinary and biliary excretion after oral administration as seen after the intravenous route (38% via urine, 53% via bile, i.e. ratio of 1:1.4), about 13% of the radioactive dose after oral administration was excreted via the bile. Hence, about 22% of the oral dose was presumably absorbed. Extensive first-pass metabolism however resulted in a very low oral bioavailability of less than 1%.

Trial 1222.1

Study Title: A randomized, double-blind, placebo-controlled (within dose groups) study to assess safety, tolerability and pharmacokinetics of single rising inhaled doses (0.5 µg to 70 µg administered with the Respimat®) of BI 1744 CL in healthy male and female volunteers.

Objectives: To investigate safety, tolerability, and pharmacokinetics of increasing single inhaled doses of olodaterol in healthy volunteers.

Study Design: In this randomized, single-centre, double-blind, placebo-controlled study, single doses of 0.5, 1, 2.5, 5, 10, 15, 20, 30, 40, 50, 60 and 70 µg were administered to healthy male subjects via the RESPIMAT inhaler. Within the dose groups 0.5 to 60 µg, six subjects received active treatment and two subjects received placebo. In the 70 µg group, five subjects received active treatment and two subjects received placebo. The study in addition included six females receiving the 15 µg olodaterol dose and two females receiving placebo. From the 2.5–70 µg dose groups, serial plasma and urine samples were taken up to least 24 hours after dosing to be analyzed on olodaterol concentrations. In order to detect and identify metabolites of olodaterol, selected plasma and urine samples of the 70 µg dose group were additionally analyzed by HPLC/high resolution ESI-QTOF mass spectrometry using a modified parent ion discovery experiment [U06-1515]. Serial blood samples for determination of selected laboratory parameters (cAMP, potassium, glucose, lactate, free fatty acids, and insulin/C-peptide) were collected over a period of 24 hours after dosing. Measurements of vital signs and ECGs were performed at multiple time points up to 24 hours after dosing.

Pharmacokinetics Results:

Sufficiently high olodaterol plasma concentrations to provide plasma concentration-time profiles and to calculate PK parameters in at least $\frac{2}{3}$ of the subjects were achieved from the 10 µg dose upwards. Maximum plasma concentrations throughout the dose groups 10–70 µg were observed 14 to 22 minutes after inhalation (median t_{max}). Thereafter concentrations declined with a multiexponential disposition kinetics. Most reliable estimates for the geometric mean terminal half-life were obtained from the 50 µg and 60 µg dose groups, and were 38.0 and 39.5 hours, respectively. Renal clearance ($CL_{R,0-24}$) was 191 to 248 mL/min, suggesting active secretion of olodaterol via the kidneys. The cumulative urinary excretion of olodaterol up to 96 hours after inhalation accounted for approximately 5 to 6% of the administered dose. Systemic exposure as assessed by C_{max} (available from the 5 µg dose upwards) and AUC_{0-24} and $AUC_{0-\infty}$ (available from the 30 µg dose upwards) increased in proportion with the dose. The females in the 15 µg

dose group displayed on average about 1.6-fold higher plasma levels and 1.2-fold higher urinary excretion of olodaterol than the males.

Metabolism: In plasma (pool of 5 min, 20 min, 0.5 h, 1 h, 4 h and 6 h samples of all individuals of the 70 µg group) only unchanged olodaterol was detected. In urine olodaterol was present in all samples collected up to 12 hours after the inhalation (0–2 h of one individual, 2–4 h and 8–12 h samples of all individuals of the 70 µg group pooled per time interval). In the 0–2 h urine sample additionally the glucuronide CD 992 was unambiguously identified.

Pharmacodynamics: Among the various tested laboratory parameters, cAMP and potassium most sensitively and dose-dependently responded to olodaterol treatment. Statistically significant increases of plasma cAMP concentrations as compared to the placebo group were observed in the dose groups of 15 µg olodaterol and above. The cAMP concentrations in these groups reached their maximum between 1 and 3 hours (median time), and had returned to baseline at 24 hours after the inhalation of olodaterol.

Statistically significant decreases of serum potassium concentrations as compared to the placebo group were observed in the dose groups 20 µg olodaterol and above. Potassium concentrations in these groups reached their minimum between 2 and 3 hours (median time), and had returned to baseline at 24 hours after dosing.

Slight and transient decreases of diastolic blood pressure became apparent in the dose groups 15–30 µg, and became more prominent in the dose groups 40–70 µg olodaterol. Increases in heart rate were observed in the dose groups above 30 µg olodaterol. Increases in QTcF were observed at the dose level of 15 µg in female subjects and from 30 µg upwards in male subjects.

Conclusions: Olodaterol showed linear pharmacokinetics within the dose range of 5 µg to 70 µg inhaled via the RESPIMAT inhaler. Although systemic exposure in the females appeared to be higher than in males, the low number of females included in the study precluded a firm conclusion about gender difference. Slight, but dose-dependent systemic pharmacodynamic effects of olodaterol were observed starting with doses of 15–20 µg olodaterol.

Trial 1222.2

Study Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising inhalative doses (2.5 µg, 10 µg, and 30 µg) of BI 1744 CL for 14 days in healthy male and female volunteers (double blind, randomized, placebo controlled [at each dose level] study)

Objectives: To investigate safety, tolerability, pharmacokinetics and pharmacodynamics of increasing multiple inhaled doses of olodaterol in healthy volunteers.

Study Design: In this randomized, single-centre, double-blind, placebo-controlled study, once daily doses of 2.5, 10, and 30 µg were administered to healthy male subjects via the RESPIMAT inhaler for 14 days. Within each dose group, nine subjects received active treatment and three subjects received placebo. In an additional dose group, nine females received 10 µg olodaterol and three females received placebo. On the first and the last administration day, serial

pharmacokinetic blood and urine samples, and blood samples for determination of cAMP and potassium were taken. Additional pharmacokinetic blood samples were taken prior to dosing on Days 10 and 13 to confirm attainment of steady state.

Pharmacokinetics Results: Olodaterol plasma concentrations in the 2.5 µg dose group were generally below the lower limit of quantification (LLOQ: 2.0 pg/mL). In the 10 and 30 µg dose groups, maximum plasma concentrations were observed 10 and 20 minutes after drug inhalation, respectively (median t_{max}). Steady state was reached latest by Day 10, and accumulation based on olodaterol $C_{max,ss}/C_{max}$ ratios accounted for a factor of 1.25 to 1.45.

Values for C_{max} , $C_{max,ss}$ and $AUC_{0-24,ss}$ increased less than proportionally from the 10 µg dose group to the 30 µg dose group. In line with this finding, urinary excretion of olodaterol (expressed as percentage of the dose administered) tended to be lower in the 30 µg dose group than in the 2.5 µg and 10 µg dose groups. Comparison between male and female subjects within the 10 µg dose group revealed similar C_{max} values and urinary excretion both after single inhalation and at steady state. The geometric mean terminal half-life of olodaterol was most reliably determined at steady state in the dose groups 10 µg (females) and 30 µg (males), and was 45.9 and 45.1 hours, respectively. Excretion of olodaterol in urine within the 24 h dosing interval accounted for approximately 2-3% of the dose after single inhalation and for 5-7% at steady state.

Pharmacokinetic analysis of the olodaterol metabolites SOM 1522 and olodaterol glucuronide was performed for the 30 µg dose group. SOM 1522 was detected in none of the plasma samples (LLOQ: 10 pg/mL), and only in a few individual urine samples (LLOQ: 100 pg/mL). Maximum plasma concentrations of olodaterol glucuronide were observed 2 hours after single and multiple inhalation of olodaterol. Accumulation of olodaterol glucuronide in plasma based on C_{max} values accounted for a factor of 1.25. Comparable values for $AUC_{0-24,ss}$ and $AUC_{0-\infty}$ suggested no change of elimination and distribution processes of olodaterol glucuronide with repeated dosing of olodaterol. The molar ratio between olodaterol glucuronide and olodaterol was 0.498 for $AUC_{0-24,ss}$ and 0.869 for the amounts excreted in urine ($Ae_{0-24,ss}$).

