94. Drug delivery and pharmacokinetics I

P820

The effect of ketoconazole on the pharmacokinetics (PK) and pharmacodynamics (PD) of inhaled fluticasone furoate (FF) and vilanterol (VI) administered in combination in healthy subjects

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Rationale: A combination of the novel corticosteroid FF and long acting beta$_2$-agonist VI administered via dry powder inhaler (FF/VI) is being developed as a once-daily treatment for asthma and COPD. Both FF and VI are predominantly metabolised via CYP3A4 and their PK and PD could be affected by CYP3A4 inhibition.
Objective: To investigate the effects of the strong CYP3A4 inhibitor ketoconazole on the PK and PD of FF and VI.
Methods: Double-blind, randomised, placebo (P)-controlled, repeat dose, two-way crossover study. Healthy male and female subjects [N=18] received once daily oral ketoconazole (400mg) or P for 11 days with FF/VI (200/25mcg) for the final 7 days. PD and PK data were obtained up to 48h following the Day 11 dose.
Results: Co-administration of ketoconazole and FF/VI had no effect on 0-4h maximum heart rate or minimum blood potassium (treatment difference [90%CI] -0.6bpm [-5.8, 4.5] and 0.04mmol/L [-0.03, 0.11], respectively) whilst there was a measurable but clinically insignificant decrease in 24h weighted mean serum cortisol (treatment ratio [90%CI] 0.73 [0.62, 0.86]). Co-administration of ketoconazole increased (percent change [90%CI]) FF AUC(0-24) and Cmax by 36% [16, 59] and 33% [12, 58] and VI AUC(0 t') and Cmax by 65% [38, 97] and 22% [8, 38], respectively. Both treatments were well tolerated and there were no serious adverse events or withdrawals.
Conclusion: Co-administration of FF/VI with ketoconazole resulted in a less than two-fold increase in systemic exposure to FF and VI with no clinically significant systemic effects.
Funded by GSK (HZA105548; NCT01165125)

P821

Vilanterol, a novel inhaled long-acting β_2 adrenoceptor agonist (LABA), demonstrates extensive first pass clearance to metabolites with negligible pharmacological activity in man

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Introduction: Vilanterol (VI) trifenatate is a novel LABA with demonstrated 24-hour clinical duration of action, currently in development in combination with an inhaled corticosteroid for once-daily treatment of COPD & asthma.
Objectives: The excretion and metabolism of radio-labelled VI was investigated following oral dosing to represent the swallowed portion of an inhaled dose.
Methods: Open label, single dose study. Healthy male subjects [N=6] received an oral solution dose of 200 ug of [^{14}C]VI (2 uCi). Plasma samples and all urine and faeces were collected up to 168 h post dose and analysed for total radioactivity, VI and VI metabolites (as appropriate).
Results: VI was well absorbed (>50% of the radioactive dose). VI represented a very small percentage (<0.5%) of the total circulating drug-related material in the plasma indicating extensive first-pass metabolism of VI. In total 70% of the recovered radiolabel was collected in the urine with the remainder recovered in the faeces. The primary route of clearance of VI was via O-dealkylation to pharmacologically inactive metabolites which were predominantly excreted in the urine. VI was well tolerated with no notable changes in heart rate, serum potassium and glucose levels or ECG parameters.

Conclusion: VI undergoes extensive first-pass metabolism in man. VI was well tolerated after an oral dose (200 ug) considerably in excess of the likely clinical inhaled dose (25 ug), indicating absent pharmacological activity of the metabolites in man (in agreement with pre-clinical data).
Funded by GSK (B2C106181; NCT01286831)

P822

Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of single doses of GSK573719 inhalation powder, a new long-acting muscarinic antagonist (LAMA), in patients with COPD

