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: Ethanolic Solutions from HFA134a-MDI and Respimat®				
Name of active ingredient: None		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: August 2nd, 1999	**Number:**	**Study period (years):** 1998		

Title of study:	**The effect of alcoholic-carrier solutions within-devices (HFA134a-MDI or Respimat®) on breath alcohol measured by Ethylometer in healthy volunteers.** **An open, randomised, single-dose, 4-way crossover study**
Investigator:	[redacted]
Study centre(s):	[redacted]
Publication (reference):	None
Clinical phase:	I
Objectives:	Primary To determine if the alcohol contained in the formulations of the HFA134a-MDI and the Respimat® device, when inhaled by normal healthy volunteers interferes with measurements of a breath alcohol recording device. Secondary To determine if there was a dose relationship after inhalation of the three HFA134a-MDI doses.
Methodology:	An open, randomised, single-dose, 4-way crossover study
No. of subjects entered: **total:** **each treatment:**	 16 16
Diagnosis and main criteria for inclusion:	Healthy volunteers non-smoking and without dental prosthesis, male or female, 18-45 years old, with a gamma-glutamyl-transferase level below 32 UI/L at the screening visit.
Test product: **dose:** **mode of admin.:** **batch no.:**	Ethanolic solution from HFA134a-MDI / Ethanolic solution from Respimat® One, two or four puffs (15.6, 31.2 or 62.4 mg of ethanol) from HFA134a- MDI and two puffs (18.4 mg of ethanol) from the Respimat® Inhalation via HFA134a-MDI or via Respimat® 9805205 (802025): HFA134a-MDI formulations 9805202: Respimat® formulation / 98060230: Respimat® device
Duration of treatment:	4 x 1 day observations
Reference therapy: **dose:** **mode of admin.:** **batch no.:**	Not applicable

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Criteria for evaluation:

Efficacy: Not applicable

Breath alcohol Evaluation

- Evaluation of blood alcohol level estimated from breath alcohol concentration at all time-points for each tested inhalation.
- AUC: Area under curve of the blood alcohol level estimated from breath alcohol concentration after the four formulation inhalations (three HFA134a-MDI formulations and the Respimat® inhalation)
- Td: Maximum duration of alcohol detection in exhaled air for each tested inhalation,
- Cmax: Highest blood alcohol level (estimated from breath alcohol concentration) measured
- Tmax: Time to C max

Safety: Final examination and reports of adverse events.

Statistical methods: Analysis of variance, Quadratic Linear Regression.

SUMMARY - CONCLUSIONS:

For the treatment of respiratory diseases such as asthma, chronic bronchitis, aerosolised drugs are commonly used to introduce drugs easily to the lungs. In some cases, the active drug is dispersed in alcoholic solution which can be detected by an Ethylometer Draeger (instrument used frequently by local Police to measure the breath alcohol concentrations in drivers) and can contribute to a false positive ethanol level.

This device incorporates electrochemical methodology to measure breath ethanol concentrations and gives a read-out in terms of apparent estimated blood alcohol concentration based on a 2100: 1 breath-to-blood conversion factor. Consequently, breath alcohol concentrations were expressed in estimated blood alcohol levels (g/L).

In order to evaluate the effects of ethanol-containing inhalation systems (HFA134a-MDI or Respimat®) on breath alcohol testing in healthy volunteers, an open, randomised, single-dose, four way cross-over phase I study has been conducted.

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SUMMARY – CONCLUSIONS (continued):

Blood alcohol levels estimated from breath alcohol concentrations were determined before and after inhalations of four ethanolic solution dosages: 15.6 mg, 31.2 mg and 62.4 mg of ethanol delivered from HFA134a-MDI and 18.4 mg of ethanol delivered via Respimat®. Additionally, the dose relationship after HFA134a-MDI inhalations has been examined.

The time points of the measurements were the following: three minutes at pre-dose and immediately after the drug inhalation then, every 90 seconds for the first 15 minutes and every three minutes until T30 minutes.

In the aim to determine the blood alcohol level in laboratory, two blood samples were collected to evaluate by an enzymatic method, the actual blood alcohol concentration before and 30 minutes after each inhalation.

Twenty healthy non-smoking volunteers without dental prosthesis were enrolled in this study for a duration of five days (+2/-1). Eighteen volunteers were randomised and seventeen completed the trial. They were stratified into three groups in accordance to the predicted value of their total lung capacity.

There was one volunteer who discontinued due to a moderate adverse event during the blood sample collection on this second test.

The population baseline characteristics were as follows: mean (± SD) age was 25 ± 5 years, mean (± SD) height was 166 ± 10.4 cm, mean (± SD) weight was 63.8 ± 13.3 kg. The mean baseline FEV_1 (± SD) was 3.75 ± 0.66 L [range 2.80 - 5.15].

