Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: Berodual® Respimat®			
Name of active ingredient: fenoterol hydrobromide + ipratropium bromide		**Page 1 of 8**	
Report date: 24 AUG 06	**Number:** 215.1364	**Study period (dates):** 26 SEP 05 - 07 DEC 05	**Date of Revision**

Title of study:	A randomised open label, six way, cross-over scintigraphic evaluation of the effect of inspiratory flow rate on lung and oropharyngeal deposition with the Respimat® inhaler vs. a Metered Dose Inhaler (HFA-MDI) using Berodual® in patients with Chronic Obstructive Pulmonary disease (COPD).
Investigator:	[redacted]
Study center(s):	Inamed Research GmbH & Co. KG Robert-Koch-Allee 29 82131 Gauting Germany
Publication (reference):	--
Clinical phase:	IV
Objectives:	The objective of this trial was to compare the total and regional deposition of aerosol in the lungs and oropharynx of patients with COPD at 3 different inspiratory flow rates following inhalation of Berodual® delivered via the Respimat® inhaler and Berodual® delivered via an HFA-metered dose inhaler. The primary endpoint was the percentage whole lung deposition. The Respimat® inhaler was also compared with the MDI in terms of • Central lung zone deposition • Intermediate lung zone deposition • Peripheral lung zone deposition • Ratio of peripheral to central zone deposition • Oropharyngeal deposition • Device deposition and exhaled air filter deposition • FEV_1 15, 30 and 60 minutes post-administration (safety only)
Methodology:	Controlled, randomised, crossover design; prospective comparison over 6 test days using gamma-scintigraphy

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No. of subjects:	
planned:	enrolled: 25 entered: 18
actual:	enrolled: 19 entered: 19 analysed (for primary endpoint): 19
Diagnosis and main criteria for inclusion:	Males and non-pregnant females with COPD, age ≥ 40 years
Test product:	Berodual® Respimat®
dose:	fenoterol hydrobromide 50 µg + ipratropium bromide 20 µg (strength per puff)
mode of admin.:	Inhalation via Respimat®
Batch-No.:	404 446, exp. date 05/2007 (non-labelled)
Duration of treatment:	1 administration of Berodual® (1 puff) delivered from a Respimat® inhaler on 3 study days and 1 administration of Berodual® (2 puffs) delivered from an HFA-MDI on 3 study days. Each study day to be separated by at least 48 hours.
Reference therapy:	Berodual® HFA-MDI
dose:	fenoterol hydrobromide 50 µg + ipratropium bromide (anhydrous)* 20 µg (strength per puff) *each valve actuation delivers 50 µg of fenoterol hydrobromide + 21 µg of ipratropium bromide monohydrate (corresponds to 20 µg ipratropium bromide anhydrous)
mode of admin.:	Inhalation via HFA-MDI
Batch-No.:	502 692, exp. date 08/2006 (non-labelled)
Criteria for evaluation:	
Efficacy:	Deposition of aerosol assessed via gamma-scintigraphy
Safety:	Physical examination, ECG, Adverse events
Statistical methods:	Sign Test

SUMMARY – CONCLUSIONS:

Efficacy results:

This study was not assigned as a drug efficacy study.

Deposition of aerosol assessed via gamma-scintigraphy.

Table 2: 1 Summary of percentage total lung deposition (FAS)

Ranked observed flow rate category	Mean (SD)	Minimum	Median	Maximum
Respimat® low	62.9 (14.7)	21.6	65.5	79.8
HFA-MDI low	20.0 (4.3)	12.0	21.0	27.8
Respimat® medium	60.1 (16.1)	29.7	67.5	83.7
HFA-MDI medium	24.9 (6.5)	13.6	24.5	36.0
Respimat® high	44.3 (11.5)	21.7	43.8	59.9
HFA-MDI high	26.3 (7.4)	22.9	28.1	35.9

SD = Standard Deviation
N=19
Source data:
Respimat® is based on the % of the emitted dose and HFA-MDI is based on the % of the ex valve dose.