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Introduction: GSK573719 is a new LAMA offering sustained 24-hour bronchodilation in development for the treatment of COPD.
Objectives: To investigate the safety, tolerability, PK and PD of GSK573719 in ipratropium-responsive COPD patients.
Methods: In a randomised, double-blind, dose-ascending, 4-way crossover study, 24 patients enrolled received single doses of 4 of the following 5 treatments by dry powder inhalation: GSK573719 (250/500/1000μg), placebo (PBO), tiotropium bromide (TB; 18μg). Doses were separated by 14 days.
Results: 20 patients completed all dosing periods. Adverse events (AEs) were reported with 31–41% GSK573719, 38% TB and 29% of PBO doses, most of mild or moderate intensity. There were 5 severe AEs and 4 patients withdrew due to AEs (none were drug related). No clinically meaningful differences in clinical chemistry, vital signs or ECG parameters were seen for GSK573719 vs PBO, although lower heart rates were observed for all active treatments (up to 7.7bpm lower with 1000μg vs PBO). GSK573719 was rapidly absorbed (median t_{max} 5–15min), but 40–61% of plasma PK samples were nonquantifiable. Urine $t_{\frac{1}{2}}$ was on average 11–12h. Specific airway conductance (sG_{aw}) and FEV_1 responses were significantly higher for all active treatments vs PBO, and responses for all GSK573719 doses were higher than TB. No correlation was observed between GSK573719 systemic exposure and PD variables.
Conclusion: Single doses of GSK573719 250–1000μg were well tolerated and associated with clinically relevant improvements in lung function in COPD patients.
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P823

The pharmacodynamics of GSK961081 in patients with COPD

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Introduction: GSK961081 is a dual pharmacophore with both muscarinic antagonist and $beta_2$ agonist (MABA) activity.
Objective: To assess the pharmacodynamics of GSK961081.
Methods: This was a randomised, double-blind, double-dummy, placebo-controlled, incomplete block crossover study in 50 COPD patients. Patients were randomised to 3 of 4 possible treatments: 400μg GSK961081 once daily (OD) (n=29); 1200μg GSK961081 OD (n=32); salmeterol 50μg twice daily+tiotropium 18μg OD (SAL+TIO) (n=41); and placebo (n=43) by inhalation for 14 days. Pharmacodynamics (lung and systemic), safety and tolerability were monitored.
Results: After 14 days' dosing there were significant improvements in trough FEV_1 for all active treatments. For 400μg GSK961081, 1200μg GSK961081 and SAL+TIO mean (95% CI) differences vs placebo were 0.115L (0.024,0.205), 0.168L (0.080,0.255) and 0.103L (0.026,0.180), respectively (all $p<0.05$). There was no significant difference in maximum change from baseline heart rate, glucose or QTcF 0–4h after the final dose of any active treatment vs placebo. There was a small decrease in potassium 0–4h after the final dose of all active treatments. For 400μg GSK961081, 1200μg GSK961081 and SAL+TIO mean (95% CI) minimum change from baseline potassium vs placebo was –0.11 (–0.22,–0.01), –0.19 (–0.29,–0.09) and –0.10 (–0.19,–0.01) mmol/L, respectively. Adverse events were similar across all groups with the exception of tremor (n=2, 1200μg dose), dysguesia (n=2, 1200μg dose; n=2, 400μg dose) and dry mouth (n=1, 1200μg dose) seen after GSK961081 only.
Conclusions: GSK961081 was well tolerated and showed significant bronchodilatation, meriting further evaluation as a potential therapy for COPD.
Funded by GSK (MAB104958; NCT00478738)

P824

The safety, tolerability, pharmacodynamics and pharmacokinetics of inhaled fluticasone furoate (FF) and vilanterol (VI) are unaffected by administration in combination

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Introduction: A combination of the novel corticosteroid FF and long acting $beta_2$-agonist VI (FF/VI) is currently under development as a once-daily inhaled treatment for asthma and COPD.
Objectives: To assess whether the pharmacodynamics (PD) and pharmacokinetics (PK) of FF and VI are affected when delivered as the FF/VI combination in comparison with FF and VI alone administered from the same novel dry powder inhaler.
Methods: Single centre, randomised, double-blind, placebo-controlled, four-way crossover study. Healthy male and female subjects [N=16; 21-57 years] received single supra-therapeutic doses of FF (800mcg), VI (100mcg), FF/VI (800/100mcg) and placebo. PD and PK were monitored post-dose.
Results: FF/VI decreased serum cortisol (0-24h weighted mean vs placebo) by 14.7% vs. 24.1% for FF alone; the difference of 12.3% (90% CI: 4.4, 20.9) was considered non-inferior (defined as lower CI > -20%). FF/VI increased heart rate (0-4h maximum vs placebo) by 5.7bpm vs 6.9bpm for VI alone; the difference of -1.2bpm (90% CI: -4.6, 2.1) was considered non-inferior (defined as upper CI < +10bpm). There were no differences in minimum blood potassium (0-4h). FF and VI mean exposure (AUC0-t') (90% CI) were 15% (5, 24) and 3% (-14, 18) lower, respectively for the combination vs FF or VI alone. The adverse event profile for all treatments was similar to placebo.
Conclusion: Administration of FF and VI in combination was not associated with an increase in systemic exposure or systemic pharmacodynamic effects compared with administration of either compound alone.
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P825

