214. Trials in asthma: asthma exacerbations and severe asthma

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Use of steroid receptor related STIP1 gene analysis as an asthma marker

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Introduction: Inhaled steroids are first choice for asthma treatment. However, some patients do not respond, needing higher doses or combined therapies. This difference in responsiveness might be associated to genetic makeup. We evaluated the possible association between variations in treatment requirement and single nucleotide polymorphism (SNP) in importin-13 and STIP1 (steroid receptor related genes).
Aims: Study SNP in importin-13 and STIP1, in healthy and asthmatic children.
Methods: Healthy children were enrolled by a public call. Asthmatics treated with ≥3 months of inhaled steroids were enrolled in outpatient clinics. A clinical questionnaire was applied. SNP were analyzed by PCR-RFLP assay.
Results: 125 children between 2 and 18 years of age were included, 227 healthy and 75 with asthma. Analysis of STIP1 SNP (rs2236647) was obtained in all healthy children and in 63 of the 75 asthmatics. The C allele (minor allele) was present in all asthmatic patients, 46 were heterozygous and 17 homozygous. In contrast, in healthy children, none were homozygous for this allele, 43/50 were heterozygous and 7/50 did not have the C allele ($p<0.0001$). When considered as a diagnostic test, STIP1 SNP analysis showed to have a sensibility of 100% with the presence of al least one C allele, and a specificity of 100% considering being homozygous. We did not find differences regarding asthma control and treatment requirement. No association could be established with importin-13 SNP (rs6671164 and rs2301993).
Conclusions: Analysis of STIP1 genetic variant rs2236647 serves as an asthma marker. Further investigation with a bigger N is needed to fully validate this study and establish other possible applications of these findings.

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Over-expression of Th17-related cytokines in bronchial and nasal submucosa in severe asthma

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In severe asthma neutrophil recruitment in bronchial submucosa is associated with steroid resistance, and in addition Th17-derived cytokines are important in induction and activation of neutrophils.
We evaluated the differences in inflammatory cells and Th17-related cytokine in bronchial and nasal submucosa between severe asthmatics (SA) and mild asthmatics (MA).
Bronchial and nasal biopsies obtained from 20 SA and 20 MA were investigated by immunohistochemistry.
Bronchial sub-mucosa (BS) of SA showed a higher number of neutrophils, CD4+ and CD8+ compared to MA. Furthermore, the number of IL17-A+, IL17-F+ e IL-22+ cells in SA was significantly higher. Forced Expiratory Volume (FEV1) negatively correlated with: CD8+, neutrophils and IL 22+ cells in BS; the number of neutrophils correlated with IL 17F+ cells and CD8+; CD4+ and CD8+ with IL22+ cells. Double staining for CD4 or CD8 and IL17F or IL22 showed that all IL 17F+ and IL22+ cells are also CD4+ or CD8+.
In nasal sub-mucosa (NS) of SA we found higher number of lymphocytes CD4+, CD8+, mast cells and macrophages, but also of IL 17A+, IL17F+, IL 21+ and IL22+ cells. FEV1 negatively correlated with: IL-17A+, IL-17F+, IL-21+ and IL-22+cells in NS. Moreover, the number of CD4+, IL-17F+and IL-22+cells in BS correlated positively with the equivalent cells in NS.
We showed that in SA an exaggerated neutrophil/lymphocyte infiltration in conjunction with an amplified expression of Th-17 related cytokines in both bronchial and nasal submucosa suggesting an involvement of IL-17 pathway in the progression to an irreversible steroid-resistant inflammatory process.

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Effect of corticosteroids on lymphocytes from severe asthma patients

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Patients with severe asthma have persistent airway inflammation that responds poorly to corticosteroids. Lymphocytes play a central role in disease pathogenesis; we hypothesized that lung lymphocytes from patients with severe asthma are insensitive to the effects of corticosteroids.
We investigated suppression of lung lymphocyte cytokine production by corticosteroids in healthy non smokers (HNS) and patients with mild asthma (MA) and severe asthma (SA).
Patients with MA (n=11), SA (n=11) and HNS controls (n=7) underwent bronchoscopy. Cells obtained by lavage were treated with and without dexamethasone (0.01, 0.1 & 1μM) for 1 h prior to lymphocyte stimulation with CD 2/3/28 activation beads for 24 h. Supernatants were assayed for IL-2 and IFN-γ by ELISA and IL-13 and IL-17 by luminex. Mean maximal inhibition data are shown in table 1.

