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350. Recent advances in the treatment of asthma and allergic rhinitis

P3851**The nasal decongestant oxymetazoline prevents inflammatory and oxidative stress responses**

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Oxymetazoline not only reduces the symptoms but also the duration of upper respiratory tract infections (URTI). Since tissue eicosanoid metabolism is enhanced in URTI, we investigated whether oxymetazoline affects arachidonic acid-derived metabolites. Oxymetazoline's ability to model inflammation and oxidative stress was evaluated in cell-free systems using the activities of 5-lipoxygenase (5-LO) as pro-inflammatory and 15-lipoxygenase (15-LO) as anti-inflammatory pathway. Oxidative stress was simulated by methionine oxidation by ultrafine carbon particles (UCP). Canine alveolar macrophages (AM), stimulated by UCP and zymosan, were used as cellular model for activated eicosanoid synthesis. Oxymetazoline's effect on phospholipase A₂ (PLA₂), prostaglandin E₂ (PGE₂), 15-LO-dependent 15-hydroxy-eicosatetraenoic acid (15-HETE), 5-LO-induced leukotriene B₄ (LTB₄), respiratory burst and oxidative stress marker 8-isoprostane was analyzed. In cell-free systems, oxymetazoline inhibited 5-LO but not 15-LO and did not affect methionine oxidation. In AM, oxymetazoline induced PLA₂, PGE₂ and 15-HETE but strongly inhibited LTB₄ and respiratory burst ($p < 0.05$). 8-Isoprostane was not affected. In UCP-stimulated AM, oxymetazoline did not alter UCP-induced PLA₂, PGE₂ and 15-HETE, but reduced UCP-induced LTB₄, respiratory burst and 8-isoprostane ($p < 0.05$). Oxymetazoline also inhibited zymosan-induced LTB₄ and respiratory burst ($p < 0.05$). In conclusion, oxymetazoline inhibited pro-inflammatory reactions including 5-LO dependent LTB₄ and respiratory burst and prevented particle-induced cellular oxidative stress, whereas PLA₂ and anti-inflammatory mechanisms such as PGE₂ and 15-HETE were maintained.

P3852**Efficacy of Montelukast in patients with concomitant persistent allergic rhinitis and asthma**

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Background: Asthma and allergic rhinitis (AR) are frequently comorbid conditions. The pathophysiological mechanism underlying AR and asthma is likely to be a similar inflammatory process, with eosinophils and mast cells acting as important

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effector cells. The cysteinyl leukotriene type (CySL-T1) receptor antagonist has demonstrated efficacy for treatment of asthma and of AR. We evaluated the efficacy of treatment with Montelukast in patients with concomitant asthma and persistent allergic rhinitis (PER) compared to placebo (PB).

Methods: This double-blind placebo-controlled study included 84 patients aged >18 years (54 males, 30 female, mean 40.5±9.8 years) with concomitant active asthma and active PER, treated with Montelukast 10 mg/die (56 patients) or PB (28 patients) for 4 weeks. Asthma symptoms included cough, wheeze and difficulty in breathing. The sum of which formed the total asthma symptom score (TASS). Symptoms of PER included rhinorrhea, itching, nasal congestion, sneezing. Endpoints, also, included global evaluation (GE) of asthma and of PER.

Results: Improvements from baseline in the daytime nasal symptoms score and nighttime symptoms score were significantly greater in the Montelukast treatment group compared with placebo group as compared to PB, the treatment with montelukast improved asthma total symptoms and reduced B2-agonist use for control of asthma symptoms, while maintaining FEV₁.

Conclusions: In this study, Montelukast demonstrated benefit in patients with concomitant PER and asthma. Benefit of Montelukast for both PER and asthma was supported by significant improvements of global evaluation of each condition.

P3853

Efficiency of once-daily mometasone furoate in school children with seasonal allergic rhinitis and severe nasal congestion

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Background: Mometasone furoate, an intranasal corticosteroid, is a logical treatment for nasal congestion associated with allergic rhinitis. Nasal congestion can have an adverse impact on school children and is often associated with disturbed sleep, fatigue and difficulties with breathing.