Aspirin inhalation treatment for COPD patients: Preliminary studies on PK and inflammatory biomarkers

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We are currently investigating if the use of aspirin (ASA), administered via inhalation, can exert a local anti-inflammatory effect, to propose it as a treatment for COPD, an inflammation-related pathology.
As little is known on inhaled ASA's PK, a 3-way crossover study was performed on 14 moderate COPD subjects, which were administered 250/500/750mg of ASA's lysine salt via nebulizer, with/without concomitant charcoal intake (all subjects also assumed orally a 500mg dose). The inhalation resulted in a linear PK for ASA and salicylic acid in plasma. Variability appeared important after inhalation, while modest after oral intake. Only approximately 10% of the administered dose was recovered in urine (70% after oral dose).
The efficacy of inhaled ASA was investigated in 4-week placebo-controlled clinical trial performed on 59 moderate COPD subjects, who inhaled 250, 500 or 750mg of ASA BID. Functional respiratory parameters were measured together with inflammatory markers in serum and induced sputum.
A statistically significant decrease was observed for serum IL6 and IL8 and sputum TNFα (trend test: 0.0004, 0.0144 and 0.0275). The 250mg dose was observed to statistically increase FEV1 and FEV/FVC from T0 to T4 (p=0.02 and 0.008). The same dose also showed important effects, compared to placebo, both on inflammation (reduction of sputum neutrophil elastase, p=0.031) and sputum production (p=0.008). These results are not conclusive to prove the efficacy of the treatment (large intra-patient variation, lack for specific biochemical marker for COPD). However, also considering the good tolerability, they support the opportunity for a larger clinical trial.

P826

Pharmacokinetic bioequivalence of inhaled CHF 1535 50/6 vs. the free combination of beclomethasone and formoterol in asthmatic children

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Rationale: To develop a new fixed formulation of Beclomethasone dipropionate (BDP) 50μg and Formoterol fumarate 6μg (CHF 1535 50/6) delivered via a pMDI for treatment of children with severe asthma.

Objective: To investigate pharmacokinetic of B17MP (active BDP metabolite) and Formoterol in children with asthma after inhalation of CHF 1535 50/6 vs. the licensed free combination of BDP and Formoterol dispensed with AeroChamber Plus™.
Methods: 22 children (5-11yrs) with mild asthma were included in this open-label, randomised, 2-way cross-over study of inhaled BDP 200µg and Formoterol 24µg. Eight-hour pharmacokinetic profiles (Cmax and AUC0-t) for B17MP and Formoterol after single inhalation were primary endpoints evaluated by analysis of variance and 90% bioequivalence limits.
Secondary endpoints were pharmacodynamics: serum potassium, heart rate, and cortisol excretion.
Results: B17MP and Formoterol pharmacokinetic parameters showed comparable values and the upper limit of the 90% CI was well within the bioequivalence limit. The pharmacodynamic parameters also showed similar values after both treatments.
Conclusion: After CHF 1535 50/6 administration, the BDP and Formoterol systemic exposure was similar to the systemic exposure of BDP and Formoterol administered as free combination supporting a comparable safety profile in children aged 5-11yrs.