Pharmacodynamics: Transient increases of cAMP from baseline concentrations statistically significantly higher than in the placebo group were observed in the dose groups 10 µg (Day 1: males and females, Day 14: males only) and 30 µg. The time of maximum cAMP concentrations in these groups was 2 to 3 hours after dosing (median values).

Transient decreases of potassium from baseline concentrations statistically significantly exceeding those in the placebo group were observed in the females after the dose of 10 µg on Days 1 and 14, and in the males after the dose of 30 µg on Day 14 only. The time of minimum potassium concentrations in these groups was 0.5 to 1 hour (median values).

Conclusions: Upon once daily inhalation of olodaterol via the RESPIMAT inhaler, steady state of olodaterol was attained latest by Day 10, and $t_{1/2,ss}$ was found to be about 45 hours. Systemic exposure was similar in males and females, however increased less than dose-proportionally when comparing the 10 and 30 µg dose groups. Systemic exposure to olodaterol glucuronide as assessed by $AUC_{0-24,ss}$ amounted to approximately 50% of the olodaterol systemic exposure, while molar amounts excreted via the urine were similar. Accumulation of both, olodaterol and

olodaterol glucuronide was low. Exposure to the metabolite SOM 1522 after the 30 µg dose was negligible. Beta-agonist mediated transient increases in plasma cAMP concentrations and decreases in serum potassium concentrations were observed from the dose level of 10 µg olodaterol upwards. Females appeared to be more susceptible to effects on potassium concentrations than the males.

Trial 1222.7

Study Title: Safety, tolerability and pharmacokinetics of single rising doses of 0.5 µg, 2.5 µg, 5 µg, 10 µg, 15 µg, 20 µg, 25 µg and 30 µg BI 1744 CL (calculated as free base) given as intravenous infusion over 30 minutes to healthy male subjects. A single-centre, single-blind, placebo-controlled, randomized study

Objectives: To investigate the safety, tolerability, and PK of single intravenous doses of olodaterol in healthy volunteers.

Study Design: In this placebo controlled, single blind, randomized, single centre study, male healthy volunteers received single intravenous doses from 0.5 µg up to 25 µg olodaterol. Within each dose group, six volunteers received the active drug and two received placebo. The dose levels were investigated serially in ascending sequence starting with the lowest dose of 0.5 µg. Up to the dose level of 15 µg, the doses were administered as a 30 minute infusion. Based on an interim analysis of safety and pharmacokinetic data, the infusion time thereafter was prolonged to 3 hours for the higher dose groups of 20 µg and 25 µg, based on the assumption that the degree of pharmacodynamic effects would be lower with slower infusion. In order to prove this hypothesis, the 15 µg dose was retested as a 3-hour infusion with the same individuals that had been tested with the 30-min infusion at this dose level before. The initially planned dose of 30 µg was omitted due to the systemic pharmacodynamic effects observed with the lower doses (see below, Pharmacodynamic Results). In all groups, serial pharmacokinetic and pharmacodynamic (cAMP and potassium) blood samplings, and measurements of blood pressure, pulse rate and ECGs were performed up to at least 24 hours after the start of infusion. Pharmacokinetic urine samples were collected up to 96 hours after the start of infusion.

Pharmacokinetics Results: With 30-min infusion of 0.5 µg olodaterol, olodaterol plasma concentrations were quantifiable only until the end of infusion. Following the 30-min infusion of 2.5, 5, 10 and 15 µg olodaterol, plasma concentrations could be quantified up to 0.833, 1.33, 4 and 12 hours relative to the start of the infusion, respectively, in the majority of subjects. Following 3-h infusion of 15, 20 and 25 µg olodaterol, olodaterol plasma concentrations could be quantified up to 10 hours after start of the infusion. Maximum plasma concentrations with both infusion schemes were reached only by the end of the infusion. After the end of infusion, olodaterol plasma concentrations decreased multiexponentially with a terminal half-life of 16.1 hours (Figure 2.1.3: 1). The most reliable estimates for volume of distribution at steady state (V_{ss}) and total clearance were 1190 L and 1520 mL/min, respectively. Excretion of olodaterol in urine was almost complete after 24 hours; in total 14% of the dose were excreted as olodaterol within 96 hours. Inspection of dose normalized C_{max} (within each

infusion scheme separately) and AUC_{0-∞} values (both infusion schemes together) suggested no deviation from dose-proportionality for intravenous doses of 0.5–25 µg olodaterol.

In the highest dose group (25 µg) plasma and urine concentrations of the metabolites olodaterol glucuronide and SOM 1522 were analyzed. Maximum plasma concentrations of olodaterol glucuronide were observed around the end of infusion (2.98–3.17 hours) and were lower compared to parent compound. The molar ratio between olodaterol glucuronide and olodaterol was 0.508 for AUC_{0-tz} and 0.961 for Ae₀₋₂₄. SOM 1522 could neither be quantified in plasma, nor (with the exception of one subject) in urine.

Conclusions: Olodaterol showed linear pharmacokinetics when intravenously infused at doses of 0.5 µg to 25 µg. Total clearance was high (1520 mL/min), renal clearance however contributed only to a minor degree (about 14%) to the overall elimination of the drug. A high value for volume of distribution (V_{ss}) indicated extensive tissue distribution of olodaterol. Systemic exposure to olodaterol glucuronide as assessed by AUC_{0-tz} amounted to approximately 50% of the olodaterol systemic exposure, while molar amounts excreted via the urine were similar for olodaterol glucuronide and olodaterol. The typical β_2 -agonist mediated systemic effects of olodaterol increased with escalating dose, but were attenuated when olodaterol plasma concentrations were reduced through prolongation of the infusion time.

Trial 1222.19

Study Title: A randomized, single-blind, placebo-controlled (within dose groups) study to assess safety, tolerability and pharmacokinetics of single rising peroral doses (15, 30, 40 µg free base) BI 1744 CL in healthy male volunteers

Objectives: To investigate safety, tolerability, and pharmacokinetics of single rising peroral doses of olodaterol.

Study Design: In this randomized, single-blind, placebo-controlled single centre study, single rising doses of 15 µg, 30 µg and 40 µg olodaterol were orally administered to three groups of six healthy male subjects each. Within each group, two additional subjects received placebo. Administration was performed using a peroral solution taken with a glass of water. Serial pharmacokinetic blood samples were taken up to 48 hours, and pharmacodynamic blood samples (potassium, cAMP) were taken up to 6 hours after administration. Urine for pharmacokinetic purposes was collected up to 48 hours after the administration.

Results:

Pharmacokinetics: Olodaterol could not be detected in plasma after the oral dose of 15 µg. In the 30 and 40 µg dose groups, olodaterol was quantifiable in plasma up to maximally 2 and 4 hours after administration, respectively. Maximum concentrations were observed at 1.50 and 0.875 hours, respectively. Geometric mean C_{max} values increased about proportionally with increasing dose from 30 to 40 µg. Urinary excretion of olodaterol accounted for only a very minor percentage of the administered dose (below 0.5%).