Table 1. Maximal cytokine inhibition achieved by dexamethasone

Cytokine	Maximum % inhibition		
	HNS	MA	SA
IL-17	54.5	58.0*	49.1
IL-13	90.9***	92.4***	70.4
IL-2	63.1**	66.3***	51.9
INFγ	63.0	65.8*	56.7

*Denotes significantly higher inhibition compared to severe asthma patients. *p<0.05, **p<0.01, ***p<0.001.

Cytokine release was inhibited by dexamethasone in a dose dependent manner. Dexamethasone had a reduced effect on all cytokines in SA compared to HNS or MA. Dexamethasone had the greatest effect on the Th2 cytokine IL-13, but had a lower effect on Th1 and Th17 cytokines
Cytokine production from SA BAL lymphocytes show corticosteroid insensitivity compared to cells from controls. This phenomenon may be important in the poor clinical response often observed with corticosteroids. Furthermore, corticosteroids have a reduced effect on Th1 and Th17 cytokines, which may predominate in SA.

P1785

Association of glucocorticoid receptor gene polymorphisms of R23K and R477H and steroid-resistant asthma in Chinese Han population

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Some previous studies have shown that steroid resistance in asthma is associated with the mutation of glucocorticoid receptor (GR) gene. Other studies, however, have reached the opposite conclusion. The aim of this study was to detect the GR polymorphisms of R23K and R477H in steroid-resistant (SR) asthma patients and steroid-sensitive (SS) asthma patients in Chinese Han population, and to elucidate the association between GR polymorphisms and steroid resistance in asthma. Sixty-four SR patients and 68 SS patients were recruited for the detection of R23K and R477H variants, using polymerase chain reaction-sequence specific primers. Cortisol contents in serum were examined. The equilibrium dissociation constants (K_d) were calculated by dexamethasone radioligand-binding assay and Scatchard analysis to determine GR affinity to glucocorticoids. No statistically significant difference was found in the distribution of R23K polymorphism between SR patients and SS patients. In R477H, the wild genotype GG and AA frequencies were significantly lower in SR patients than in SS patients (P=0.043). The cortisol content in serum was found no significant difference between SR patients and SS patients, and among different genotypes. No significant differences in K_d were found between GG genotype and GA genotype of R23K variant, GG genotype and GA+GG genotype of R477H variant. In SR patients, the K_d values were significant higher than in SS patients (P<0.001). These findings suggest that GR polymorphisms of R23K and R477H exist in Chinese Han population. R477H variant is associated with steroid-resistant asthma in this population.

P1786

The effect of single-nucleotide polymorphism in IL-13 on airway hyperresponsiveness in asthmatics

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Background: Single-nucleotide polymorphism (SNP: rs20541) of IL-13 has been recognized as a risk factor of asthma. We recently demonstrated that FEV1 in asthmatics with the Q110 variant IL-13 declined faster (Allergol Int 2011). However, the effects of the variant IL-13 on airway hyperresponsiveness (AHR) have never been elucidated.
Objectives: To evaluate the effects of SNP (rs20541) in IL-13 on AHR in asthmatics, we analyzed the relationship between SNP and AHR.
Methods: We recruited 182 asthmatics to the current study who visited the asthma out-patient clinic in Iwate Medical University Hospital from 2006 to 2011. Subjects were genotyped using rs20541 by 7500 Fast Real-Time PCR System, (Applied Biosystems USA). Therapeutic steps (GINA 2011), eosinophil counts in peripheral blood and serum IgE concentration in those asthmatics were also studied. AHR to methacholine was measured by Astograph; Jupitor 21 (Chest, Japan). AHR was expressed as Dmin (U) (average ± SE). Statistical analysis was performed by one way ANOVA. This study was approved by the ethics committee of Iwate Medical University.
Results: Genotyping of rs20541 showed that 26 A/A, 77 A/G and 79 G/G. D min (U) of the 3 genotypes was 1.17±0.300 in A/A, 1.99±0.35 in A/G and 2.85±0.39 in G/G. D min in the 3 genotypes was proved to be significantly different by Kruskal-Wallis One Way Analysis of Variance (p=0.007). There was no significant difference in therapeutic steps, eosinophil counts or serum IgE concentration among the 3 genotypes of asthmatics.
Conclusion: SNP (rs20541) in IL-13 was associated with AHR, suggesting that IL-13 was involved in the progress of AHR through its biological activity on airway smooth muscles.