Method: School children received MFNS 200 mcg OD monotherapy (n=50) or placebo (n=51) for 2 wks. Total nasal symptom scores were assessed on a scale of 0 (none) to 3 (severe) at baseline and twice daily for 2 wks. The primary parameter was the 2-wk average of AM and PM total nasal symptom scores. Congestion data were pooled and school children categorised based on severity of congestion at baseline (score of >2.5, >2.75 and 3.0).

Results: Significant improvement in nasal congestion was seen after 2 wks of MFNS therapy compared with placebo (P<0.001). MFNS school children experienced over twice the improvement (mean 26.0%, std=33.7) in congestion score compared with placebo school children (mean 13.2%, std=29.5). Similar improvements from baseline of 32, 33 and 34% in congestion score were seen in MFNS school children with baseline scores of >2.5, >2.75 and 3.0, respectively. MFNS demonstrated significant improvements in congestion score including school children with the most severe symptoms (P<0.001 in school children with baseline nasal congestion score=3.0). No serious adverse events (AEs) were observed. The most common treatment-related AEs were headache, pharyngitis and nasal burning.

Conclusion: This meta-analysis confirms the effectiveness of MFNS in the treatment of congestion and demonstrates efficacy in school children suffering from severe congestion.

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CS-003, a novel triple neurokinin receptors antagonist, inhibits symptoms of respiratory diseases models in guinea pigs

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Rationale: CS-003, a novel triple neurokinin receptors antagonist, shows high binding affinities to guinea pig neurokinin receptors and potent *in vivo* antagonism to exogenous neurokinins.

Objectives: Effects of CS-003 on several animal models of respiratory diseases were evaluated.

Methods: Effects of CS-003 on capsaicin-induced cough, ovalbumin-induced asthma model, ovalbumin-induced rhinitis model and cigarette smoke-induced responses were evaluated in guinea pigs.

Measurements and Main Results: CS-003 (10 mg/kg, p.o.) inhibited the number of coughs induced by capsaicin aerosol (p<0.01), and the effect was comparable to codeine (50 mg/kg, p.o.). CS-003 (10 mg/kg, p.o.) also inhibited airway hyperresponsiveness to methacholine both in an acute and chronic ovalbumin-induced asthma model (p<0.01), whereas montelukast (10 mg/kg, p.o.), a leukotriene receptor antagonist, inhibited it only in the acute model (p<0.05). In an ovalbumin-induced rhinitis model, CS-003 (33 mg/kg, p.o.) inhibited the nasal blockage (p<0.01), and the effect was almost equal to that of dexamethasone (10 mg/kg, p.o.). CS-003 (1.0 mg/kg, i.v.) also inhibited several airway responses induced by cigarette smoke (p<0.05), bronchoconstriction, vascular hyperpermeability and mucus secretion.

Conclusions: These data show that CS-003, a triple neurokinin receptors antagonist, may be useful for the treatment of respiratory diseases associated with neurokinins such as allergic asthma, allergic rhinitis, chronic obstructive pulmonary disease and cough.

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Negligible exposure of infants to budesonide via breast milk

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Objective: Infants are exposed to a number of drugs that pass from maternal plasma to breast milk. This study assessed budesonide concentrations in breast milk and plasma of asthmatic women on maintenance treatment with budesonide (Pulmicort® Turbuhaler®) and estimated the systemic exposure of breast-fed infants.

Methods: Breast milk and plasma samples were collected predose and up to 8 h after morning inhalation of budesonide from 8 mothers on maintenance treatment with budesonide (Pulmicort® Turbuhaler®; 200 or 400 µg bid). Pharmacokinetic parameters were calculated from plasma and breast milk concentrations. A single blood sample was taken from infants 1.0-1.5 h after the first breast feed following drug administration (expected C_{max}). Infant exposure was estimated based on the average breast milk budesonide concentration and a breast milk intake of 0.15 L/kg/day.

