Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: COMBIVENT HFA Inhalation Aerosol (MDI)				
Name of active ingredient: Salbutamol sulfate, Ipratropium bromide		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:** I	**Page to**		**Addendum No.:**
Report date: 09 February 2001	**Number:** 1012.24	**Study period (years):** 10/99 – 11/99		

Title of study:	A randomised, placebo-controlled, double-blind, 3 way cross-over safety and tolerability study of single and repetitive dosing of COMBIVENT HFA compared to COMBIVENT® CFC and placebo HFA in healthy male and female subjects (cumulative dose: 1600 mcg (HFA) or 1648 mcg (CFC) of salbutamol sulfate, 288 mcg of ipratropium bromide)
Investigator:,	[redacted]
Study centre(s):	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, FRG
Publication (reference):	Not applicable
Clinical phase:	I
Objectives:	Safety and tolerability of COMBIVENT HFA
Methodology:	Randomised, placebo-controlled, double-blind, 3 way cross-over
No. Of subjects entered:	
total:	12 (6 males/6 females)
each treatment:	12 (6 males/6 females)
Diagnosis and main criteria for inclusion:	Healthy subjects, age 21 – 50 years, Broca Index ± 20%
Test product:	COMBIVENT HFA (18 µg ipratropium bromide, 100 µg salbutamol sulfate/puff; "ex mouthpiece" dose)
dose:	1, 1, 2, 4 and 8 puffs
mode of admin.:	Inhalation
batch no.:	PD-1836
Duration of treatment:	Three period cross-over, single day dosing, three days

Reference therapy 1:	COMBIVENT® CFC (18 µg ipratropium bromide, 103 µg salbutamol sulfate/puff; "ex mouthpiece" dose)	**Reference therapy 2:**	Placebo HFA
dose:	1, 1, 2, 4 and 8 puffs	**dose:**	1, 1, 2, 4 and 8 puffs
mode of admin.:	Inhalation	**mode of admin.:**	Inhalation
batch no.:	PD-1870	**batch no.:**	PD-1868

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Criteria for evaluation:

Efficacy: Not applicable

Safety: Physical examination, vital signs, ECG, spirometry, tremor measurement, symptom assessments (cough, wheeze, shortness of breath), adverse events and standard laboratory evaluation.

Statistical methods: Descriptive statistics

SUMMARY - CONCLUSIONS:

Efficacy results: Not applicable

Safety results: Nine (six females, three males) out of 12 subjects reported mild to moderate adverse events. Almost all adverse events were regarded as drug-related. The most common adverse events were: palpitations (four subjects on COMBIVENT HFA, five subjects on COMBIVENT® CFC), bitter taste (five subjects on COMBIVENT® CFC, one subject on placebo HFA), nervousness (four subjects on COMBIVENT HFA, two subjects on COMBIVENT® CFC), feeling of flushing (one subject on COMBIVENT HFA and COMBIVENT® CFC respectively).
None of the subjects showed any signs of paradoxical bronchoconstriction (relevant decrease in FEV_1, occurrence of cough, wheeze and shortness of breath).
The small changes in lung function tests confirmed the expected pharmacodynamic response (especially a slight increase in MMEF25/75 after dosing with COMBIVENT HFA and CFC).
The findings in ECG tracings such as flattening of T-waves are typical ECG changes after dosing with $beta_2$ agonists, especially when given in higher doses like in this study.
There were no clinically relevant changes in vital signs (blood pressure, pulse and respiratory rate). A slight increase in pulse rate after dosing with COMBIVENT HFA and COMBIVENT® CFC was observed.
Also, the moderate increase in tremor as well as the mild to moderate decrease in serum potassium levels after both active formulations is typical for $beta_2$ agonists.
All measurements and the reported adverse events did not show any obvious difference between COMBIVENT HFA and COMBIVENT® CFC.

Conclusions: COMBIVENT HFA administered as single and repetitive doses via 16 inhalations within 140 minutes was safe and well tolerated in healthy male and female volunteers. No signs of paradoxical bronchoconstriction were observed.