P1787

Preventive effect of carbocysteine on exacerbation of asthma, GAIA randomised, placebo-controlled multi-centre study

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Background: Management of exacerbation is clinically very important in asthma control. Carbocysteine, which improves airway mucus clearance and has anti-inflammatory effects, including antioxidant effect, is expected to prevent asthma exacerbation in addition to COPD exacerbation.
Objective: To evaluate the preventive effect of carbocysteine (C) on exacerbation in asthma patients using placebo (P) as a control.
Methods: A total of 286 patients with mild to moderate asthma were randomly assigned to receive either C (1500mg/day) or P for 48 weeks. Patients were allowed to use long-term asthma control medications. The primary endpoint was annual frequency of exacerbations, and the secondary endpoints were pulmonary function and asthma control by ACQ.
Results: At the time of enrollment, the disease type (atopic or non-atopic asthma) was significantly different (p = 0.02) between the two groups (C, n = 140; P, n = 140), but no statistically significant differences were observed in any other baseline characteristics of patients. The frequency of asthma exacerbations, the primary endpoint, was 5.40/year in the C group and 8.04/year in the P group, showing a significant decrease in the C group compared with the P group. The risk ratio of exacerbation was 0.658 (95% CI, 0.595-0.727; p < 0.001). No significant differences were observed in the pulmonary function or in the asthma control between the two groups.
Conclusion: C significantly reduced the frequency of asthma exacerbations and thus provides a new therapeutic concept for long-term asthma management.

P1788

Effect of fluticasone furoate (FF)/vilanterol (VI) once daily (OD) on risk of severe exacerbations in asthma

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Introduction: FF is a novel inhaled corticosteroid in development for the treatment of asthma as a monotherapy and in combination with VI, a long-acting beta$_2$ agonist.
Objectives: To evaluate whether FF/VI significantly decreases the risk of severe asthma exacerbations vs FF.
Methods: Patients (N=2019; ITT) received OD FF/VI 100/25mcg or FF 100mcg for ≥24 weeks (up to 76 weeks; study planned to finish after 330 events; event defined as a patient's first on-treatment severe asthma exacerbation). Primary endpoint was time to first severe asthma exacerbation. Secondary endpoints: rate of severe asthma exacerbations per patient per year (PPPY) and change from baseline trough FEV_1. Safety assessments included adverse events (AE), vital signs and number of hospitalisations due to a severe asthma exacerbation.
Results: Compared with FF, FF/VI delayed the time to first severe exacerbation (hazard ratio 0.795 [95% CI: 0.642,0.985]; interim adj p=0.036). The adjusted probability of experiencing a severe exacerbation by 52 weeks was 12.8% for FF/VI and 15.9% for FF. PPPY rate was reduced (FF/VI 0.14 vs FF 0.19; p=0.014). There were greater improvements in trough FEV_1 with FF/VI vs FF at Weeks 12, 36 and 52 (p<0.001). Incidence of treatment-related AEs: FF/VI 7%, FF 7% (on-treatment serious AEs: FF/VI 4%, FF 3%). Number of hospitalisations due to severe exacerbation was similar between treatments. There were no clinically relevant differences in vital sign assessments.
Conclusions: FF/VI significantly reduced the risk of severe asthma exacerbations and improved lung function compared with FF alone. Safety and tolerability were similar between groups.
Funded by GSK: HZA106837; NCT01086384.