Olodaterol glucuronide was quantifiable in plasma generally up to 6, 8, and 10 hours after

oral administration of 15, 30 and 40 µg olodaterol, respectively. Maximum plasma concentrations were observed between 1 and 2 hours, and increased about proportionally with the olodaterol dose. The molar ratio between olodaterol glucuronide and olodaterol in the dose groups 30 µg and 40 µg was 6.34 and 8.34, respectively, for C_{max} , and 4.67 and 7.83, respectively, for the amounts excreted in the urine (Ae₀₋₄₈).

The metabolite SOM 1522 after all three doses investigated was neither detectable in plasma (except for one single sample) nor in urine.

Pharmacodynamics: Serum potassium and plasma cAMP concentrations throughout the observation period of 6 hours in all three treatment groups were not statistically significantly different from the placebo group.

Conclusions: After oral administration, olodaterol was rapidly absorbed (t_{max} at approximately 1–1.5 h) and substantially converted into glucuronide. Although a statistical assessment of doseproportionality based on the limited data available was regarded as unreasonable, comparison of geometric mean C_{max} values suggested dose proportional increase of systemic exposure to olodaterol and olodaterol glucuronide within the dose range 15–30 µg. No effects on serum potassium and plasma cAMP concentrations were observed at any of the investigated doses.

Trial 1222.47

Study Title: Relative bioavailability of 10 µg olodaterol (solution for inhalation administered with the Respimat®) at steady state alone or in combination with multiple doses of 400 mg q.d. ketoconazole (tablet) in healthy male and female volunteers (an open label, fixed sequence, Phase 1 study)

Objectives: To investigate whether and to what extent the P-gp inhibitor ketoconazole affects pharmacokinetic parameters (AUC and C_{max}) of olodaterol at steady state.

Study Design: This study was an open-label trial in 32 healthy male and female subjects with a fixed sequence in a single centre. In the first treatment period, the subjects received once daily doses of 10 µg olodaterol via the RESPIMAT inhaler for 8 days. In the subsequent second treatment period of 14 days they additionally received daily doses of 400 mg ketoconazole one hour prior to the inhalation of olodaterol. On the last day of both treatment periods plasma and urine samples were collected up to 23 hours after olodaterol inhalation and analyzed for olodaterol, olodaterol glucuronide and SOM 1522 concentrations. On the last day of the second treatment period, additional plasma samples up to 4 hours after ketoconazole administration (i.e. 3 hours after olodaterol inhalation) were taken and analyzed for ketoconazole to confirm sufficient exposure to the inhibitory drug. Further plasma samples taken 10 minutes after olodaterol inhalation on the last 4 days of each treatment period, and pre-dose samples taken on the last 4 days of the second treatment period served to confirm attainment of steady state for olodaterol and ketoconazole, respectively.

Results: Pharmacokinetics: Attainment of steady state for olodaterol and ketoconazole on the days of plasma concentration-time profiles, and sufficient exposure to ketoconazole were confirmed.

Primary endpoints for the assessment of steady state exposure to olodaterol were $C_{max,ss}$ and $AUC_{0-1,ss}$. The results of statistical comparison of these PK parameters in the presence and absence of ketoconazole by ANOVA. Adjusted gMean ratios of 166.1% for $C_{max,ss}$ and 168.4% for $AUC_{0-1,ss}$, with 90% confidence intervals of 153.6–179.6% and 155.5–182.4%, respectively, indicated increased systemic exposure to olodaterol when ketoconazole was coadministered.

The amount of olodaterol excreted in urine within 24 hours at steady state ($Ae_{0-24,ss}$) was increased by approximately 44% in the presence of ketoconazole (90% CI: 133.9–155.4%) as compared to olodaterol alone.

Parameter	Olodaterol + ketoconazole		Olodaterol alone		gMean ratio of olodaterol + ketoconazole to olodaterol (90% CI) [%]	Intra-individual gCV [%]
	N	Adjusted gMean	N	Adjusted gMean		
Primary endpoints						
$C_{max,ss}$ [pg/mL]	31	5.17	26	3.11	166.1 (153.6, 179.6)	16.8
$AUC_{0-1,ss}$ [pg-h/mL]	31	4.23	24	2.51	168.4 (155.5, 182.4)	16.4
Secondary endpoint						
$Ae_{0-24,ss}$ [ng]	32	618.7	32	429.0	144.2 (133.9, 155.4)	17.8

Steady state systemic exposure to olodaterol glucuronide based on adjusted gMean ratios of 106.6% (90% CI: 100.2–113.5%) for $C_{max,ss}$ and 100.8% (90% CI: 92.5–109.7%) for $AUC_{0-8,ss}$ was similar in the presence and absence of ketoconazole. The amount of olodaterol glucuronide excreted via the urine in contrast was higher when ketoconazole was coadministered as indicated by the adjusted gMean ratio of 132.9% (90% CI: 122.7–143.8%) for $Ae_{0-24,ss}$.

The olodaterol metabolite SOM 1522 in plasma and urine in both treatment periods was always below the limit of quantification.

Conclusions:

Coadministration of ketoconazole, a potent inhibitor of P-gp, increased the steady state exposure to olodaterol by approximately 70%. As ketoconazole besides P-gp also inhibits CYPs (2C9, 2C8) and UGTs (1A1, 1A9 and 2B7) relevant for the metabolism of olodaterol, this trial is assumed to represent a worst-case scenario with ketoconazole affecting several mechanisms involved in the up-take and elimination of olodaterol.

Trial 1222.48

Study Title: Relative bioavailability of 10 µg olodaterol (solution for inhalation administered with the Respimat®) at steady state alone or in combination with multiple doses of 400 mg q.d. fluconazole (hard capsule) in healthy male and female volunteers (an open label, fixed sequence, Phase 1 study)

Objectives: To investigate whether and to what extent the CYP2C9 inhibitor fluconazole affects the pharmacokinetic parameters AUC and C_{\max} of olodaterol at steady state.

Study Design: This study was an open-label trial in 35 healthy male and female subjects with a fixed sequence in a single centre. In the first treatment period, the subjects received once daily doses of 10 µg olodaterol via the RESPIMAT inhaler for 8 days. In the subsequent second treatment period of 14 days they additionally received daily doses of 400 mg fluconazole one hour prior to the inhalation of olodaterol (loading dose of 800 mg on the first day). On the last day of both treatment periods, plasma and urine samples were collected up to 23 hours after olodaterol inhalation and analyzed for olodaterol and olodaterol glucuronide concentrations. On the last day of the second treatment period additional plasma samples up to 4 hours after fluconazole administration (i.e. 3 hours after olodaterol inhalation) were taken and analyzed for fluconazole to confirm sufficient exposure to the inhibitory drug. Further plasma samples taken 10 minutes after olodaterol inhalation on the last 4 days of each treatment period, and pre-dose samples taken on the last 4 days of the second treatment period served to confirm attainment of steady state for olodaterol and fluconazole, respectively.

Pharmacokinetic Results: Attainment of steady state for olodaterol and fluconazole on the days of plasma concentration-time profiles and sufficient exposure to fluconazole were confirmed. Primary endpoints for the assessment of steady state exposure to olodaterol were $C_{\max,ss}$ and $AUC_{0-6,ss}$. The results of statistical comparison of these PK parameters in the absence and presence of fluconazole are analysed by ANOVA. Adjusted geometric mean parameter ratios for $C_{\max,ss}$ and $AUC_{0-6,ss}$ were close to 100% (109% and 113%, respectively) and the corresponding 90% confidence intervals (CIs) were completely within the generally applied acceptance range for bioequivalence of 80–125%. Similar results were obtained for the amount of olodaterol excreted in urine over a 24 h period at steady state ($Ae_{0-24,ss}$; adjusted gMean ratio: 114.8%, CI: 99.9–131.9%). Steady state systemic exposure and urinary excretion of olodaterol glucuronide were slightly decreased when fluconazole was co-administered with olodaterol as compared with administration of olodaterol alone, based on adjusted gMean ratios of 86.0% (90% CI: 79.3–93.3%) for $C_{\max,ss}$, 74.1% (90% CI: 69.1–79.4%) for $AUC_{0-12,ss}$, and 74.5% (66.6 to 83.3%) for $Ae_{0-24,ss}$.