Flow rate had more effect on the Respimat® inhaler than on the MDI inhaler.

Table 2: 2 Summary of percentage central, intermediate and peripheral lung deposition - mean (SD) and range (FAS)

Ranked observed flow rate category	Central lung	Intermediate lung	Peripheral lung	Lung penetration index*
Respimat® low	30.6 (9.4) 7.8 to 43.9	21.2 (5.2) 7.6 to 28.4	11.1 (3.4) 6.2 to 18.1	0.40 (0.18) 0.17 to 0.84
HFA-MDI low	9.1 (2.6) 3.7 to 12 5	6.8 (1.4) 4.5 to 9.7	4.2 (0.9) 3.1 to 6.6	0.49 (0.18) 0.31 to 0.86
Respimat® medium	29.9 (9.7) 10.4 to 41.7	19.4 (5.6) 9.3 to 28.9	10.8 (3.0) 5.1 to 18.6	0.40 (0.19) 0.16 to 0.95
HFA-MDI medium	11.9 (4.0) 5.7 to 21 1	8.2 (2.2) 4.4 to 12.5	4.8 (1.5) 1.7 to 7.6	0.43 (0.17) 0.16 to 0.71
Respimat® high	22.1 (7.7) 8.3 to 35.4	13.7 (3.8) 11.1 to 21.6	8.6 (2.4) 5.3 to 14.9	0.44 (0.20) 0.16 to 0.90
HFA-MDI high	14.2 (5.4) 3.6 to 22.8	7.7 (1.9) 3.5 to 10.1	4.4 (1.4) 2.2 to 7.4	0.37 (0.20) 0.11 to 0.83

* Lung penetration index is the ratio of peripheral to central lung deposition.
SD = Standard Deviation: range is minimum and maximum values.
N=19
Source data:
Respimat® is based on the % of the emitted dose and HFA-MDI is based on the % of the ex valve dose.

Table 2: 3 Summary of percentage deposition outside the lung - mean (SD) and range (FAS)

Ranked observed flow rate category	Extrathoracic*	Actuator / Mouthpiece	Filter
Respimat® low	33.8 (14.6) 17.7 to 76.1	25.7 (2.6) 22.3 to 30.6	3.3 (2.7) 0.8 to 11.8
HFA-MDI low	57.4 (4.5) 47.6 to 64.8	20.8 (3.3) 16.8 to 27.4	1.7 (0.9) 0.5 to 4.5
Respimat® medium	36.7 (16.1) 14.1 to 65.9	27.8 (4.5) 22.5 to 42.9	3.2 (1.2) 1.1 to 5.0
HFA-MDI medium	56.1 (7.1) 44.0 to 70.3	17.1 (2.6) 9.7 to 20.0	1.9 (0.7) 0.6 to 3.3
Respimat® high	50.2 (11.4) 31.8 to 76.2	28.2 (5.4) 9.3 to 35.8	5.5 (3.1) 2.1 to 12.8
HFA-MDI high	49.0 (8.3) 38.1 to 70.7	23.2 (5.9) 9.9 to 35.7	1.6 (0.7) 0.7 to 3.5

*Extrathoracic equals oropharynx + oesophagus + stomach
SD = Standard Deviation: range is minimum and maximum values.
N=19
Source data:
Respimat® is based on the % of the emitted dose and HFA-MDI is based on the % of the ex valve dose.

The mean extrathoracic deposition is lower for Respimat-low (33.8%) and Respimat-medium (36.7%) than for HFA-MDI-low (57.4%) and HFA-MDI-medium (56.1%) whereas Respimat-high and HFA-MDI-high are very similar (50.2% and 49.0% respectively). The percentage deposited on the actuator/mouthpiece is higher for the Respimat® device than the HFA-MDI device and similarly for the percentage deposited on the filter.