P1789

The value of magnesium sulfate nebulization in treatment of acute bronchial asthma during pregnancy

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Little is known about the effect of inhaled Mg sulfate when added to B2 agonist in acute asthma with pregnancy.
Objective: To evaluate the bronchodilator effect of nebulized magnesium sulfate with B2 agonist in the treatment of acute asthma during pregnancy, and its safety on pregnancy outcome.
Material and methods: Patients were divided into two groups in a double blind randomization. Group A" received the routine treatment of acute asthma exacerbation plus nebulized salbutamol in dose of (1 ml of salbutamol solution dissolved in 9 ml of normal saline). "Group B" received the same above treatment plus (500 mg (1ml) of magnesium sulfate). Two hours after three sets of nebulization pulmonary function test and blood gas analysis were done.
Results: Sixty pregnant women's with acute asthma, 30 patients in each group with mean age were (25.9±4.01 & 25.7±3.8) in both groups respectively. Comparison between both groups in pulse rate, arterial oxygen tension and oxygen saturation were highly significant (P<0.001). FEV1 was (32.68±7.15&56.31±8.25) in group A& B respectively and the percentage of change was 69% with (highly significant

P value <0.001). The frequency of acute asthma exacerbation till delivery in both groups was (3.2±0.98 & 0.4±0.57) in group A and B respectively (95% CI 2.4 to 3.1) with highly significant p value (P<0.001). All patients were delivered either normal delivery (60% & 66.6%) or C.S (40%& 33.6%) with smooth neonatal period.
Conclusion: Adding magnesium sulfate to salbutamol nebulization as a therapy for acute asthma during pregnancy is effective and safe. The availability, cheapness of this drug especially for the developing countries added to its advantage.

P1790
The effect of a single high dose vitamin D3 on neutrophilic airway inflammation in nonatopic asthma
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Rationale: Vitamin D deficiency has been associated with asthma and increased risk of respiratory tract infections. An infectious origin in its turn, has been proposed for nonatopic asthma (Joseph Ann All Asthma Immun 2003) as well as neutrophilic asthma (Simpson Thorax 2007). Vitamin D enhances anti-microbial defence and might thereby influence the inflammatory process in the airways. Therefore, we hypothesized that treatment with high dose vitamin D3 reduces neutrophilic airway inflammation in patients with nonatopic, neutrophilic asthma
Methods: 28 nonatopic, neutrophilic (≥53% sputum neutrophils (Spanevello, AJRCCM 2000)) stable asthma patients were included in a randomized double-blind placebo controlled trial. Patients received 400000 IU vitamin D3 or placebo orally in one dose. All completed questionnaires and underwent blood sampling, lung function tests and sputum induction at baseline and after 8 weeks
Results: Baseline characteristics were similar in both arms. Results: see table

	Placebo		Vitamin D		p (between group)
	baseline	8 wks	baseline	8 wks	
Vitamin D, nmol/l	59 (30-113)	57 (34-92)	56 (27-98)	92 (54-115)	0.001
sputum neutro, %	74 (63-93)	68 (36-92)	75 (55-98)	79 (16-97)	0.4
FEV1/VC, %pred (SD)	95 (11.1)	92 (9.6)	94 (9.8)	95 (8.8)	0.09
ACQ	1.2 (0.1-2.6)	1.1 (0.1-2.6)	1.2 (0.1-3.1)	0.9 (0-2.9)	0.007

Conclusion: Treatment with a single high dose vitamin D3 in nonatopic, neutrophilic asthma, does not reduce neutrophilic inflammation, but improves ACQ as compared to placebo
Implications: The association between vitamin D and asthma is not explained by its effect on sputum neutrophils. The improvement in asthma control by vitamin D suggests that other beneficial mechanisms might be involved.

P1791
Long-term efficacy of QMF149 in persistent asthma
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QMF is an investigational once-daily (QD) fixed-dose combination of indacaterol (IND) and mometasone furoate (MF). The efficacy of QMF was assessed in a randomised, double-blind, multi-centre, 6–21 month, Phase II study. Patients (12–70 years) received QMF (IND maleate 500μg/MF 400μg) or MF (400μg), both QD via the Twisthaler®*. Based on systemic exposure, this QMF dose is comparable to 150μg IND/160μg MF in the Concept1 (Breezhaler®) inhalation device, the delivery device to be used in future QMF studies. The primary endpoint was time to first serious exacerbation (resulting in hospitalisation, intubation or death). Secondary endpoints included time to first exacerbation requiring systemic corticosteroids (SCS), annual rate of exacerbations requiring SCS, lung function and symptoms. 1519 patients were randomised (QMF 756, MF 763), of which 8 (QMF 2, MF 6) were hospitalised for a serious exacerbation (none required intubation or resulted in death). QMF reduced the risk of a serious exacerbation vs MF by 69% (HR=0.31; 90% CI 0.08, 1.19; p=0.076). QMF had a significant risk reduction of 30% in time to first exacerbation requiring SCS (HR=0.70; 95% CI: 0.56, 0.89; p=0.003), and significantly reduced the annual rate of exacerbations requiring SCS by 29% (RR=0.71; 95% CI: 0.55, 0.90, p=0.005) vs MF. Trough FEV_1 significantly improved with QMF vs MF at all visits (100 to 140 mL, p<0.001). % days with no asthma symptoms and no rescue medication use significantly increased with QMF vs MF (p≤0.001). QMF significantly improved mean ACQ scores vs MF at all visits (–0.13 to –0.23, p<0.001). This study demonstrates the efficacy of QMF in patients with persistent asthma.
* Twisthaler® is a registered trademark of Schering-Plough LTD.