The molar ratios of olodaterol glucuronide to olodaterol in plasma and in urine were 0.579 (based on $AUC_{0-6,ss}$) and 0.568 (based on $Ae_{0-24,ss}$) during treatment with olodaterol alone. The ratios decreased slightly to 0.415 and 0.369, respectively, when fluconazole was administered concomitantly with olodaterol.

Conclusions: Systemic exposure to olodaterol after multiple once daily inhalations was only slightly increased by fluconazole, a model inhibitor of CYP 2C9. A concomitant slight decrease of olodaterol glucuronide exposure suggests that inhibition of UGT isoforms may have contributed to the effects of fluconazole.

Trial 1237.3

Study Title: A randomized, double-blind, 3-way crossover study to compare pharmacokinetics and safety of 10 µg BI 1744 CL plus 5 µg tiotropium bromide given as fixed dose combination via the Respimat® Inhaler with the pharmacokinetics and the safety of the single agents, i.e. 10 µg BI 1744 CL and 5 µg tiotropium bromide, delivered via the Respimat® Inhaler following 21 day-treatment periods in patients with chronic obstructive pulmonary disease (COPD)

Objectives: The primary objective was to compare the steady state systemic exposure to olodaterol and tiotropium when inhaled as fixed dose combination (10 µg olodaterol plus 5 µg tiotropium bromide) with the systemic exposure after inhalation of each of the compounds alone.

Study Design: This multi-centric study was conducted in 45 male and female COPD patients according to a double-blind, randomized, 3-way crossover design. In three treatment periods of 21 days each the patients received either 10 µg olodaterol and 5 µg tiotropium bromide given as fixed dose combination (test), or 10 µg olodaterol (reference 1) or 5 µg tiotropium (reference 2) once daily via the RESPIMAT inhaler. On the last day of each treatment period, plasma and urine samples for analysis of olodaterol and tiotropium were collected up to 24 hours after the inhalation to obtain plasma concentration-time profiles. Additional plasma samples were taken 20 minutes post-dosing on Days 8 and 14 of each treatment period to confirm attainment of steady state.

Pharmacokinetic Results: Attainment of steady state for olodaterol and tiotropium by the end of each treatment period was confirmed. Primary endpoints for the assessment of steady state exposure were $C_{max,ss}$ and $AUC_{0-1,ss}$ for olodaterol, and $Ae_{0-24,ss}$ for tiotropium. The results of statistical comparison of these PK parameters between the different treatments are summarized by ANOVA. The upper bound of the 90% confidence interval for $AUC_{0-1,ss}$ of olodaterol (127%) was slightly outside the 80%–125% acceptance limits for equivalence of mono therapy and fixed dose combination with tiotropium. However, for $C_{max,ss}$ of olodaterol and $Ae_{0-24,ss}$ of tiotropium, confidence intervals were completely within the acceptance limits, with point estimates close to 100% (111 and 98%, respectively).

Table: Adjusted geometric mean PK parameters of olodaterol, ratios and two-sided 90% confidence intervals following administration of the olodaterol + tiotropium (test) and olodaterol (reference), respectively.

Parameter	Adjusted. gMean		Ratio [%]	Intra-indiv. gCV [%]	2-sided 90% CI	
	Test BI 1744 + tio	Reference BI 1744			Lower Limit (%)	Upper Limit (%)
$C_{max,ss}$ (pg/mL)	5.87	5.28	111	27.17	101	122
$AUC_{0-1,ss}$ (pg·h/mL)	4.67	4.15	112	32.15	99	127
$AUC_{0-2,ss}$ (pg·h/mL)	8.52	8.36	102	21.33	93	112
$Ae_{0-24,ss}$ (ng)	360.98	344.17	105	19.85	98	113
$AUC_{0-tz,ss}$ (pg·h/mL)	12.20	9.25	132	96.12	98	177

Table: Adjusted geometric mean PK parameters of tiotropium, ratios and two-sided 90% confidence intervals following administration of the olodaterol + tiotropium (test) and tiotropium (reference), respectively

Parameter	Adjusted. gMean		Ratio [%]	Intra-indiv. gCV [%]	2-sided 90% CI	
	Test BI 1744 + tio	Reference tiotropium			Lower Limit (%)	Upper Limit (%)
$Ae_{0-24,ss}$ (ng)	900.57	918.63	98	20.43	91	106
$C_{max,ss}$ (pg/mL)	15.55	16.15	96	29.92	87	107
$AUC_{0-4,ss}$ (pg·h/mL)	21.92	24.00	91	22.61	84	100
$AUC_{0-6,ss}$ (pg·h/mL)	29.97	33.24	90	19.81	83	98
$AUC_{0-tz,ss}$ (pg·h/mL)	32.67	32.91	99	72.08	79	125

Conclusions: Olodaterol and tiotropium did not relevantly affect each others pharmacokinetics when inhaled in combination.

Trial 1222.21

Study Title: A double-blind, randomised, placebo-controlled (within a dose group) study to evaluate safety, tolerability and pharmacokinetics of multiple rising inhalative doses (5 µg, 10 µg and 20 µg) of BI 1744 CL for 14 days in healthy male volunteers

Objectives: To evaluate safety, tolerability, and pharmacokinetics of BI 1744 CL in healthy Japanese male volunteers

Study Design: Randomised, double-blind within a dose group, placebo-controlled, multiple rising dose. Olodaterol will be administered at 5, 10, 20 ug orally inhaled.

Pharmacokinetic Results: The plasma concentrations of BI 1744 BS reached a maximum at 0.333 to 0.500 hour after drug inhalation in the case of multiple inhaled administration and declined rapidly thereafter. The geometric mean terminal half-life at the steady state was 35.6 hours in the BI 1744 CL 20 µg group. The cumulative fraction of BI 1744 BS excreted in the urine was approximately 7% to 10 % of the dose within the dosing interval of 0 to 24 hours in the steady state. The accumulation ratios of BI 1744 BS based on C_{max} and AUC₀₋₁ were 1.19 to 1.26 and 1.34 to 1.51, respectively. The results of visual inspection and statistical analysis indicated that C_{max} and AUC of BI 1744 BS increased doseproportionally within the dose range investigated.

The plasma concentration of BI 1744 BS-glucuronide increased more slowly than that of BI 1744 BS, reached a peak at 1 to 4 hours after drug inhalation in the case of multiple inhaled administration, and then gradually declined. The cumulative fraction of BI 1744 BS-glucuronide excreted in the urine was approximately 2% to 3% of the dose within the dosing interval of 0 to 24 hours in the steady state.

SOM 1522 BS was detected in only 1 plasma sample and was detected in urine samples from only a few subjects, precluding any conclusion as to the pharmacokinetics of SOM 1522 BS after once-daily inhalation of BI 1744 CL for 14 days in healthy Japanese male volunteers.

C_{max(ss)} and AUC_{0-1(ss)} of BI 1744 BS-glucuronide were lower than those of BI 1744 BS as shown by RC_{max(ss)}, Met values of 0.147 to 0.376 after a single dose and 0.273 to 0.505 after multiple doses and RAUC_{0-1(ss)}, Met values of 0.101 to 0.126 after a single dose and 0.135 to 0.200 after multiple doses. BI 1744 BS and BI 1744 BS-glucuronide were considered to have reached the steady state at least 7 days after the start of once-daily administration.