Results: Budesonide breast milk concentrations followed those in maternal plasma, with the breast milk concentration always lower than that in plasma. The mean milk/plasma ratio based on AUC was 0.46. Measured budesonide concentrations in plasma samples from 5 infants were below the limit of quantitation (0.02-0.04 nmol/L). The estimated daily infant dose based on the average breast milk concentration was 0.3% of the daily maternal dose. The estimated average plasma concentration in the infant was about 600 times lower than the average maternal plasma concentration, assuming 100% infant oral bioavailability (compared with 10% oral bioavailability in adults).

Conclusion: Maintenance treatment with budesonide (Pulmicort® Turbuhaler®) 200 or 400 µg bid in asthmatic women results in negligible systemic exposure to budesonide in breast-fed infants.

P3856

Different pharmacological effects of *carum copticum* on respiratory system

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The results of a series of studies showed: 1) Aqueous and ethanol extracts from *Carum copticum* and its essential oil showed significant relaxant effect compared to saline (p<0.001). The extracts caused a non parallel rightward shift in methacholine concentration response curve and EC₅₀ methacholine obtained in the presence of extracts were significantly greater than that of saline (p<0.05-p<0.001). 2) plant extracts caused parallel right ward shifts in histamine concentration response curves obtained compared to saline. The EC₅₀ histamine in the presence of extracts were significantly greater than saline (p<0.05 to p<0.001). 3) There was a leftward shift in isoprenaline concentration response curve in the presence of ethanol extract. 4) Different extracts showed significant relaxant effect on incubated tracheal chains incubated with atropine, Chlorpheniramine and propranolol, contracted by KCl (p<0.001). The relaxant effect of increment concentrations of essential oil of the plant also showed a significant positive correlation with theophylline (P<0.001). 5) There were concentration dependent relaxant effects of fractions 3 and specially 2 (p<0.05-p<0.002). 6) The relaxant effect of different concentration of carvacrol was observed (p<0.05-p<0.001) which correlated with increment in concentrations (p<0.001). 7) Boiled extract of this plant caused significant increases in all PFTs, (p<0.05-p<0.001) comparable to the effect of theophylline. 8) Concentrations of extracts of the plant showed significant reduction of cough number (p<0.001 for all cases) which were significantly greater than that of codeine (p<0.05-P<0.001). Results showed a different pharmacological effect of *Carum copticum* on respiratory system.

P3857

Absence of respiratory effects in asthmatic subjects with the I_f inhibitor ivabradine, a novel anti-anginal agent

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Background: Ivabradine, a selective and specific inhibitor of the sinoatrial node I_f current involved in the cardiac pacemaker activity, is a novel agent for the treatment of patients with angina due to its heart rate lowering properties. The use of β-blockers for treatment of angina is well established but their use in asthmatic patients is limited by its adverse effects.

Objectives and methods: This placebo-controlled, randomised double-blind, crossover study assessed the effects of ivabradine (10 mg bid for 5 days), on lung function (PEFR and FEV₁) in 20 stable asthmatics. Inclusion criteria were history of asthma based on GINA guidelines and a reversibility of at least 12% in FEV₁ to short acting bronchodilator. For each efficacy parameter, the maximal percentage of variation (relative to H0) over 6 hours was calculated on the first day of each period and compared between ivabradine and placebo. In addition PEFR was measured daily during the 5 days of treatment.

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Results: The maximum percentage of variation of PEF over 6 hours on the first day of administration was $3.52 \pm 12.29\%$ with ivabradine compared to $2.52 \pm 12.83\%$ with placebo and of FEV₁ was $0.94 \pm 9.63\%$ with ivabradine compared to $1.12 \pm 10.00\%$ with placebo. Ivabradine did not have an effect on the PEF during the 5 days of treatment. Asthma symptoms or rescue medication use was also not different between the two groups. A decrease in heart rate was observed with ivabradine compared to placebo and no SAE was reported during the study.

Conclusion: Ivabradine represents a valuable new alternative to beta-blockers for the treatment patients with coexistent obstructive airway disease and angina.