P1792
Efficacy and safety of BI 671800, an oral CRTH2 antagonist, as add on therapy in poorly controlled asthma patients prescribed an inhaled corticosteroid
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Background: BI 671800 is an antagonist of the PGD2 receptor, CRTH2. PGD2 stimulates bronchoconstriction and allergic airway inflammation in animal models. Inhibition of CRTH2 may reduce airway inflammatory cells, IL -4, -5, -13 production, serum IgE and airway hyper reactivity.
Objective: To investigate the efficacy and safety of BI 671800 versus placebo and montelukast in poorly controlled asthma patients as add on therapy to fluticasone propionate (FP) MDI (88 μg, bid).
Methods: Adults with asthma (FEV_1 60-85% and ACQ >= 1.5) were enrolled in a randomized, double-blind, parallel arm study comparing BI 671800 400 mg bid with matching placebo bid or montelukast 10 mg qd for six weeks. The primary study outcome was change in trough FEV_1.
Results: 243 patients were randomised (mean age 41.6 years, FEV_1 72%, ACQ 2.1). Change from baseline in adjusted mean (SE) trough morning FEV_1% predicted versus placebo was 3.87% (1.49) for BI 671800 and 2.37% (1.57) for montelukast, (one sided p < 0.025 for BI 671800), achieving the primary efficacy outcome for the study. Change in ACQ mean (SE) scores versus placebo were -0.28 (0.12) and -0.18 (0.12) for BI 671800 and montelukast respectively (one sided p < 0.025 for BI 671800). No significant imbalance in adverse events, or differences in vital signs or laboratory assessments were observed.
Conclusion: Treatment with BI 671800 in poorly controlled asthmatic patients receiving FP was associated with a significant improvement in FEV_1. BI 671800 was well tolerated at a total daily dose of 800 mg for 6 weeks.

P1793
Improvements in asthma control and quality of life with omalizumab in allergic (IgE-mediated) asthma patients
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Introduction: Optimizing asthma control and improving health-related quality of life (QoL) are key goals in the management of asthma. The asthma control test (ACT), the asthma control questionnaire (ACQ), and the asthma quality of life questionnaire (AQLQ) are important patient-reported outcomes often used to evaluate treatment efficacy.
Methods: eXpeRience is a global, post-marketing, observational registry established to evaluate the efficacy and safety of omalizumab for 2 years during standard clinical practice. Data (means [SD]) are presented for the ACT, ACQ, AQLQ and mini-AQLQ at Months 12 and 24.
Results: Of the 943 patients who entered the registry, 916 were included in the intent-to-treat population (mean age 45.0±15.0 years). Asthma control and QoL scores improved in patients receiving omalizumab at Months 12 and 24 compared with baseline (Table). Improvements exceeded the minimum clinically important difference at both timepoints (≥3 point increase for the ACT, ≥0.5 point decrease for the ACQ, and ≥0.5 point increase for the AQLQ and mini-AQLQ).

	Baseline (N=916)		Month 12 (N=734)		Month 24 (N=643)	
	n	Score (SD)	n	Score (SD)	n	Score (SD)
ACT*	496	13.0 (4.58)	417	19.1 (4.40)	361	19.7 (4.45)
ACQ†	181	2.74 (0.976)	94	1.73 (1.116)	62	1.80 (1.068)
AQLQ*	132	4.27 (1.270)	92	5.58 (1.055)	81	5.49 (1.299)
mini-AQLQ*	204	3.81 (1.189)	163	5.04 (1.326)	125	5.20 (1.299)

*An increase in score reflects an improvement. † A decrease in score reflects an improvement.