P827
Contamination and carry-over in clinical pharmacokinetic trials with aerosolized budesonide
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Background: Contamination and carry-over by active drug components is a major issue, especially in pharmacokinetic studies carried out with aerosolized substances. Measures to avoid contamination and carry-over in blood samples remain poorly standardized and validated.
Objective: To investigate the space- and time-related distribution pattern of budesonide aerosolized via MDI.
Methods: A matrix of crystallization dishes was set up in a measurement chamber. One puff of budesonide MDI (184 µg emitted dose, 200 µg nominal dose) was aerosolized and aerosol was allowed to sediment for 0.25 to 6.5 hours. Recovery of budesonide in the crystallization dishes was measured via HPLC and correlated to time course and spatial matrix.
Results: In 1 m distance of actuating the MDI, a mean recovery of budesonide of 0.688 µg after 0.25 hours and 1.423 µg after 6.5 hours was observed. The surface concentration in 1 m distance was 9.7 ng/cm^2 after 0.25 hours and 20.1 ng/cm^2 after 6.5 hours.
Conclusion: This study is a valid basis for risk assessment of carry-over effects in clinical trials with aerosolized drugs. Regarding surface concentrations in the nanogram range as shown in our study compared to serum drug concentrations in the picogram range as determined in pharmacokinetic trials, carry-over effects via aerosols seem probable. Further studies to determine the extent and origin of these effects will therefore be performed.

P828
Fluticasone/salmeterol combined in the new Forspiro® inhaler is as effective and safe as Seretide® Accuhaler® in adult and pediatric asthmatics
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Objective: To compare the clinical efficacy and safety of fluticasone/salmeterol (Flu/Salm) combined in the new "Forspiro" DPI with Seretide Accuhaler (Glaxo Wellcome).
Methods: We conducted two large clinical phase III studies with twice daily treatment over 12 weeks including more than 770 children and adolescents/adults suffering from moderate or moderate-to-severe asthma. Primary endpoints were FEV1 change from baseline and the area under the FEV1 curve at study termination. Asthma symptom score, reliever use, morning PEF, adverse events (AEs) were also assessed.
Results: Mean increase of FEV1 for the 100/50 mcg (low dose) was 276 mL in adolescents/adults and 476 mL in children aged 6-11 years, and 344 ml for 500/50 mcg (high dose) in adults at endpoint. Morning PEF increased with the low dose by 17.5 L/min in adolescents/adults and 31.5 L/min in children, and by 35 L/min with the high dose in adults. Asthma symptom scores and reliever use had already decreased substantially after the first treatment week. The number of drug-related AEs was comparable between treatments. Serum cortisol measured during 12 hours at endpoint tended to lower levels with the reference product. Patients' assessment at study termination revealed an overall preference for the "Forspiro" DPI due to its mouthpiece fit, device size and shape.
Conclusions: Flu/Salm in the "Forspiro" inhaler was shown to be as efficacious and safe as Seretide Accuhaler.

P829
Effect of systemic and extra-fine particle inhaled corticosteroids on corrected alveolar nitric oxide (CANO) in COPD
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Background and objectives: Alveolar nitric oxide or (CANO), has been used as a surrogate marker of distal airway inflammation, which is important in COPD. Coarse particle inhaled corticosteroids (ICS) do not suppress CANO. We evaluated whether extra-fine particle size ICS or systemic oral corticosteroids could suppress CANO in COPD.
Methods: COPD patients with a smoking pack history >15years, FEV1/FVC ratio <0.7, FEV1<80% predicted with small airways inflammation characterized by CANO >2ppb underwent a double-blind randomised controlled crossover trial with an open label systemic steroid comparitor. Following a 2wk steroid washout period, patients were randomised to 2wks, 100mcgHFA-BDP 1 puff b.i.d and then 2 weeks 400mcgHFA-BDP or matched placebos with subsequent crossover. All patients received 1wk open-label, 25mg/day prednisolone. Spirometry, body plethysmography, impulse oscillometry and exhaled nitric oxide were recorded.
Results: 16 patients completed per protocol. Compared to respective placebo there were no significant differences with extra-fine particle ICS. Oral prednisolone caused a significant reduction in FENO and J'awNO but not CANO (see table1).