P3858**Efficacy of the novel very long-acting β_2 -agonist carmoterol following 7 days once daily dosing: comparison with twice daily formoterol in patient with persistent asthma**

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Introduction: Carmoterol [8-Hydroxy-5-((1R)-1-hydroxy-2-[N-((1R)-2-(4-methoxyphenyl)-1-methylmethylamino)ethyl]-carbostyril] hydrochloride is a potent, long acting and selective β_2 -agonist formulated as an HFA 134-a pMDI (Chiesi Modulite™ HFA technology). Carmoterol is currently undergoing clinical development for once a day use in asthma and COPD.

Methods: We performed a randomised, double blind 3-arms parallel group comparison of Carmoterol HFA pMDI 2 μ g (2x1 μ g metered doses) administered once daily (qd) in the morning versus formoterol dry powder capsules via inhaler (Foradil® Aerolizer®, Novartis Pharmaceuticals) 12 μ g bid and placebo, over an 8-day treatment period in patients with persistent asthma (mean FEV₁ = 64.95% pred.). The primary efficacy variable was the mean 23-24 hours FEV₁ (trough FEV₁) following 7 days of dosing.

Results: The difference in trough FEV₁ between treatments in the morning of day 8 was: Carmoterol qd vs placebo 160 ml (p=0.029); Formoterol bid vs placebo 150 ml (p=0.039); Carmoterol qd vs Formoterol bid 10ml (ns). Trough FEV₁ after first day of dosing also did not differ between Carmoterol qd and Formoterol bid. There was no difference in peak FEV₁ between Carmoterol and Formoterol both on the 1st, 2nd and 8th day of treatment (Carmoterol 2.29 L, 2.31 L, 2.25 L; Formoterol 2.32 L, 2.29 L, 2.26 L, respectively).

Conclusion: Carmoterol administered once daily was as effective as formoterol twice daily in patients with persistent asthma. Efficacy results of the study support the further clinical development of Carmoterol at the dose of 2 μ g as a once daily treatment of asthma.

P3859**Safety and tolerability of the novel very long acting β_2 -agonist Carmoterol given as a 2 μ g qd dose; 8 days comparison with formoterol and placebo in patients with persistent asthma**

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Introduction: Carmoterol [8-Hydroxy-5-((1R)-1-hydroxy-2-[N-((1R)-2-(4-methoxyphenyl)-1-methylmethylamino)ethyl]-carbostyril] hydrochloride is a potent, long acting and selective β_2 -agonist formulated as an HFA 134-a pMDI (Chiesi Modulite™ technology).

Methods: We performed a randomised, double blind 3-arms parallel group comparison of Carmoterol HFA pMDI 2 μ g (2x1 μ g metered doses; Chiesi Farmaceutici) once daily in the morning vs formoterol (Foradil® Aerolizer®, Novartis) 12 μ g bid and placebo, over an 8 days treatment period in 124 patients with persistent asthma (mean FEV₁=64.9% pred.). The evaluation of safety and tolerability included the monitoring for Adverse Events (Aes), Serious Adverse Events (SAEs), and investigation of effect on vital signs, serum potassium and QTc interval.

Results: There was one SAE in a formoterol taking patient (asthma exacerbation). There were 8 Aes in 5 patients in the carmoterol group, 18 Aes in 7 patients in the formoterol group and 6 Aes in 6 patients in the placebo group. There were 2 withdrawals of patients caused by an AE (asthma exacerbation (SAE) & Nausea, Vertigo); both patients were taking formoterol. Headache was reported by 3 patients with carmoterol treatment and 1 with placebo. Tremor was reported in 2 patients on formoterol and in 1 patient on carmoterol. The effect on vital signs, serum K⁺ and QTc was similar between carmoterol and formoterol and not significantly different to placebo.

Conclusion: Safety and tolerability results support the further clinical development of Carmoterol at a daily dose of 2 μ g for use in patients with persistent asthma.

P3860**Adrenal crisis and hypercorticism induced by inhaled corticosteroids**

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Several cases of acute adrenal crisis and paradoxical Cushing's syndrome have been reported with the use of inhaled corticosteroids. We have therefore investigated the occurrence of these side effects between 2000 and 2005.

All French paediatricians, pulmonologists and endocrinologists (N=11783) were sent a questionnaire inquiring whether they encountered cases of acute adrenal crisis or hypercorticism they thought related to inhaled corticosteroids. More detailed clinical and biological questionnaires were sent to responding physicians. All cases were reviewed by an expert committee. Patients treated with systemic corticosteroid in the 3 past months were excluded.