Conclusions: In patients with severe allergic asthma, treatment with omalizumab resulted in sustained and clinically meaningful improvements in asthma control and asthma-related quality of life.

P1794

Efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) once daily (OD) for 24 weeks in persistent asthma

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Introduction: FF and VI are, respectively, a novel inhaled corticosteroid and long-acting beta$_2$ agonist in development as a combined OD therapy for asthma and COPD.
Objectives: To compare the efficacy and safety of FF/VI with FF and fluticasone propionate (FP) in patients (≥12 years old; on ICS) with moderate-to-severe persistent asthma.
Methods: Patients (N=586; intent-to-treat) received FF/VI 200/25mcg OD PM, FF 200mcg OD PM or FP 500mcg twice daily (AM/PM) for 24 weeks. Co-primary endpoints were change from baseline in trough (pre-bronchodilator) FEV_1 and weighted mean 0–24h serial FEV_1. Secondary endpoints were change from baseline in %rescue-free and %symptom-free 24h periods and Asthma Quality of Life Questionnaire (AQLQ) score. Safety assessments included adverse events (AEs), 24h urinary cortisol (UC) excretion, vital signs and ECG.
Results: FF/VI improved trough FEV_1 (diff. 193mL and 210mL; both $p<0.001$) and weighted mean serial FEV_1 (diff. 136mL [p=0.048] and 206mL [p=0.003]) vs FF and FP. Significantly more %rescue-free (11.7 [$p<0.001$]) and %symptom-free (8.4 [p=0.01]) 24h periods were reported with FF/VI vs FF. There was no statistical difference between FF/VI and FF in AQLQ score. Incidence of AEs was similar across groups. No clinically significant difference was seen across treatments with respect to 24-h UC excretion, vital signs or ECG.
Conclusions: Treatment with FF/VI over 24 weeks was associated with statistically greater improvements in lung function and asthma stability vs FF and FP, and was well tolerated in this asthma population.
Funded by GSK (HZA106829; NCT01134042).

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Efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) compared with fluticasone propionate/salmeterol combination (FP/SAL) in adults and adolescents with persistent asthma

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Introduction: The combination of FF, a novel inhaled corticosteroid and VI, a long-acting beta$_2$ agonist, is under development as a once-daily treatment for asthma and COPD.
Objectives: To compare the efficacy of FF/VI with FP/SAL in patients with persistent asthma.
Methods: In a randomised, double-blind, double-dummy, parallel-group study, 806 patients received FF/VI (100/25mcg, n=403) or FP/SAL (250/50mcg, n=403) via a new dry powder inhaler, or DISKUS™, respectively. FF/VI was taken once daily in the evening, FP/SAL twice daily. Primary efficacy measure was 0–24h serial weighted mean (wm)FEV_1 after 24 weeks of treatment.
Results: Clinically significant improvements from baseline in 0–24h wmFEV_1 were seen with both FF/VI (341mL) and FP/SAL (377mL); the adjusted mean treatment difference was not statistically significant (–37mL, p=0.162). Changes from baseline in 0–4h wmFEV_1 and trough FEV_1 supported the primary findings, as did AQLQ+12, ACT and EQ5-D scores. No difference between treatments in reported exacerbations was found. Both treatments were well tolerated, with no clinically relevant effects on urinary cortisol excretion or vital signs, and no treatment-related serious adverse events; safety profiles were similar across treatment groups.
Conclusions: Once-daily FF/VI was as effective as twice-daily FP/SAL in improving lung function in patients with persistent asthma, and no safety issues were identified. No statistically significant treatment difference in efficacy was observed between the two combination treatments.
Funded by GSK (HZA113091; NCT01147848).