Conclusions: The plasma concentrations of BI 1744 BS rapidly increased after multiple inhaled administrations, and reached a peak at around 0.333 to 0.500 hour. The terminal half-life at the steady state was 35.6 hours. Cumulative fraction of BI 1744 BS excreted in the urine was approximately 7% to 10% of the dose within the dosing interval of 0 to 24 hours in the steady state. BI 1744 BS showed a dose-proportional increase in $C_{max(ss)}$ as well as in $AUC_{0-1(ss)}$ within the dose range examined. The accumulation ratios of BI 1744 BS on the basis of C_{max} and AUC_{0-1} were 1.19 to 1.26 and 1.34 to 1.51, respectively. $C_{max(ss)}$ and $AUC_{0-1(ss)}$ of BI 1744 BS-glucuronide were lower than those of BI 1744 BS, as shown by a $RC_{max(ss),Met}$ value of 0.147 to 0.505 and a $RAUC_{0-1(ss),Met}$ value of 0.101 to 0.200. BI 1744 BS and BI 1744 BS-glucuronide were considered to have reached a steady state after at least 7 days after the start of once-daily treatment. Systematic exposure of BI 1744 BS in Japanese subjects generally tended to be higher than those in the non-Japanese subjects. These were attributed to difference in body weight, such that the dose and the body-weight normalised parameters were similar between Japanese subjects and non-Japanese subjects.

Trial 1222.21

Study Title: Randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 4 weeks of once daily treatment of orally inhaled BI 1744 CL (2 µg, 5 µg, 10 µg) delivered by the Respimat® inhaler in Japanese patients with COPD

Objectives: To determine the optimum dose of olodaterol inhalation solution delivered by the Respimat® inhaler once daily for 4 weeks in Japanese patients with chronic obstructive pulmonary disease (COPD)

Study Design: Randomised, double-blind, placebo-controlled, parallel-group design comparing four groups (0, 2, 5, 10 ug) over 4 weeks

Pharmacokinetic Results: The plasma concentrations of olodaterol reached the maximum at around 0.333 hours after drug inhalation in the case of multiple inhaled administrations. The accumulation ratios of olodaterol based on C_{max} and AUC_{0-1} were 1.59 to 1.60 and 1.69 to 1.77, respectively. The results of visual inspection indicated that C_{max} and AUC_{0-1} of olodaterol increased dose-proportionally within the dose range investigated. The systemic exposure ($C_{max,norm}$, $AUC_{0-1,norm}$, $C_{max,ss,norm}$, and $AUC_{0-1,ss,norm}$) of olodaterol was not affected by age, gender, weight, renal function, liver function, or lung function. Systemic exposures in patients taking cytochrome P450 (CYP)2C8, CYP2C9, CYP3A4, UDP-glucuronosyltransferase (UGT) or P-glycoprotein (P-gp) inhibitors were similar

to these in patients not taking these inhibitors, though the number of patients taking comedication in this trial was small.

Conclusions: The plasma concentrations of olodaterol reached the maximum at around 0.333 hours after drug inhalation in the case of multiple inhaled administrations. The accumulation ratios of olodaterol based on C_{max} and AUC₀₋₁ were 1.59 to 1.60 and 1.69 to 1.77, respectively. Olodaterol showed dose-proportional increase in C_{max}(,ss) as well as in AUC₀₋₁(,ss) within the dose range investigated. The systemic exposure to olodaterol was not affected by age, gender, weight, renal function, liver function, or lung function.

Trial 1222.11/.12/.13/.14

Study Title: Randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD) [1222.11/.12]

A randomized, double-blind, double-dummy, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® Inhaler, and 48 weeks of twice daily Foradil® (12 µg) delivered by the Aerolizer® Inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD) [1222.13/.14]

Objectives: The primary objective of these studies was to assess the long-term efficacy and safety of once daily treatment of olodaterol inhalation solution (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the RESPIMAT inhaler in subjects with COPD.

Study Design: Studies 1222.11/.12/.13/.14 were designed as multi-centre, multinational randomized, double-blind, (1222.13 and 1222.14: double-dummy), placebo-controlled, parallel group studies. In each study, 207–235 COPD patients per treatment group received once daily doses of placebo, 5 µg olodaterol or 10 µg olodaterol, or (1222.13 and 1222.14 only) twice daily doses of 12 µg foradil, over a period of 48 weeks. Pharmacokinetic blood samples were taken prior to the first treatment, and at 10 minutes after the dosing (i.e. approximately t_{max}) on Days 43, 85 and 127. On Days 43 and 85, additional blood samples were taken at 1 and 3 hours after the treatments for determination of potassium concentrations. PK, PD and PK/PD analyses were performed for each of the four studies individually, as well as for the two twin studies combined (1222.9992 and 1222.9993 [U10-3303, U10-3302]).

The relationship between potassium concentrations and treatment, and between potassium concentrations and olodaterol plasma concentrations was additionally analyzed using the data from all four studies combined (SCS supplement [U10-3689]). The summary given below integrates the results of all mentioned analyses.

Pharmacokinetic Results: Olodaterol plasma concentrations at 10 minutes post-dosing (C0.167,ss) were comparable between Days 43, 85, and 127, i.e. after 6, 12 and 18 weeks of treatment with the study drug, and were similar to Cmax values previously observed in COPD patients after 4 weeks of olodaterol inhalation (1222.5).

Pharmacokinetic Conclusions: Chronic inhalation of 5 µg or 10 µg olodaterol by COPD patients did not significantly influence blood potassium levels. Systemic exposure to olodaterol in Asians was slightly higher than in Whites.

4.4 New Drug Application Filing and Review Form

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA/BLA Number	203108		Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II		Generic Name	Olodaterol
Medical Division	DPARP (OND-570)		Drug Class	Long-acting β2 agonist (LABA)
OCP Reviewer	Ping Ji, Ph.D.		Indication(s)	Maintenance Treatment of COPD
OCP Team Leader	Suresh Doddapaneni, Ph.D.		Dosage Form	Inhalation Spray
Pharmacometrics Reviewers	Satjit Brar, Ph.D. Venkatesh Bhattaram, Ph.D.		Dosing Regimen	2 inhalations (2.5 mcg/actuation) QD
Pharmacogenomic Reviewer	Michael Pacanowski, Pharm.D.			
Date of Submission	5/14/2012		Route of Administration	Oral Inhalation
Estimated Due Date of OCP Review	1/17/2013		Sponsor	Boehringer Ingelheim
Medical Division Review Due Date	1/17/2013		Priority Classification	S
PDUFA Due Date	March 14, 2012			March 14, 2013
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
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	17	17	5 studies related to tiotropium
I. Clinical Pharmacology				
Mass balance:	X	1	1	

Isozyme characterization:		6	6	Includes in vitro characterization of olodaterol metabolism
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-		12	11	
single dose:	X	5	5	Includes TQT Study
multiple dose:	X	4	4	Includes 2 DDI Studies
Patients-		11	11	
single dose:	X	4		Includes renal and hepatic impairment studies
multiple dose:	X	8	8	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	X	1	1	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2	2	
In-vivo effects of primary drug:	X	1	1	
In-vitro:	X	4	4	
Subpopulation studies -				
ethnicity:	X	2	2	
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD -				
Phase 2:	X			
Phase 3:	X			
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:				
Population Analyses -	X	1	1	
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	X			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X			
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		43	43	Not including analytical reports