Table 1. Study measurements

Outcome	Placebo 1	HFA-BDP 100µg	Placebo 2	HFA-BDP 400µg	Prednisolone 25mg
Extended Exhaled Nitric Oxide					
FENO ppb#	17.3 (13.3-22.4)	15.2 (11.2-20.5)	16.4 (12.5-21.6)	12.7 (9.1-17.7)	12.6 (9.6-16.5)*†
J'aw,NO nl/s#	1375(1039-1820)	1169 (836-1635)	1170(875-1564)	1000(675-1484)	903 (598-1365)*
$CANO_{ex}$ ppb	2.5 (1.4-3.6)	1.9 (0.5-3.4)	1.7 (0.9-2.5)	1.9 (0.8-2.9)	1.5 (0.7-2.3)
CANO ppb	3.8 (2.6-5.0)	3.1 (1.8-4.4)	2.9 (2.1-3.8)	2.4 (1.4-3.3)	2.5 (1.8-3.2)
Spirometry					
FEV_1 % pred	48 (38 – 57)	51 (42 – 61)	49 (38 – 59)	49 (39 – 59)	47 (38 – 56)
FEV_1/FVC	47 (41 – 54)	47 (41 – 54)	46 (39 – 53)	47 (40 – 54)	45 (37 – 52)
Impulse Oscillometry					
R5 % pred	200 (164 - 235)	185 (155 - 216)	200 (168– 231)	195 (159– 231)	197 (168 – 225)
R20 % pred	137 (118 – 157)	138 (114 – 162)	135 (114– 156)	136 (115– 157)	137 (116 – 158)
Body Plethysmography					
sRaw kPa s^{-1}	3.6 (2.1 – 5.1)	3.2 (2.1 – 4.4)	3.6 (2.1- 5.0)	3.4 (2.1 – 4.7)	3.1 (2.2 – 4.0)
RV/TLC	0.57 (0.49–0.64)	0.55 (0.49-0.60)	0.54 (0.49-0.64)	0.56 (0.50-0.62)	0.55 (0.49-0.62)

*p<0.05 versus placebo 1, †p<0.05 versus placebo 2
Data presented as arithmetic mean (95%CI) unless stated. #Data presented as geometric mean (95%CI).

Conclusions: Whilst CANO remains a biomarker of interest in COPD, it is not suppressed by systemic or extra-fine particle ICS. Hence CANO is unlikely to be a useful marker for monitoring response of small airway disease to therapies in COPD.

P830
Lung deposition of the extra fine dry powder fixed combination beclomethasone dipropionate plus formoterol fumarate via the NEXT DPI® in healthy subjects, asthmatic and COPD patients
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Background: Chiesi has developed the new pocket size, medium air flow resistant, breath actuated multidose-reservoir dry powder inhaler NEXT DPI®.
Objectives: The lung deposition and distribution pattern of the extrafine fixed combination of beclomethasone dipropionate 100µg and formoterol fumarate 6µg administered via the NEXT DPI® was assessed using a gamma-scintigraphic technique after inhalation of a single dose of the ^{99m}Tc-radiolabelled combination (total dose BDP/formoterol 400/24µg).
Methods: 10 healthy subjects, 9 asthmatic patients (30%≤FEV_1<80%) and 9 patients with stable chronic obstructive pulmonary disease (COPD) (FEV_1/FVC≤70%, 30%≤FEV_1<50%) were treated according to an open, single dose design.
Results: Similar lung and extra-thoracic deposition were observed between the groups. The average lung deposition was 55% relative to the emitted dose in healthy subjects, 56% in patients with asthma and 55% in COPD patients. The extra-thoracic deposition was 43% in healthy subjects, 42% in asthmatic patients and 42% in COPD patients. The amount exhaled ranged between 1.6 to 3.3%. The distribution pattern, evaluated by measuring the central/peripheral (C/P) ratio confirmed distribution throughout the airways, including periphery (C/P 1.23, 2.02 and 1.57 for healthy subjects, asthmatic and COPD patients, respectively).
Conclusions: These results demonstrated that a high amount of the extrafine dry powder fixed combination BDP/formoterol administered via the NEXT DPI® was deposited in the lungs regardless the pathophysiological condition.
Research funding source: Chiesi Farmaceutici S.p.A.