46 cases of adrenal insufficiency or Cushing's syndrome were found. The expert committee reviewed biological data for 32 cases of adrenal insufficiency. Patients had a mean age of 34.6 ± 26.2 years (37.5% children), and 62.5% were women. Patients were treated for asthma (53%), COPD (19%) and mucoviscidosis (16%). Inhaled corticoids associated to adrenal crisis were fluticasone (59.4%; mean dose=1222 μ g/day), budesonide (31.3%; mean dose=1270 μ g/d) and beclometasone (9.4%; mean dose=916 μ g/d). 85% of the cases were with doses over beclometasone equivalent 500 μ g/d in children and 1000 μ g/d in adults. For 8 of the 32 patients, a potential drug-drug interaction was observed: association of fluticasone with itraconazole (n=3) or ritonavir (n=3), and budesonide with itraconazole (n=2).

Inhaled corticosteroids are safe since only few cases of adrenal insufficiency were reported. However, most of these cases might have been avoided by using no more than beclometasone equivalent 500 μ g/d in children and 1000 μ g/d in adults.

P3861**Cardiac safety of the novel very long-acting beta₂-agonist carmoterol following single rising doses in healthy volunteers**

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Introduction: Carmoterol is a potent, long acting and selective β_2 -agonist formulated as an HFA 134a pMDI (Chiesi Modulite™ HFA technology).

Methods: The study was a randomized, double-blind, placebo-controlled, escalating single inhaled dose comparison. The administered doses of carmoterol were 1, 2, 4, 8, 12 and 16 μ g, in rising-dose panels of 10 subjects each (8 carmoterol and 2 placebo). The evaluation of cardiac safety included 12-lead ECGs and 24-hour Holter monitoring. Pre-set limits on changes in heart rate and QTc qualified the administration of the next higher dosage to the next panel of volunteers. Serum potassium was also determined and evaluated.

Results: The lowest serum potassium value was observed in the highest dosage group, but remained relatively close to the lower limit of normal in all groups. Heart rate at dosages of 8 μ g and below fluctuated around the baseline value. Higher dosages of 12 and 16 μ g resulted in heart rate increases of approximately 5 and 10 bpm, respectively. Maximum changes in QTc relative to baseline remained similar to placebo for dosages up to 12 μ g during the first 4 hours post dose. The time-averaged mean increase in QTc over placebo with the 16 μ g dose was 8.4 msec. Isolated supraventricular beats were more frequent with placebo. Isolated ventricular beats were more frequent in the 16 μ g group.

Conclusion: The safety results of this study support the further clinical evaluation of carmoterol at doses less than 16 μ g.

P3862**Subcutaneous anti-immunoglobulin E (Omalizumab) as a steroid-sparing agent in allergic asthma – a systematic review of randomised controlled trials**

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Background: Omalizumab is a recombinant humanised antibody which inhibits IgE-binding to mast cells and which has been shown to reduce asthma symptoms. The aim of this study was to examine the efficacy of subcutaneous Omalizumab as a steroid-sparing agent in patients with allergic asthma.

Methods: A systematic review and meta-analysis of randomised controlled trials comparing subcutaneous Omalizumab at any dose with placebo in patients on inhaled and/or oral steroids undergoing steroid reduction identified from the Cochrane Library, MEDLINE, Embase, and CINAHL and the FDA website.

Results: 5 trials with 1746 patients were included. There was a moderate (~14-20%) reduction in inhaled steroid use in patients treated with Omalizumab compared with placebo (WMD -119mcg/day (95% confidence interval (CI) -154 to -84), three trials). Significantly more Omalizumab-treated patients were able to reduce inhaled steroids by > 50%: odds ratio (OR) 2.50 (95% CI 2.02 to 3.10); or completely withdraw their daily inhaled steroid intake: OR 2.50 (2.00 to 3.13) compared to placebo. There was no difference in oral steroid reduction.