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Tiotropium reduces asthma exacerbations in asthmatic patients with persistent airflow obstruction uncontrolled despite treatment in accordance with guidelines

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Introduction: Some asthmatics remain symptomatic despite high-dose (HD) inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA) and additional treatments in accordance with guidelines and may have frequent asthma exacerbations.
Methods: We performed a prespecified combined analysis of 2 replicate double-blind, parallel group trials comparing the effect of adding tiotropium Respimat® 5 mcg or placebo on exacerbation frequency in 912 asthmatics receiving at least HD ICS+LABA. At study entry, patients had a postbronchodilator (BD) FEV_1 <80% predicted, asthma control questionnaire score (ACQ) ≥1.5, and at least one severe exacerbation in the preceding year. Severe exacerbations were defined as necessitating systemic corticosteroids for ≥3 days.
Results: Baseline characteristics were similar between treatment groups. The addition of tiotropium was associated with a 21% risk reduction (HR 0.79, P=0.03) in time to first severe exacerbation. Tiotropium also reduced the risk of any asthma exacerbation by 31% (P<0.0001), defined by significant increase in symptoms or PEF drop ≥30% over ≥2 days. There were significant improvements in ACQ and Asthma Quality of Life Questionnaire in one trial and a trend towards improvement in the ACQ in the other one. No deaths occurred; adverse events were balanced across treatments in both trials.
Conclusion: In asthmatics that remain uncontrolled despite HD ICS+LABA, the addition of tiotropium significantly reduces the risk of asthma exacerbations requiring treatment with systemic corticosteroids.
Study supported by Boehringer Ingelheim and Pfizer.

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Usability evaluation of NEXThaler® versus Diskus® and Turbuhaler®

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Inhaler device characteristics may impact real-world treatment effectiveness. NEXThaler® (Chiesi Farmaceutici) is a new dry powder inhaler (DPI) designed for persistent asthma with an innovative full dose feedback system incorporating a novel breath-actuated mechanism: a click is heard and a dose counter decrements by one count, only after effective full dose delivery. Effectiveness, efficiency and satisfaction are key components of device usability (ISO 13407:1999). NEXThaler®, Diskus® and Turbuhaler® were compared in a crossover trial in 66 asthmatic patients with no previous experience of using DPIs. After reading the patient information leaflet, patients performed two inhalations. Device-use errors and device preference were assessed through video recording and a standardized questionnaire.
The proportion of patients completing both the first and second inhalation without making an error was significantly higher with NEXThaler® than Diskus® and Turbuhaler® ($p<0.001$) (Fig. 1A). Confidence that the dose had been successfully

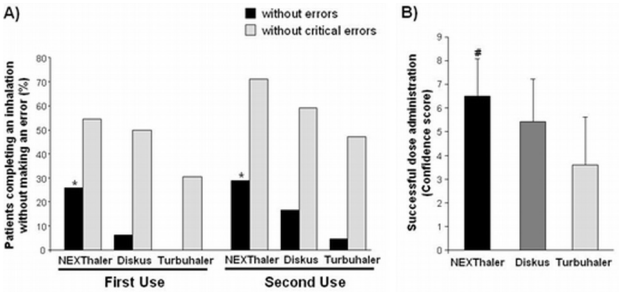

Figure 1. Successful device usage and confidence in the administration of a successful dose. A) The number of participants successfully completing an inhalation without making an error was significantly higher with NEXThaler than Diskus and Turbuhaler on both first and second use (*p<0.001 vs Diskus and Turbuhaler). A critical error was defined as "an error that will prevent any kind of dose being delivered". **B)** Confidence in administration of a successful dose was significantly higher for NEXThaler than both Diskus and Turbuhaler (#p<0.001 vs Diskus and Turbuhaler).

administered was greater with NEXThaler® than other DPIs ($p<0.001$) (Fig. 1B). Additionally, NEXThaler® was superior to both Diskus and Turbohaler in terms of ease of use (74 vs 17 and 9% respectively; $p<0.001$) and patient preference (75 vs 17 and 8%, respectively; $p<0.001$).
Overall, effectiveness, efficiency and satisfaction measures each demonstrate that the usability of NEXThaler® is superior to Diskus® and Turbuhaler®.

