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SYNOPSIS

Study No.: **H-00982-3256** **Report No.:** **H-00982 / 9359000002**
Eudra-CT No.: **2007-002553-23**

Title of the study:

Clinical trial to assess the protective effect of the fixed drug combination of disodium cromoglycate plus reproterol in comparison to the single components and placebo in adults with exercise induced asthma

Coordinating investigator (LKP according to AMG):
Prof. Dr. Roland Buhl, 55131 Mainz, Germany

Study centre(s):
7 centres in Germany (listed in Section 9.1)

Publication (reference): n.a.

First visit of first subject: 30 Nov 2007 **Clinical phase:** II

Last visit of last subject: 29 Oct 2008 **Type of study:** Therapeutic confirmatory

Duration of treatment per subject: 4 days; single dose, 4-fold cross-over

Objectives:

- Primary objective: To demonstrate superiority of the protective effect of the fixed combination of disodium cromoglycate plus reproterol (COMB) in comparison to the single component reproterol (REP) in adults suffering from exercise induced asthma (EIA).
- Secondary objectives: To demonstrate superiority of the protective effect of COMB in comparison to the single component disodium cromoglycate (DSCG); to demonstrate superiority of the protective effect of each single component in comparison to placebo (PLA). In addition, the tolerability of medications was documented.

Methodology:

This was a multicentre, randomised, double-blind, placebo-controlled, 4-way cross-over study. At each study visit a standardised treadmill test was performed to provoke EIA. Before and after the challenge test pulmonary function variables (e.g. forced expiratory volume in one second (FEV_1)) were measured in order to assess the protective effect of the study medication.

Number of subjects planned:

It was planned to randomise 60 subjects. Finally 62 subjects were randomised.

Diagnosis and main selection criteria:

Aged 18 - 65 years, EIA with reversible airway obstruction: twice proven EIA (maximum decrease in FEV_1 against baseline value of at least 15%), stable asthma condition (baseline $FEV_1 \geq 70\%$ predicted, no exacerbation, no change of inhaled glucocorticosteroid dosage within the last 4 weeks prior to or during the study), no significant cardiovascular diseases.

Study medication, dose and mode of administration, batch number:

Study medication	Mode of administration	Total dose	Batch No.
COMB	Single dose inhalation of two puffs through FISONAIR® spacer	1 mg reproterol hydrochloride + 2 mg disodium cromoglycate	A60080
REP		1 mg reproterol hydrochloride	A60083
DSCG		2 mg disodium cromoglycate	A60084
PLA		No active substance	A60082

Criteria for evaluation:

a) Primary analysis: Maximum percentage decrease in FEV_1 from baseline, t = -5 (5 minutes before challenge) for COMB vs. REP and t = -25 (25 minutes before challenge) for other comparisons
b) As a) but t = -25 for COMB vs. REP and t = -5 for other comparisons
c) Percentage of subjects with maximum decrease in FEV_1 ≤0%, >0% to ≤10%, >10% and ≤20%, >20% from both baselines (t = -5 and t = -25)
d) Baseline corrected $AUC_{5\text{-}60min}$ of FEV_1 (baselines t = -5 and t = -25)
e) Maximum percentage decrease of FEV_1 from baseline within 15 min (baselines t = -5 and t = -25)
f) Baseline corrected $AUC_{5\text{-}15min}$ of FEV_1 (baselines t = -5 and t = -25)
g) Protection index (baselines t = -5 and t = -25)
h) Use of rescue medication
i) Vital signs
j) Adverse events (AE)

Statistical methods:

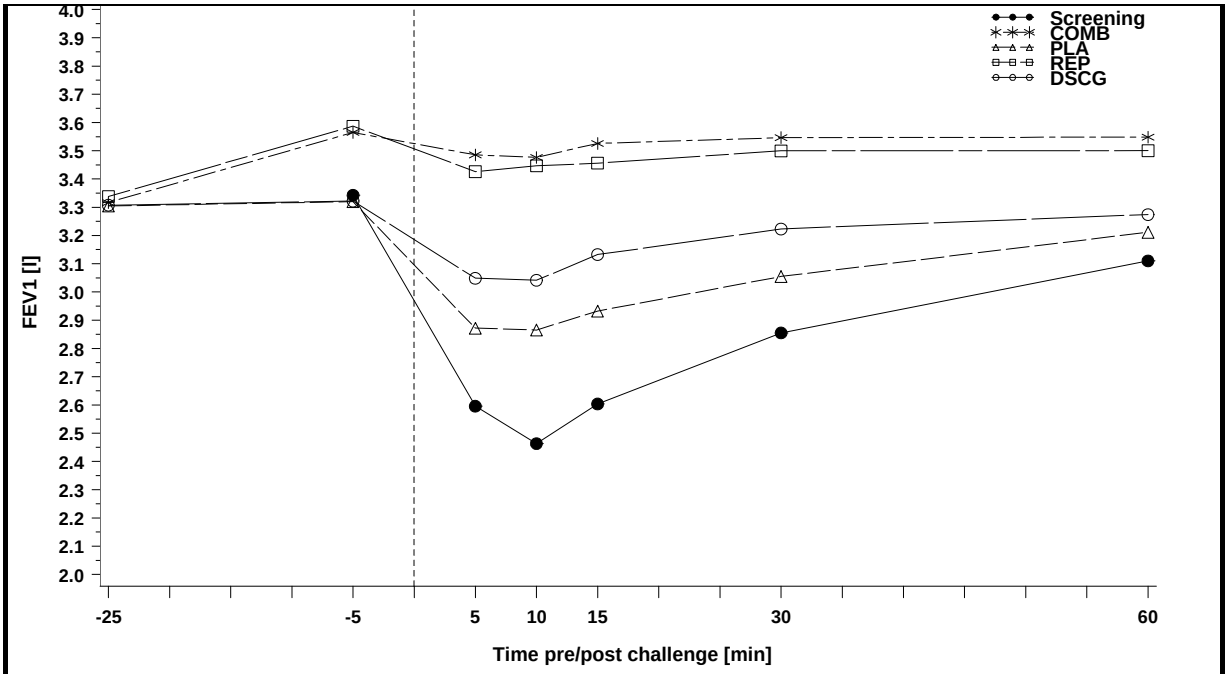
a) Hierarchical test procedure based on cross-over ANOVA: 1.) COMB vs. REP, 2.) COMB vs. DSCG, 3.) COMB vs. PLA, 4.) REP vs. PLA, and 5.) DSCG vs. PLA.
b) According to a)
c) Pairwise comparisons by paired rank test
d)-g) According to a)
h)- j) Descriptive statistics only