Conclusions: The mean reduction in inhaled steroid consumption achieved was small in patients treated with Omalizumab compared to placebo. Omalizumab was significantly more effective than placebo at increasing the numbers of patients who could reduce or withdraw their inhaled steroids. Larger trials in severe asthmatic patients and children in addition to head-to-head comparison of efficacy and adverse events with inhaled corticosteroids are necessary to establish the place of Omalizumab in current asthma management.

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Comparison of ciclesonide (MDI) once daily and fluticasone propionate (Diskus®) twice daily in the treatment of patients with moderate asthma

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Introduction. We compared efficacy, tolerability, and quality of life (QoL) in patients with moderate asthma (GINA 2002), who were treated with either ciclesonide (CIC) 320 µg (ex-actuator) once daily, or fluticasone propionate (FP) 200 µg twice daily for 12 weeks.

Methods. During the baseline period (1-4 weeks) of this open-label study, 472 patients (12-75 y) received either FP ≤250 µg/d (or equiv.) or rescue medication. Patients with FEV₁ ≥80% predicted (FP) or 60-80% pred. (rescue medication), and defined criteria for rescue medication use and asthma symptoms, were randomised by IVRS. FEV₁ (spirometry), symptoms and rescue medication use (from diary), and QoL (standardised questionnaire, AQLQ(S)) were assessed.

Results. Mean baseline FEV₁ was high in both groups (CIC [88% pred.], FP [90% pred.]). Improvements in FEV₁ were comparable between CIC (171 mL) and FP (186 mL; p<0.0001 vs baseline, both groups). Median percentage of asthma symptom- and rescue medication-free days was similar with CIC (85%) and FP (84%), as was the low percentage of exacerbations (CIC [1.29%], FP [2.09%]). Despite high baseline AQLQ(S) scores, statistically significant improvements were achieved in both groups. CIC provided significantly greater improvement in the overall AQLQ(S) score than FP (CIC [+0.29], FP [+0.11]; p=0.0051). CIC was superior to FP regarding the frequency of oropharyngeal candidiasis (CIC [0%], FP [3.8%], p=0.002).

Conclusions. CIC (MDI) 320 µg once daily and FP (Diskus®) 200 µg twice daily showed similar efficacy in patients with moderate asthma. CIC was more favourable in improving QoL, and superior with regard to oropharyngeal candidiasis.

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Unbound pharmacologically active metabolite des-CIC is not detectable in human skeletal muscle and subcutaneous adipose tissue after inhalation of high-dose ciclesonide

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Introduction. The systemic exposure to unbound steroids is associated with the potential of causing adverse effects. Ciclesonide (CIC), a novel inhaled corticosteroid with high lung deposition (~52%), and its active metabolite desisobutryl-ciclesonide (des-CIC) are highly protein-bound (~99%). We investigated to what extent des-CIC reaches skeletal muscles and adipose tissue.

Methods. In this open-label study, 8 healthy subjects (median 25.5 y) received a single dose of 2880 µg CIC via HFA-MDI (ex-actuator). Microdialysis probes were implanted in muscle and adipose tissue. Microdialysates were collected over defined time periods for up to 8 h. Samples for pharmacokinetics and serum *in vitro* microdialysis were taken at several time points up to 10 h after inhalation. HPLC-MS/MS was used to determine des-CIC concentrations in serum and microdialysates.

Results. Des-CIC was detected in serum samples of all subjects. The maximum total concentration of des-CIC in serum was 2.93 µg/L at 1 h. In almost all microdialysate samples obtained from muscle and adipose tissue, des-CIC concentrations were below the lower limit of quantitation (<0.025 µg/L). In the dialysate-samples obtained from *in vitro* microdialysis of serum, unbound des-CIC was detectable even at 8 h after inhalation, confirming the sensitivity of the method. The inhalation of 2880 µg CIC was safe and well tolerated.

Conclusions. After the inhalation of a high dose of CIC, concentrations of unbound active metabolite (des-CIC) were negligible in skeletal muscle and subcutaneous adipose tissue, indicating a low potential of CIC for systemic adverse effects.