Safety results:

Table 2: 4 Mean (SD) FEV_1 (L) before and after dosing on each test day

Test day	Pre-dose	15 minutes post dose	30 minutes post dose	60 minutes post dose
Respimat® 15L/min	1.12 (0.30)	1.33 (0.35)	1.38 (0.38)	1.34 (0.38)
HFA-MDI 15L/min	1.12 (0.32)	1.28 (0.34)	1.26 (0.38)	1.28 (0.39)
Respimat® 30L/min	1.13 (0.30)	1.34 (0.36)	1.35 (0.38)	1.37 (0.42)
HFA-MDI 30L/min	1.08 (0.29)	1.25 (0.31)	1.27 (0.32)	1.29 (0.33)
Respimat® 90L/min	1.08 (0.30)	1.28 (0.37)	1.30 (0.36)	1.34 (0.40)
HFA-MDI 90L/min	1.04 (0.27)	1.28 (0.33)	1.30 (0.35)	1.31 (0.38)

SD = Standard Deviation
N=19
Source data:

Table 2: 5 Mean (SD) FVC (L) before and after dosing on each test day

Test day	Pre-dose	15 minutes post dose	30 minutes post dose	60 minutes post dose
Respimat® 15L/min	2.85 (0.80)	3.21 (0.92)	3.20 (0.87)	3.18 (0.85)
HFA-MDI 15L/min	2.81 (0.89)	3.12 (0.98)	3.02 (1.00)	3.13 (1.01)
Respimat® 30L/min	2.80 (0.80)	3.16 (0.85)	3.17 (0.89)	3.16 (0.91)
HFA-MDI 30L/min	2.74 (0.75)	3.04 (0.76)	3.06 (0.75)	3.07 (0.79)
Respimat® 90L/min	2.79 (0.83)	3.13 (0.80)	3.15 (0.77)	3.16 (0.77)
HFA-MDI 90L/min	2.60 (0.72)	3.05 (0.72)	3.09 (0.78)	3.07 (0.80)

SD = Standard Deviation
N=19
Source data:

Radio-labelled Berodual® delivered via Respimat® and via HFA-MDI was safe and well-tolerated. Safety measurements did not reveal clinically relevant findings. There were no serious adverse events reported during the trial or post study.

Conclusions:

In conclusion, it was not possible to prove the primary hypothesis of this study, a similar inhalation flow dependency of Respimat® and HFA-MDI. The Respimat® inhaler shows a considerably higher lung deposition (for all flows) and a considerably lower oropharyngeal deposition (for flows 15-30 L/min, i.e. low to medium flow rates) than the HFA-MDI. With low flow rates the Respimat® inhaler has a lung deposition of approx 63% of label dose (HFA-MDI 20%) and a corresponding oropharyngeal deposition of approx 34% of label dose (HFA-MDI approx 57%). There appears to be a decrease (ca. 26%) in drug delivery to the lungs between mean (of average) inspiratory flows of 30 and 60 L/min (observed medium and high flow rates) for the Respimat® inhaler. Lung deposition from the Respimat® inhaler appears to depend on inspiratory flow (30-60 L/min, i.e. medium to high flow rates). This could have two reasons: a) increased premature impaction in the oropharynx; and or b) reduced 'effective' drug inspiratory time for inhaling the generated aerosol (during fast inhalation in many patients inhalation time is shorter than the aerosol generation time of the Respimat®). The penetration index (PI) remains unaltered with increased inspiratory flows for the Respimat® inhaler. In contrast, the PI decreases for the HFA-MDI (i.e. lung deposition is more proximal). The HFA-MDI demonstrates a lesser dependence on inspiratory flow (between 30-60 L/min, medium to high flow rates); the lung deposition increases with increasing flows (mainly between 15 and 30 L/min). Overall the results demonstrate a high lung deposition of the Respimat® at low flow rates. The whole lung deposition values observed for this device at low flow rates (63%) are unique in the field of inhalation therapy and may, after adequate patient training or application of a mechanical flow limitation system, contribute to a considerable improvement of the efficacy of inhalation drug delivery.