Appears this way on original

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
01/17/2013

SATJIT S BRAR
01/17/2013

VENKATESH A BHATTARAM
01/17/2013

SURESH DODDAPANENI
01/17/2013

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203108	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Olodaterol
Medical Division	DPARP (OND-570)	Drug Class	Long-acting β 2 agonist (LABA)
OCP Reviewer	Elizabeth Shang, Ph.D. R.Ph	Indication(s)	Maintenance Treatment of COPD
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Inhalation Spray
Pharmacometrics Reviewers	Satjit Brar, Ph.D. Venkatesh Bhattaram, Ph.D.	Dosing Regimen	2 inhalations (2.5 mcg/actuation) QD
Pharmacogenomic Reviewer	Michael Pacanowski, Pharm.D.		
Date of Submission	5/14/2012	Route of Administration	Oral Inhalation
Estimated Due Date of OCP Review		Sponsor	Boehringer Ingelheim
Medical Division Due Date		Priority Classification	S
PDUFA Due Date			March 14, 2013

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
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	17		5 studies related to tiotropium
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:		6		Includes in vitro characterization of olodaterol metabolism
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -	X	12		
Healthy Volunteers-				
single dose:	X	5		Includes TQT Study
multiple dose:	X	4		Includes 2 DDI Studies
Patients-				
single dose:	X	4		Includes renal and hepatic impairment studies
multiple dose:	X	8		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		
In-vivo effects of primary drug:	X	1		
In-vitro:	X	4		
Subpopulation studies -				

ethnicity:	X	2		
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		
hepatic impairment:	X	1		
PD -				
Phase 2:	X			
Phase 3:	X			
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	X			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X			
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		41		

On **initial** review of the NDA/BLA application for filing:

	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		To-be-marketed product was used in studies
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?	X			
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)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
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?			X	Sponsor requested full waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
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 another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

_____Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

We request that you submit the following information:

1. Submit the datasets and codes/scripts for reviewers to recreate the analyses described in the report entitled “Clinical Report- Pharmacokinetic Meta-Analysis Report” Doc. No. U10-2212-01. All model codes or control streams, output listings and scripts used to generate analyses and plots should be provided for all analyses performed. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
2. Submit all electronic clinical pharmacokinetic data sets as SAS transport files and a definition file which describes the contents of the electronic data sets. If possible, submit all data sets in CDISC SDTM format.
3. Submit a brief summary of the genotyping methods, tested alleles, and quality control procedures with regard to the UGT pharmacogenetic analyses, in addition to submitting each subject’s genotype data for the four genes in the meta-analysis dataset(s).

Elizabeth Shang, Ph.D.	July 13, 2012
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni, Ph.D.	July 13, 2012
Team Leader/Supervisor	Date

Background

This is a new drug application submitted by Boehringer Ingelheim for olodaterol inhalation spray administered by a hand-held, pocket-sized, multi-dose, oral inhalation device (RESPIMAT) intended for use in patients with chronic obstructive pulmonary disease (COPD). Olodaterol, a new molecular entity, is a long-acting selective β_2 -adrenoceptor agonist (LABA) acting as a bronchodilator under development for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. The proposed dose is 5 μg (2 inhalations of 2.5 μg) once daily. Other LABAs currently available on the market for this indication are salmeterol, formoterol, arformoterol, and indacaterol. As of May 2012, Olodaterol Respimat Inhalation Spray has not been commercialized in any country.

The efficacy and safety of olodaterol 5 μg QD is based on the results of 2 sets of replicate, pivotal, randomized, double-blind, 48-week placebo controlled Phase 3 studies (1222.11, 1222.12) and additional 2 sets of replicate, randomized, double-blind, 48-week placebo controlled, versus active controlled (formoterol) Phase 3 studies (1222.13, 1222.14).

Overview of Clinical Pharmacology submission and data

A total of 12 Phase 1 clinical pharmacology trials were conducted (See Table 1 in Appendix).

Five trials were conducted to investigate primarily the PK of inhaled olodaterol in healthy subjects (1222.1, 1222.2, 1222.7, and 1222.19), including one study investigated the PK of olodaterol in healthy Japanese subjects (1222.21). Two clinical studies investigated the influence of the intrinsic factors of hepatic and renal impairment on PK parameters of olodaterol (1222.20 and 1222.35). Three clinical studies investigated the drug-olodaterol interactions. Impact of Pgp inhibitor and CYP2C9 inhibitor upon olodaterol PK were evaluated in healthy subjects (1222.47 and 1222.48, respectively). PK interaction between olodaterol and tiotropium was evaluated in COPD patients (1237.3). There was one ADME trial investigating mass balance following IV administration and oral administration (1222.9). A thorough QT/QTc study (1222.8) report was also submitted.

Pharmacokinetics of olodaterol was also evaluated in COPD and asthma patients during the Phase 2 and Phase 3 drug development. Pharmacokinetics in COPD patients was assessed in 4 Phase 2 studies: 1222.3 (single dose study), 1222.5 (4 weeks once daily dosing), 1222.22 (4 weeks once daily dosing in Japanese COPD patients), 1222.26 (3 weeks once daily vs. twice daily dosing). Pharmacokinetics in COPD patients was also assessed in 4 Phase 3 studies, which are all 48 weeks once daily dosing: 1222.11, 1222.12, 1222.13, 1222.14.

Pharmacokinetics of olodaterol in asthma patients was assessed in 3 Phase 2 studies: 1222.4 (single dose study), 1222.6 (4 weeks once daily dosing) and 1222.27 (4 weeks once daily dosing).

Bioanalytical methods have been developed for the determination of plasma and urine concentrations of olodaterol, and its major metabolites, CD992 and SUM BI 1744 BS (analyte name for olodaterol determined in samples treated with glucuronidase, representing the total of

free olodaterol and glucuronic acid conjugates of olodaterol in the sample). All bioanalytical reports including validation reports were properly submitted for review.

The RESPIMAT A4 inhalation device was used in the very first clinical trial (1222.1), whereas the to-be-market RESPIMAT A5 was employed in all other clinical studies. The two RESPIMAT versions are identical in their performance parameters and properties in terms of duration of spray, spray velocity, particle size distribution and delivered volume. The only difference between the two versions is that the RESPIMAT A5 is equipped with a locking mechanism that prevents the use of olodaterol RESPIMAT beyond the labelled number of doses.

As there were no formulation changes and no relevant device changes during the clinical development of olodaterol RESPIMAT solution for inhalation, no relative BA or BE studies were conducted.

Absolute bioavailability of olodaterol following inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was below 1% when given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is mainly determined by lung absorption. Following inhalation, olodaterol is rapidly absorbed, reaching maximum plasma concentrations generally within 10 to 20 minutes following drug inhalation. Olodaterol showed linear pharmacokinetics with a dose-proportional increase of systemic exposure after single inhaled doses of 5 mcg to 70 mcg and multiple once daily inhaled doses of 2 mcg to 20 mcg. Olodaterol showed linear PK, with an overall dose-proportional increase of systemic exposure after repeated QD inhaled doses of 2 to 20 mcg. Steady state plasma concentrations of olodaterol were achieved within 8 days of QD inhalation. Accumulation ratios were in the range of 1.3 to 1.8 for AUC values (AUC0-1h or AUC0-3h).

Binding of olodaterol to human plasma proteins is independent of concentration and is approximately 60%. The volume of distribution is high (1110 L), suggesting extensive distribution into tissue.

In vitro studies showed that the major route of metabolism of olodaterol is via glucuronidation. CYP2C9 was reported to be the main responsible enzyme for CYP mediated elimination of olodaterol in liver. Olodaterol was found to be stable when incubated with human lung microsomes. Thus, an extensive phase I metabolism of olodaterol in the lung following inhalation is unlikely.