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Comparison of the efficacy and safety of 5 different doses of the novel very long acting β2-agonist carmoterol

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Introduction: Carmoterol [8-Hydroxy-5-((1R)-1-hydroxy-2-[N-((1R)-2-(4-methoxyphenyl)-1-methylmethyl)amino]ethyl)-carboxy] hydrochloride is a potent, long acting and selective β₂-agonist formulated as an HFA 134-a pMDI (Chiesi Modulate™ HFA technology).

Methods: We performed a dose finding, randomised, double blind, single dose, incomplete block 7 period cross over clinical study in 119 patients with asthma. Single doses of 0.5 µg, 1 µg, 1.5 µg, 2 µg and 3 µg were tested and also a single day administration of formoterol [12 µg bid (Foradil® Aerolizer®, Novartis Pharmaceuticals)] and placebo. Primary efficacy variables were the FEV₁ AUC 0-24 hrs and the FEV₁ at 24 hrs trough expressed as % change from baseline value. Secondary variables included monitoring for safety, tolerability.

Results: There was a clear separation in terms of FEV₁ effect between the lower (0.5 µg, 1 µg) and the higher doses (1.5 µg, 2 µg and 3 µg) with the higher doses eliciting clinically meaningful FEV₁ increases over the 24 hrs. The difference over placebo for the time averaged FEV₁ AUC 0-24 hrs was 280, 300 and 300 ml for the 1.5 µg, 2 µg and 3 µg respectively (p<0.001). The % ΔFEV₁ at trough was 10.2, 5.57 and 8.6, respectively. Corresponding differences over placebo were 230 ml, 130 ml and 190 ml, respectively. Maximum changes from baseline occurred after 2 hours and ranged from 28%, 26% and 28%, respectively. Safety and tolerability was favourable.

Conclusion: Single doses of carmoterol of 1.5 µg, 2 µg and 3 µg produced clinically meaningful increases in FEV₁, which persisted for 24 hours.

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A new combination therapeutic approach challenging the current dogma of using inhaled corticosteroids as maintenance only to control asthma

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Background: Budesonide/formoterol (B/F; Symbicort®), used as maintenance and reliever therapy (SMART), can reduce asthma exacerbations and improve symptom control compared with fixed-dosing regimens. This study investigated the contribution of both monocomponents of as needed B/F to asthma control in symptomatic patients receiving B/F maintenance therapy by comparing the efficacy and safety of three different reliever strategies.

Methods: In this 12-month, double-blind study, 3394 inhaled corticosteroid-treated patients (age ≥12 years; forced expiratory volume in 1 s 50-100% predicted) who were symptomatic on B/F 160/4.5 µg bid plus as needed terbutaline (T) during run-in were randomised to the same maintenance therapy plus one of three as needed medications: B/F 160/4.5 µg, F 4.5 µg or T 0.4 mg.

Results: The time to first severe asthma exacerbation (primary endpoint) was prolonged with B/F vs F (p=0.0048) and with F vs T (p=0.0051). The rate of severe exacerbations was 19, 29 and 37 per 100 patients/year with B/F, F and T, respectively (B/F vs both groups, p<0.001; F vs T, p=0.0012). Improvements in hospitalisation/emergency room treatment rates, night-time awakenings caused by asthma, symptoms, rescue medication use and lung function all favoured B/F vs F or T. All treatments were well tolerated.

Conclusion: Both budesonide and formoterol administered in the same inhaler as needed for relief contribute to improved asthma control in patients receiving budesonide/formoterol maintenance therapy. These findings challenge the current treatment paradigm that relies on inhaled corticosteroids as maintenance therapy alone to control asthma.

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Effect of inhaled mannitol on the sputum properties in asthmatics with excessive secretions

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Background: Most asthmatics with excessive secretions have difficulty in clearing mucus and this could contribute to plug formation and airway obstruction. Inhaled mannitol has been shown to facilitate clearance of mucus. We investigated the changes in the physical properties of sputum in response to mannitol in chronic but stable asthmatics with cough and sputum production.

Methods: Sputum was collected from 12 patients (aged 26-73 yr) at baseline before & after eformoterol 24 µg and again after mannitol: 240, 360 and 635 mg on four visits. All patients had eformoterol before inhaling mannitol to prevent bronchoconstriction and on the last visit montelukast (20 mg) as well. Sputum

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measurements included viscosity, elasticity, surface tension, contact angle-glass and % solids.