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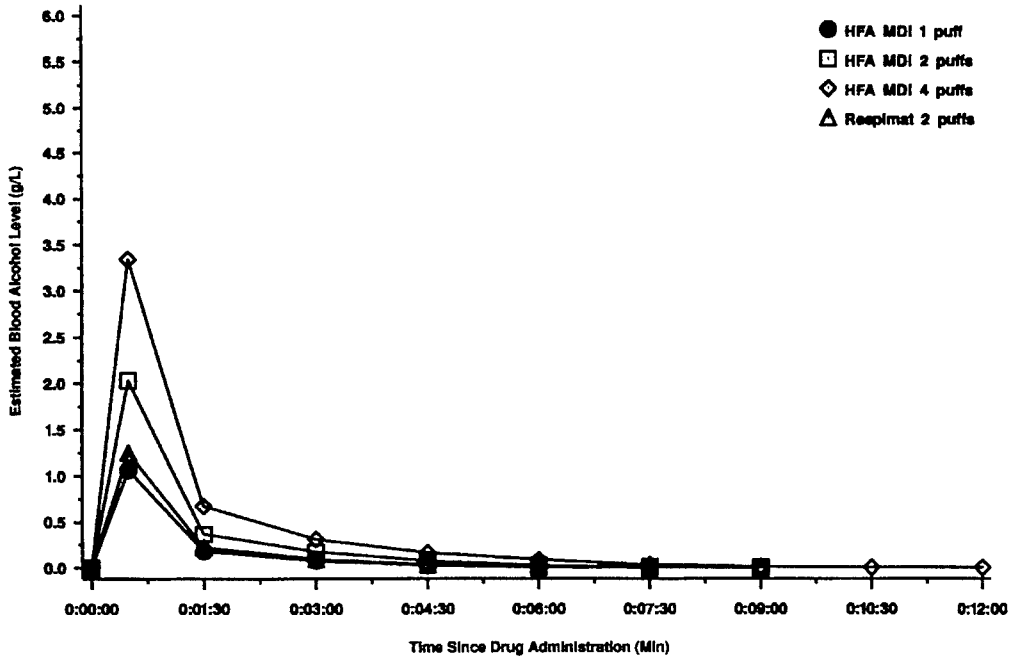
SUMMARY – CONCLUSIONS (continued):

Blood alcohol levels estimated from breath alcohol concentration results:
Breath alcohol concentrations time profiles were characterized by an increase of calculated breath alcohol concentrations after each inhalation, followed by a rapid elimination phase. All the breath alcohol concentrations were expressed in estimated blood alcohol levels.



Mean values of blood alcohol levels estimated from breath alcohol concentration after inhalation of ethanolic solution – Per-protocol population (N = 17)

Source Data: Appendix 16.3, TABLE 3.1

HFA134a-MDI and Respimat® had significantly increased breath ethanol concentration readings with a mean (± SD) of respectively 1.07 ± 0.4, 2.03 ± 0.64 and 3.34 ± 1.02 g/L (blood alcohol level) for HFA134a-MDI doses (15.6, 31.2 and 62.4 mg of ethanol) and 1.25 ± 0.35 g/L (blood alcohol level) for Respimat® (18.4 mg of ethanol) recorded just after the drug inhalations.

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SUMMARY – CONCLUSIONS (continued):

Cmax was achieved immediately after each drug inhalation with respectively 1.56, 3.44 and 5.80 g/L for HFA134a-MDI doses (15.6, 31.2 and 62.4 mg of ethanol) and 1.92 g/L (blood alcohol level) for Respimat® (18.4 mg of ethanol).

For all subjects, Tmax occurred 30 seconds after each tested dose. The area under curve was increased with the dose of ethanol inhaled with a mean of 71.6 ± 26.2, 144 ± 45.5, 256 ± 93 g/L x seconds respectively for MDI doses and of 86 ± 24.7 g/L x seconds for Respimat®.

For both inhaler devices, estimated blood alcohol levels subsequently decreased rapidly over time after inhalation. The means (± SD) of maximum duration of alcohol detection in exhaled air (Td) were respectively of 5.1 ± 1.5, 6.4 ± 1.4 and 8.3 ± 1.9 min recorded for the three HFA134a-MDI doses and 5.4 ± 1.4 min for Respimat®.

The Td maximum value was 13.5 min, obtained with 62.4 mg of ethanol inhaled from HFA-MDI formulation.

Regarding the results obtained with HFA134a-MDI doses, breath alcohol concentration profiles increased dose-proportionally after administration of the three doses.

The linearity of dose relationship was assessed using Fisher test linearity.

The inhalation of 18.4 mg of ethanol from Respimat® has similar effect to the inhalation of one puff of 15.6 mg of ethanol delivered from HFA134a-MDI. Their curves merged.

Blood alcohol level determined in laboratory:
For all the subjects and during all tests, blood alcohol concentrations were below the level of quantification of 0.02 g/L before and 30 minutes after each drug inhalation. There was not a detectable systemic absorption of ethanol following the Respimat® and HFA134a-MDI inhalations.

Safety results:
The tested inhalations were safe with regard to vital signs, laboratory evaluation and physical examination.

Conclusions:
This trial clearly demonstrated that both types of metered-dose inhalers (HFA134a-MDI and Respimat®) with alcohol formulations cause a significant apparent elevation of breath alcohol above the legal threshold for driving (in most countries) leading to false positive results. These effects are transient and may be prevented by waiting at least 15 minutes between inhalation and a breath alcohol measurement. Despite this, there is no detectable ethanol absorption in the systemic compartment after inhalation from these two devices and therefore, inhalations from the tested devices should not lead to any ethanol-related effect.