IV and oral mass balance study indicated that olodaterol is substantially metabolized. About 50% of the drug-related material excreted being metabolites after IV administration of [¹⁴C]-labeled olodaterol. After IV administration, 38% of the radioactive dose was recovered in the urine and 53% was recovered in feces, indicating considerable biliary excretion of olodaterol and its metabolites. Following oral administration of [¹⁴C]-labeled olodaterol, which mimicked the fate of swallowed portion of olodaterol, 9% of the administered radioactivity was recovered in urine, while 84% was recovered in feces.

After intravenous administration, major metabolites identified were the olodaterol glucuronide CD 992 and the SOM 1522 glucuronide CD 10915. However, only CD 992 was detectable in plasma following multiple doses administration via inhalation.

Of six metabolites identified, only the unconjugated demethylation product SOM1522 shows pharmacological activity on the β_2 -receptor, with binding affinity and agonistic potency similar to olodaterol. However, SOM1522 was not detectable in plasma after administration of multiple therapeutic dose or doses of up to 4-fold higher.

Total clearance of olodaterol in healthy volunteers following intravenous infusion is 872 mL/min, and renal clearance is 173 mL/min, indicating the presence of active secretion of olodaterol in the kidney. The terminal half-life following IV is 22 hours, while the terminal half-life following inhalation is about 45 hours. It is thought that the longer half-life following inhalation is determined by absorption rate than by elimination process.

Across-study comparisons suggest somewhat higher systemic exposure in COPD patients than in the healthy subjects.

A multivariate linear regression analysis was performed to explore the impact of selected intrinsic and extrinsic factors on systemic exposure parameters of olodaterol using data from two Phase 2 trials (1222.5 for COPD and 1222.6 for Asthma). Age, weight, height and lung function (pre-treatment baseline FEV1) were identified as factors contributing to the inter-individual variability of olodaterol plasma concentrations in COPD patients. A maximally 1.4-fold increase in olodaterol C_{max} is found in COPD patients of young age, low body weight, large body height, or low FEV1. A 2-fold increase in C_{max} may be found in COPD patients with all of these factors combined. Gender has no influence on systemic exposure. No dose adjustment was proposed.

Systemic exposure appeared to be generally higher in the Japanese population. C_{max,ss} is about 1.5 fold of the Caucasian patients. A 1.2 fold higher systemic exposure was also observed for other Asians. However, the systemic exposure in Blacks was comparable to those observed in Caucasians. No dose adjustment was proposed.

A dedicated hepatic impairment study was conducted in patients with mild and moderate hepatic impairment. Exposure to olodaterol in both groups was similar to healthy subjects.

A dedicated renal impairment study was conducted in patients with severe renal impairment. A 1.4-fold higher systemic exposure to olodaterol was observed in severely renally impaired subjects. Sponsor considered such increased was clinically insignificant. No dose adjustment was proposed.

Pharmacogenomic samples obtained from COPD and asthma patients in Phase 2 studies (1222.5 and 1222.6) were used to analyze polymorphisms in the genes related to UGT isoforms UGT1A1, 1A7, 1A9, and 2B7. The impact of these isoforms on olodaterol systemic exposure was evaluated. None of the variations in the respective UGT genes was found to statistically significantly affect systemic exposure to olodaterol or olodaterol glucuronide. (b) (4)

Clinical drug-drug interaction studies were conducted using fluconazole as a model inhibitor for CYP2C9 and ketoconazole as a P-gp (and CYP3A4, 2C8, 2C9) inhibitor. No effect of fluconazole upon systemic exposure to olodaterol. Steady-state exposure to olodaterol was found to be increased by ~70% following ketoconazole co-administration.

Clinical drug-drug interaction study with tiotropium was also conducted. Although $C_{max,ss}$ of olodaterol was statistically increased by 11% following 10 mcg olodaterol and 5 mcg tiotropium co-administration, the effect was considered clinically insignificant. No effect of olodaterol upon systemic exposure to tiotropium was found.

A thorough QT (TQT) study was conducted and the study results have been reviewed by QT-IRT in 2008 under IND 76,362 for COPD. The IRT review showed that single dose inhalation of 10 mcg olodaterol did not prolong the QTc interval. However, following a single dose of 50 µg olodaterol, the maximum mean increase in $\Delta\Delta QTcI$ was 9 ms with an upper CI exceeding the 10 ms regulatory threshold. There was a positive olodaterol concentration- $\Delta\Delta QTcI$ relationship. Based on this relationship, QT prolongation is not expected to exceed 10 ms at the steady-state C_{max} (7.13 pg/mL) for olodaterol 10 µg. The Sponsor's analysis submitted to this NDA claimed that "Olodaterol at single doses of 10, 20, 30, and 50 mcg demonstrated that compared with placebo, the mean changes in QT interval from baseline over 20 minutes to 2 hours after dosing increased dose dependently from 1.6 ms (10 mcg olodaterol) to 6.5 ms (50 mcg olodaterol), with the upper limit of the two-sided 90% confidence intervals being less than 10 ms at all dose levels". This will be a review issue.

Rationale for Dose Selection

Two dose levels were studied in Phase 3: 5 mcg QD and 10 mcg QD. Comparison of doses were made based upon a) bronchodilator efficacy endpoints of FEV1, FVC, PEFR, IC, and FRC; and b) Symptomatic benefit endpoints of TDI focal score, SGRQ total scores, and rescue medication use. The Sponsor concluded that there was no substantial evidence of a clinically meaningful incremental benefit with olodaterol 10 mcg compared to olodaterol 5 mcg. Thus, the Sponsor is seeking 5 mcg QD for approval.

Pediatric Development Plan

Sponsor has requested a full waiver as COPD is not a disease affecting pediatric patients.

Conclusions

The filing meeting took place on June 26, 2012. The NDA is considered fileable from the clinical pharmacology perspective. No DSI inspection is needed. All PK study reports including Bioanalytical assay and validation reports are available. A request for information will be generated for electronic datasets for PK, meta-analysis and pharmacogenomics. Preliminary review of the proposed label did not reveal any major issues at this time.

APPENDIX

Table 1. Overview of Clinical Pharmacology Studies conducted and submitted in NDA203108.

Study No. Report No.	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Treatment Duration
1222.1 U06-1418	Safety, tolerability, pharmacokinetics, systemic pharmacodynamics	Randomized, double-blind (within dose), placebo-controlled, parallel group	Olodaterol solution for inhalation; 0.5 µg, 1 µg, 2.5 µg, 5 µg, 10 µg, 15 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg; inhalation	Total: 102 Active: 77 Placebo: 25	Healthy subjects	Single dose
1222.2 U07-2062 [CTR] U08-1262 [metabolite report]	Safety, tolerability, pharmacokinetics, systemic pharmacodynamics	Randomized, double-blind (within dose), placebo-controlled, parallel group	Olodaterol solution for inhalation; 2.5 µg qd, 10 µg qd, 30 µg qd; inhalation	Total: 47 Active: 36 Placebo: 11	Healthy subjects	14 days
1222.7 U08-1081	Safety, tolerability, pharmacokinetics	Randomized, single blind, placebo-controlled, parallel group	Olodaterol solution; 0.5 µg, 2.5 µg, 5 µg, 10 µg, 15 µg, 20 µg, 25 µg, intravenous	Total: 64 Active: 48 Placebo: 16	Healthy subjects	Single dose
1222.19 U08-1060	Safety, tolerability, pharmacokinetics	Randomized, placebo-controlled, parallel group	Olodaterol solution; 15 µg, 30 µg, 40 µg; per oral	Total: 24 Active: 18 Placebo: 6	Healthy subjects	Single dose
1222.9 U08-2268	Human ADME	Open label, parallel group	Olodaterol solution; 20 µg; intravenous Olodaterol solution; 40 µg; per oral	Total: 11 i.v.: 5 p.o.: 6	Healthy subjects	Single dose
1222.21 U08-3758	Safety, tolerability, pharmacokinetics in Japanese	Randomized, double-blind (within dose), placebo-controlled, parallel group	Olodaterol solution for inhalation; 5 µg qd, 10 µg qd, 20 µg qd; inhalation	Total: 36 Active: 27 Placebo: 9	Healthy subjects	14 days
1222.20 U10-2864	Pharmacokinetics in hepatic impairment	Open label, parallel group	Olodaterol solution for inhalation; 20 µg, 30 µg; inhalation	Total: 32 16 patients (20 µg) 16 healthy subjects (30 µg)	Mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment; Healthy subjects	Single dose