P831

A novel NEXT DPI® dry powder inhaler and its use in asthmatic and COPD population

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Rationale: In asthma and COPD the dry powder inhalers (DPIs) facilitate patient's compliance to drug intake. Chiesi Farmaceutici developed a new inhaler, NEXT DPI® which is pocket size medium-resistant breath-actuated mechanism (BAM) multidose-reservoir to be used for drug delivery.
Objective: To verify that the peak inspiratory flow (PIF) required for the drug delivery is not influenced by patient's age and disease.
Methods: Children (n=27; age 5-11), adolescents (n=20; age 12-17) and adults (n=21; age ≥ 18) with asthma and COPD patients (n=21; age ≥ 40) were included in this multicenter open-label placebo study. After baseline pulmonary function assessments (FEV_1, FVC; PIF tested with spirometer and In-Check Dial™ device) patients inhaled through the NEXT DPI® to test the BAM activation, checked by the residual doses in the dose-counter. Usability evaluation questionnaire, adverse events (AE) and vital signs were also recorded.
Results: In all patients, spirometry showed from moderate to severe airways obstruction. All patients, irrespective of age and disease, were able to activate the BAM. The mean PIF value (asthmatic patients: 104.4±20.6 L/min, range 40-120; COPD patients: 97.9±18.8 L/min, range 51-120) measured with the In-Check was greater than the threshold set for the BAM activation and not influenced by age and disease severity. No patients had problem in using the NEXT DPI® correctly. A total of 7 AEs were reported in 5 patients, no one related with the use of NEXT DPI® or severe in intensity. No Severe Adverse Events were reported.
Conclusions: NEXT DPI® can be easily used and activated in a wide population of asthmatics and COPD patients irrespective of age and disease severity.

P832

Efficiency of ipratropium bromide and salbutamol deposition in the lung delivered via a soft-spray inhaler or chlorofluorocarbon metered-dose inhaler

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Purpose: The dose combination of ipratropium bromide (Ip) 42 mcg and albuterol (Alb) 200 mcg, propelled by CFC, is currently marketed in a single canister dosage form. A soft-spray, aqueous solution-based delivery system of this combination was developed. This pharmacokinetic study compared the efficiency of a soft-spray delivery of the combination to the lung compared to CFC delivery.
Methods: A steady state pharmacokinetic substudy comprised of 278 patients was conducted from two trials differing only by doses evaluating Ip and Alb delivered via the soft-spray inhaler or CFC-MDI in 2,578 patients. Ip alone delivered via the soft-spray inhaler and placebos delivered via either delivery system were used as controls. LC/MS/MS assays for analytes were developed for plasma and urine biofluids.
Results: Comparing AUC, Cmax, and Cmin showed that systemic exposure to Alb and Ip delivered via the soft-spray inhaler were proportional to the doses delivered. Comparability was obtained when comparing the soft-spray inhaler-delivered Ip at half the dose of the CFC-MDI. Since Ip is not significantly absorbed from the gastrointestinal tract, the systemic exposure observed is a relevant marker for lung deposition. Ip alone gave equivalent exposure as the combination demonstrating a lack of interaction.
Conclusions: These systemic exposure analyses can be regarded as a marker of lung deposition and therefore demonstrate that the soft-spray inhaler delivers drug more efficiently to the lung than CFC-MDI.

P833

Maintenance of lung function and asthma control with extrafine beclomethasone/formoterol

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Introduction: Asthma management focuses on achieving and maintaining asthma control. Very few studies have assessed whether complete and sustained asthma control is maintained after switching ICS/LABA fixed combinations in clinical practice.
Aim: To demonstrate equivalence between equipotent doses of extrafine BDP/F pMDI and fluticasone/salmeterol (FP/S) (Diskus®) in maintaining lung function and asthma control.
Methods: Prospective, double-blind, double-dummy, randomized, parallel group, controlled trial. 416 asthma patients controlled on FP/S 500/100µg/day (Diskus®, pMDI or separate inhalers) were randomized to 12-week treatment with extrafine BDP/F 400/24µg/day pMDI or FP/S 500/100µg/day (Diskus®). Pre-dose FEV_1 was the primary outcome, secondary outcomes included asthma control (ACQ-7).
Results: At the study end, pre-dose FEV_1 was equivalent between treatments (difference between means 0.01 L; 95% CI -0.03 to 0.06 L) with no changes from baseline in both groups. ACQ-7 score was equivalent between groups (Table 1). Post-dose FEV_1 in the first hour was significantly higher for extrafine BDP/F pMDI both at baseline and after 12-week treatment (Fig. 1, Table 1). No safety issues were reported in both groups.