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Beclometasone/formoterol administered via extrafine dry powder inhaler in controlled asthmatic patients: Comparison with pMDI and beclometasone monotherapy

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Background: The fixed combination of beclometasone dipropionate and formoterol fumarate (BDP/FF) 100/6 μg pMDI (Foster®) is approved for treatment of adult asthmatic patients. In order to provide physicians and patients with an alternative drug delivery system for BDP/FF, a new dry powder inhaler the NEXThaler® has been developed, able to ensure consistent dosing in patients who prefer the use of dry powder inhalers.
Aim: To compare efficacy and safety profile of BDP/FF NEXThaler® with BDP/FF pMDI or BDP DPI alone in adult patients with controlled asthma.
Methods: 8-week randomised,double-blind, triple-dummy, 3-arm parallel-group clinical study. After 4-week run-in with BDP/FF pMDI 100/6 bid, 755 patients were randomised to receive bid BDP/FF NEXThaler® 100/6, BDP/FF 100/6 pMDI or BDP DPI 100. The primary end-point was change from baseline to the entire treatment period in average pre-dose morning PEF (mPEF).
Results: Non-inferiority of NEXThaler® vs pMDI was shown for mPEF (LSmeans difference:-1.84L/min; 95%CI[-6.73;3.05]) and lower limit of the 95%CI was above the pre-defined non-inferiority margin of -15L/min. Superiority of both combinations over BDP DPI was shown ($p<0.001$) providing evidence of assay sensitivity of the study. Both BDP/FF formulations were statistically superior to BDP alone in terms of ACQ score (p=0.009 and 0.008) and % of rescue use-free days (p=0.033 and 0.006) as well as pulmonary function tests over the entire treatment period. No relevant drug related AEs were observed.
Conclusion: NEXThaler® is an effective and well-tolerated alternative delivery device for treatment of asthmatic patients with BDP/FF.

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Improving inhalation parameters through dry powder inhalers (DPIs) after an acute asthma exacerbation

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All DPIs are passive inhalers because they require the generation of an internal energy (P) from an interaction between the patient's inhalation and the device's resistance to deaggregate the formulation in the metered dose. During acute exacerbations patient inspiratory effort will be reduced and thus P will be reduced. We have measured the inhalation profiles of 18 asthmatics, mean(SD) age 42.0(11.8) years, on days 1-4 following their admission with an acute exacerbation. These measurements have been made using a Diskus (DKS), Easyhaler (EASY) and Turbuhaler (TBH) - inhalers with medium, medium/high and high resistance.

	Day 1	Day 2	Day 3	Day 4
FEV_1% pred	40.9 (12.5)	47.9 (13.6)	55.6 (12.6)	58.2 (11.8)
DKS				
PIF (L/min)	42.3 (8.9)	51.0 (8.7)	65.7 (16.0)	77.0 (15.4)
PP (kPa)	1.60 (0.74)	2.28 (0.83)	3.91 (2.07)	5.27 (2.10)
ACC (KPa/sec)	2.31 (1.38)	3.63 (2.49)	6.72 (3.68)	10.26 (8.21)
IV (L)	0.80 (0.34)	0.90 (0.30)	1.11 (0.36)	1.35 (0.31)
TBH				
PIF (L/min)	35.1 (4.9)	41.4 (5.60)	45.3 (6.3)	50.9 (7.2)
PP (kPa)	1.42 (0.41)	1.98 (0.52)	2.38 (0.66)	3.00 (0.83)
ACC (KPa/sec)	2.55 (1.12)	4.29 (2.12)	4.53 (1.71)	6.23 (3.06)
IV (L)	0.55 (0.25)	0.64 (0.29)	0.72 (0.26)	0.84 (0.26)
EASY				
PIF (L/min	31.3 (3.7)	38.3 (4.7)	43.3 (6.5)	48.2 (7.6)
PP (kPa)	2.33 (0.53)	3.51 (0.85)	4.52 (1.35)	5.59 (1.74)
ACC (KPa/sec)	4.60 (1.78)	6.94 (2.32)	9.06 (3.77)	11.15 (4.91)
IV (L)	0.53 (0.18)	0.63 (0.17)	0.77 (0.26)	0.86 (0.34)

PIF, peak inhalation flow; PP, peak turbulent energy; ACC, initial acceleration of the inhalation; IV, inhalation volume. All $p<0.001$ except TBH IV <0.05.

All parameters improved. PIF should not be considered in isolation and provides the wrong message, especially for high resistance DPIs, as PP and ACC are more important. The significance of the IV results needs to be investigated.