Study No. Report No.	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Treatment Duration
1222.35 U10-2081	Pharmacokinetics in renal impairment	Open label, parallel group	Olodaterol solution for inhalation; 30 µg; inhalation	Total: 22 8 patients 14 healthy subjects	Severe renal impairment; Healthy subjects	Single dose
1237.3 U09-1422	Pharmacokinetic interaction of olodaterol and tiotropium	Randomized, double-blind, cross-over	Olodaterol solution for inhalation; 10 µg qd; inhalation Tiotropium solution for inhalation; 5 µg qd; inhalation Tiotropium+olodaterol FDC solution for inhalation; 5 µg /10 µg qd; inhalation	Total: 47 Olo 10: 47 Tio 5: 47 T/O 5/10: 47	COPD	3 weeks
1222.47 U10-3390	Effect of Pgp inhibitor on pharmacokinetics of olodaterol	Open label, fixed sequence	Olodaterol solution for inhalation; 10 µg qd; inhalation Ketoconazole tablet; 400 mg q.d.; per oral	32	Healthy subjects	Period 1 (olodaterol): 8 days Period 2 (olodaterol plus ketoconazole): 14 days
1222.48 U10-3391	Effect of CYP 2C9 inhibitor on pharmacokinetics of olodaterol	Open label, fixed sequence	Olodaterol solution for inhalation; 10 µg qd; inhalation Fluconazole hard capsule; 400 mg qd (800 mg loading dose); per oral	35	Healthy subjects	Period 1 (olodaterol): 8 days Period 2 (olodaterol plus fluconazole): 14 days

Study No. Report No.	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Treatment Duration
1222.8 U08-1543	Thorough QT/QTc interval evaluation, pharmacokinetics	Randomized, double-blind, placebo-controlled, cross-over	Olodaterol solution for inhalation; 10 µg, 20 µg, 30 µg, 50 µg; inhalation	Total: 24 Active: 24 Placebo: 24	Healthy subjects	Single dose
1222.5 U09-3125 [CTR]	Efficacy (FEV ₁) dose-response vs. placebo, safety and pharmacokinetics	Randomized, double-blind, placebo-controlled, parallel group	Olodaterol solution for inhalation; 2 µg qd, 5µg qd, 10 µg qd, 20 µg qd; inhalation	Total: 405 Olo 2: 81 Olo 5: 80 Olo 10: 86 Olo 20: 79 Placebo: 79	COPD	4 weeks
1222.3 U07-1743 [CTR] U08-1263 [metabolite report]	Efficacy (FEV ₁) dose-response vs. placebo, safety and pharmacokinetics	Randomized, double-blind, placebo-controlled, cross-over, open label extension (?)	Olodaterol solution for inhalation; 2 µg, 5 µg, 10 µg, 20 µg, 40 µg; inhalation	Total: 36 Olo 2: 35 Olo 5: 35 Olo 10: 34 Olo 20: 35 Olo 40: 14 Placebo: 35	COPD	Single dose
1222.26 U10-1155	Efficacy (FEV ₁) once daily vs. twice daily, safety and pharmacokinetics	Randomized, double-blind, cross-over	Olodaterol solution for inhalation; 5 µg qd, 10 µg qd, 2 µg bid, 5µg bid; inhalation	Total: 47 Olo 2 bid: 47 Olo 5 bid: 46 Olo 5 qd: 47 Olo 10 qd: 46	COPD	3 weeks
1222.4 U08-3408	Efficacy dose-response vs. placebo, safety and pharmacokinetics	Randomized, double-blind, placebo-controlled, cross-over	Olodaterol solution for inhalation; 2 µg, 5 µg, 10 µg, 20 µg; inhalation	Total: 31 Olo 2: 28 Olo 5: 28 Olo 10: 30 Olo 20: 29 Placebo: 29	Intermittent Asthma	Single dose
1222.6 U09-1850	Efficacy dose-reponse vs. placebo, safety and pharmacokinetics	Randomized, double-blind, placebo-controlled, parallel group	Olodaterol solution for inhalation; 2 µg qd, 5 µg qd, 10 µg qd, 20 µg qd; inhalation	Total: 296 Olo 2: 61 Olo 5: 60 Olo 10: 60 Olo 20: 61 Placebo: 54	Persistent Asthma	4 weeks
1222.27 U11-2137	Efficacy dose-response vs. placebo, safety and pharmacokinetics	Randomized, double-blind, double-dummy, placebo-controlled, active-controlled, cross-over	Olodaterol solution for inhalation; 2 µg qd, 5 µg qd, 10 µg qd, 20 µg qd; inhalation	Total: 198 Olo 2: 121 Olo 5: 130 Olo 10: 127 Olo 20: 124 Placebo: 125 Form 12: 125	Persistent Asthma	20 weeks

Study No. Report No.	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Treatment Duration
1222.22 U10-2537	Efficacy dose-response vs. placebo in Japanese, safety and pharmacokinetics	Randomized, double-blind, placebo-controlled, parallel group	Olodaterol solution for inhalation; 2 µg qd, 5 µg qd, 10 µg qd; inhalation	Total: 328 Olo 2: 84 Olo 5: 79 Olo 10: 86 Placebo: 79	COPD	4 weeks
1222.11 U10-3192	Confirmatory long-term efficacy, safety vs. placebo, pharmacokinetics [1222.11/1222.12 replicate studies]	Randomized, double-blind, placebo-controlled, parallel group	Olodaterol solution for inhalation; 5 µg qd, 10 µg qd; inhalation	Total: 624 Olo 5: 208 Olo 10: 207 Placebo: 209	COPD	48 weeks
1222.12 U10-3193	Confirmatory long-term efficacy, safety vs. placebo, pharmacokinetics [1222.11/1222.12 replicate studies]	Randomized, double-blind, placebo-controlled, parallel group	Olodaterol solution for inhalation; 5 µg qd, 10 µg qd; inhalation	Total: 642 Olo 5: 209 Olo 10: 217 Placebo: 216	COPD	48 weeks
1222.13 U10-3194	Confirmatory long-term efficacy, safety vs. placebo, vs. Formoterol, pharmacokinetics [1222.13/1222.14 replicate studies]	Randomized, double-blind, double-dummy, placebo-controlled, active-controlled, parallel group	Olodaterol solution for inhalation; 5 µg qd, 10 µg qd; inhalation Formoterol dry powder for inhalation; 12 µg bid; inhalation	Total: 904 Olo 5: 227 Olo 10: 225 Form 12: 227 Placebo: 225	COPD	48 weeks
1222.14 U10-3195	Confirmatory long-term efficacy, safety vs. placebo, vs. Formoterol, pharmacokinetics [1222.13/1222.14 replicate studies]	Randomized, double-blind, double-dummy, placebo-controlled, active-controlled, parallel group	Olodaterol solution for inhalation; 5 µg qd, 10 µg qd; inhalation Formoterol dry powder for inhalation; 12 µg bid; inhalation	Total: 934 Olo 5: 232 Olo 10: 234 Form 12: 233 Placebo: 235	COPD	48 weeks

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/s/

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