Figure 1. Change from morning post-dose FEV1 (95% CI)

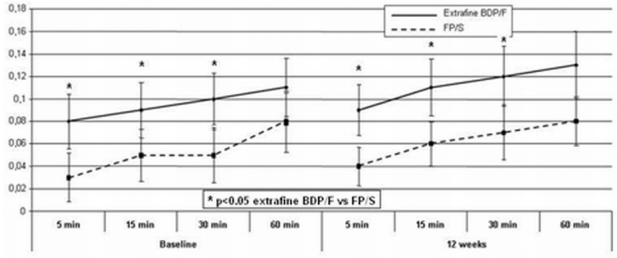

Table 1. Lung function and asthma control outcomes

	Pre-dose FEV_1 (L)		Post-dose FEV_1 (AUC_{0-1h}) (L)	ACQ-7	
	Extrafine BDP/F (n=207)	FP/S (n=209)	LS mean difference (extrafine BDP/F vs FP/S)	Extrafine BDP/F (n=207)	FP/S (n=209)
Baseline	3.10	3.15	0.04[b]	0.33	0.34
End of treatment	3.13[a]	3.16[a]	0.06[c]	0.34[a]	0.32[a]

[a] non significant difference between treatments
[b] p=0.004 between treatments
[c] p=0.019 between treatments

Conclusions: Patients previously controlled with FP/S in any device formulation can safely switch to extrafine BDP/F pMDI and maintain an equivalent asthma control with a sustained faster onset of action.

P834

Phase II study of once-daily GSK573719 inhalation powder, a new long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD)

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Introduction: GSK573719 is a new long-acting muscarinic antagonist offering sustained 24-hour bronchodilation in development for the treatment of COPD.
Objectives: To evaluate the safety, tolerability and pharmacokinetics of inhaled GSK573719 in a new dry powder (DP) formulation in COPD patients.
Methods: In this randomised, double-blind study, 38 patients with COPD received GSK573719 (250µg, n=20; 1000µg, n=9) or placebo (n=9) via a novel DP inhaler (DPI) once daily for 7 days.
Results: Of 43 adverse events (AEs) in 21 (55%) patients, 16 were drug related (all mild or moderate): placebo, 4 (headache, pruritus, flushing, hypoaesthesia); GSK573719 250µg, 5 (arrhythmia, tachycardia, dysgeusia, hypertension, bronchospasm); GSK573719 1000µg, 7 (blood pressure increase, thirst, oropharyngeal pain, headache, dry mouth, dyspnoea, feeling abnormal). Of 3 AE-related withdrawals (chest pain, respiratory tract infection, dyspnoea), only dyspnoea was considered drug-related (1000µg). The 1000µg dose showed larger increases than 250µg in heart rate (HR) (0–4h) vs placebo, but 24-h Holter monitoring showed no dose effect over 24h and the treatment effects were small. GSK573719 was rapidly absorbed (t_{max} 5–15min); 1–2% of the total dose was excreted unchanged in the urine. Accumulation (Day 7:Day 1) was low: 1.5–1.9x based on plasma data (1.8–2.4x, urine data). No correlation was seen between individual maximum HR (0–4h) and GSK573719 C_{max}.
Conclusions: GSK573719 250µg or 1000µg once daily by novel DPI was well tolerated by patients with COPD.
Funded by GSK (AC4105211; NCT00732472)

P835

Optimization of inhalation treatment – Evaluation of influence of PNEUMOlogic® and Optimiser® spacers on aerosol particle distribution from pMDI-EB

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Introduction: PNEUMOlogic® [PNL] is the first inhalation chamber [vol. 800 ml] integrated with the spirometer, used for the controlled drug delivery from pMDI-EB. Optimiser® [OPT] [vol. 50 ml] is the aerosol chamber used for drug administration from pMDI-EB.
The aim of the study was to evaluate the influence of inhalation chamber and method of performing inhalation on the quality of aerosol.
Method: Aerosol particle distribution and mass of aerosol was measured using particle counter with constant flow of 28,3L/min.
Results: Results are shown in Table 1 and Table 2.

Table 1

Drug	Salbutamol [Velaspir® 100]		
Inhalation chamber	PNL	PNL-X	OPT
MMAD [μm]	7,49	5,96	4,17
Mass of aerosol [μg]	0,2574	0,1834	0,0129

X – exhalation prior to the drug delivery into the chamber.