Results: Mannitol (360mg) acutely reduced the baseline mean value of elasticity from 30 ± 4 to 15 ± 1 Pa ($p < 0.0001$), viscosity from 18 ± 3 to 8 ± 1 Pa ($p < 0.0001$) at 1 Hz, surface tension from 92 ± 2 to 82 ± 2 mN/m ($p < 0.0001$), contact angle-glass from 58 ± 3 to 50 ± 2 degrees ($p < 0.0001$), and % solids from 6.9 ± 0.7 to $5.7 \pm 0.4\%$ ($p < 0.0001$). There were no significant differences between the sputum properties at baseline before & after efomedoterol. Mannitol had a similar effect on all the sputum properties at all doses and none was changed by montelukast ($p > 0.4$).

Conclusions: These data provide the first evidence that mannitol improves the rheological, the surface properties and the % solids of the sputum in asthmatics with excessive secretions and mucociliary dysfunction. Mannitol greatly facilitated clearance of sputum and when carefully administered after a bronchodilator it may improve airway function in these patients.

P3869**Pharmacokinetics and pharmacodynamics of a new beclomethasone dipropionate and formoterol CFC-free fixed combination in healthy volunteers**

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BDP+Formoterol 100/6 HFA (BDP/F) is a new pMDI containing beclomethasone dipropionate (BDP) 100µg and formoterol fumarate (F) 6µg developed using Chiesi proprietary Modulite® technology. By modulating the particle size, BDP/F properly tailor the quantity of drug able to reach the lungs, allowing an optimised deposition throughout the bronchial tree, including peripheral airways, with a dose reduction relative to BDP CFC. Aim of the study was to evaluate the pharmacokinetics (PK), and systemic effects (PD) after single administration of BDP/F and of a free combination of BDP CFC and F MDI formulations. Twelve healthy volunteers were administered with BDP/F (400µg BDP/24µg F), the free combination (1000µg BDP/24µg F) or placebo according to an open, placebo-controlled, three-way cross-over design.

PK parameters were calculated for unchanged BDP, its active metabolite B17MP and F. Secondary variables were serum cortisol and potassium, cardiovascular and lung function.

No statistically significant differences between treatments were observed for unchanged BDP and F PK parameters. B17MP systemic exposure was significantly lower with BDP/F than with the free combination ($p=0.001$), being the amount of swallowed BDP reduced with BDP/F. Serum cortisol was significantly less suppressed with BDP/F than with the free combination ($p=0.01$). There were no differences between active treatments for the other PD measurements. Both active treatments were well tolerated. These data support that even with a reduced BDP dose, the amount of drug delivered to the lung with BDP/F is optimal and the systemic effects are reduced compared to BDP and F free combination.

P3870**Follow-up results 10 years after early intervention with budesonide or terbutaline in mild persistent asthma**

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We have previously reported that an inhaled corticosteroid (ICS), budesonide, should be first-line treatment of patients with newly detected persistent asthma (NEJM 1991) and that a 2-year delay with initiating ICS therapy may result in an impaired response in terms of symptoms, prebronchodilator PEF, FEV₁, and bronchial responsiveness to histamine (NEJM 1994). A total of 90 of the initial 103 patients participated in a follow-up examination 13 years after being randomized to early treatment with budesonide (B) or terbutaline (T). During the follow-up patients in the B group had used 24% less asthma medication, 43% less hospital days and had had lower treatment costs per year compared with the T group. During the follow-up FEV₁ and morning PEF had decreased slightly in both groups but still remained in the range of predicted values. However, the small difference between the groups in airway function seen after 3 years treatment was still present 10 years later. BHR had improved, and asthma symptoms and need of reliever medication had decreased in both groups. At the follow-up examination the T group used a mean of 609 µg ICS compared with 447 µg in the B group. The T group also had significantly more neutrophils and MPO in induced sputum and had slightly higher NO values in exhaled air. The results support the early use of ICS in patients with persistent asthma.