Results - background:

131 subjects were screened, 62 subjects were randomised and included in the safety population. One subject discontinued the study treatment due to an AE (nausea). 61 subjects provided outcome of efficacy data and were included in the ITT subset. 9 subjects had major protocol violations; therefore, 52 subjects were included in the PP subset.
In the ITT set 32/61 subjects were male. All were Caucasian. Subjects' mean age was 31.3 ± 11.5 years. At screening, baseline FEV_1 was 92.0 ± 14.6 % predicted; the maximum percentage decrease in FEV_1 after the exercise challenge was 29.6 ± 11.8 %.

Results - efficacy:

The FEV_1 values increased until start of challenge following therapy with COMB and REP while remained unaffected following therapy with DSCG and PLA. COMB showed the lowest post-challenge decrease in FEV_1, followed by REP, DSCG and PLA. All active treatments showed evidence for efficacy although a pronounced placebo effect is obvious. On average the maximum decrease in FEV_1 values is reached at 5 to 10 min post-challenge.



Following the pre-specified hierarchical test procedure, the results of the primary analysis indicated a statistically significant superiority of COMB compared to all three comparators. Moreover, REP as well as DSCG were statistically significantly superior to PLA.

Test results[1] for FEV_1 maximum percentage decrease from baseline (ITT, n=61)

Comparison	LS means [%]	95%-confidence interval [%]	p-value
COMB-REP	-2.24	-4.10 to -0.38	0.0193
COMB-DSCG	-13.03	-16.15 to -9.91	<0.0001
COMB-PLA	-19.13	-23.06 to -15.20	<0.0001
REP-PLA	-17.04	-21.39 to -12.70	<0.0001
DSCG-PLA	-6.10	-9.23 to -2.97	0.0002

[1] derived from four period cross-over ANOVA, primary analyses

Secondary analyses and analyses of secondary variables essentially supported the results of the primary analysis. Treatment differences for baseline adjusted AUCs were even more pronounced and robust.

Only one subject used rescue medication after treatment with placebo.

Results – safety:

One treatment emergent AE was reported. The event (nausea, occurred 1 minute after EIA challenge under DSCG in the DRPC group) led to discontinuation of study participation. The relation of this event to the study medication was assessed as unlikely. Tolerability and safety of all active test products were indistinguishable from placebo.

Conclusions:

Disodium cromoglycate, reproterol, and their fixed combination showed convincing evidence for efficacy. The statistical analyses showed significant superiority in the protective effect against exercise induced asthma for the fixed combination compared to the single compounds as well as all active test products compared to placebo. All treatments were well tolerated. There was no evidence for adverse drug reactions. Thus, the study confirmed a synergistic effect of disodium cromoglycate and reproterol and the clinical usefulness of their fixed combination (Allergospasmin® N/Aarane® N) in preventing exercise induced asthma in adults.

Finished product(s): **Allergospasmin®**			

SUPPLEMENTARY INFORMATION TO SYNOPSIS

Study No.: **H-00982-3256** **Report No.:** **H-00982 / 9359000002**
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Name of Sponsor/Company:

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Substantial amendments (protocol amendments and premature interruption and/or discontinuation):

No.	Date issued	In force	Modifications
1	21 August 2007	Upon approval by EC and Competent Authorities	Protocol Version 2 incorporated comments of EC and CA
2	15 October 2007	Upon approval by EC and Competent Authorities	Protocol Version 3 included a minor change in storage conditions
3	14 November 2007	Upon approval by EC and Competent Authorities	Protocol Version 4 issued to fulfil the condition of EC
4	14 December 2007	Upon approval by EC and Competent Authorities	Protocol Amendment 1 included a change in inclusion criterion and more specific details on a couple of study procedures.

Name and address of study centres:

[not named here]

Publication

Poster presentation (*Protective effect of disodium cromoglycate in exercise-induced asthma in adults and its synergistic effect in a fixed drug combination with reproterol*) at American Thoracic Society Annual Congress 2010, May 14-19, New Orleans, LA, USA. Contact/Presenting Author: Prof. Roland Buhl.