Table 2

Drug	Beclomethason [Cortare® 100]			Beclomethason [Cortare® 250]		
Inhalation chamber	PNL	PNL-X	OPT	PNL	PNL-X	OPT
MMAD [μm]	4,18	3,28	4,83	5,01	3,35	3,03
Mass of aerosol [μg]	0,0331	0,0194	0,0062	0,0456	0,0328	0,0057

X – exhalation prior to the drug delivery into the chamber.

Our study demonstrated statistically significant influence of chamber's size and the air exhaled into the chamber on quality and mass of aerosol.
Conclusion: Application of the chamber integrated with the spirometer opens up new possibilities for optimization of inhalation treatment.

P836

In vitro comparison of aerosol characteristics of HFA ipratropium bromide pressurized metered dose inhaler (pMDI) formulation from three valved holding chambers (VHCs)

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Inhaled bronchodilators and anticholinergics are the mainstay in the management of patients with chronic obstructive pulmonary disease. This study compared the in vitro aerosol characteristics from an HFA ipratropium bromide pMDI (Atrovent, 20 μg ipratropium bromide, Boehringer Ingelheim Ltd) with two anti-static VHCs, a preproduction OptiChamber Diamond (Diamond; Philips Respironics) and an AeroChamber Plus Z-Stat (Z-Stat; Monaghan Medical Corp.) VHC, a conventional AeroChamber Plus (AC+, Monaghan Medical Corp.) VHC, and the pMDI alone.
Six pMDIs were primed before use and six of each VHC were washed and air dried. For each run (n) the pMDI was actuated into the VHC or next generation impactor (NGI) (for pMDI alone - tested before and after VHC tests), followed by 20 s extraction at 30 L/min, repeated 10 times. Drug deposits from the NGI were analyzed using HPLC. The Emitted Dose (ED; drug entering the NGI), Fine Particle Dose (FPD; amount of drug ≤ 4.7 μm), Fine Particle Fraction (FPF;% of ED in particles ≤ 4.7 μm), and Mass Median Aerodynamic Diameter (MMAD) were determined using Copley Inhalation Testing Data Analysis Software (CITDAS).

Table 1. Results: Mean (Standard Deviation)

Device	ED (μg)	FPD (μg)	FPF (%)	MMAD (μm)
pMDI alone (n=12)	16.5 (0.9)	5.7 (0.6)	34.6 (4.7)	0.87 (0.05)
pMDI with Diamond VHC (n=6)	8.2 (0.6)	6.1 (0.9)	74.3 (6.7)	0.92 (0.04)
pMDI with Z-Stat VHC (n=6)	8.6 (0.7)	6.3 (1.1)	73.0 (7.9)	0.87 (0.02)
pMDI with AC+ VHC (n=6)	7.4 (1.0)	5.2 (0.9)	69.6 (3.9)	0.87 (0.02)

The aerosol characteristics were similar between the VHCs and removed significant potential throat deposition compared to the pMDI alone.

P837

Airway humidity during oxygen therapy: Impact of humidification and applicator design

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Background: Stationary oxygen therapy is usually combined with a humidification device in order to prevent mucosal dryness. The impact of the applicator design on airway humidity however has not been investigated to date.
Rationale: To investigate the impact of oxygen applicator design on airway humidity.
Method: First we developed a sampling and analysis system with a heated sampling probe to measure humidity of air samples under standard conditions during the inspiratory cycle.
We measured 12 individuals with an intranasal (standard nasal cannula) and prenasal (Oxynasor) applicator at different flow rates with and without humidification devices. The Oxynasor device is characterized by a cyclone effect of the emitting gas which reduces the oxygen velocity at the outlet.
Results: Intranasal humidity dropped significantly from 40.3±8.7% to 29.0±6.8% at a flow rate of three litres when oxygen was given intranasally without humidification ($p<0.01$). We observed no significant change in airway humidity when oxygen was given prenasally with and without humidification.
Conclusion: We propose two mechanisms to be responsible for this phenomenon: First prenasal application with low outlet velocity of dry oxygen allows for absorption of humidity from the surrounding air prior to nasal entry and second intranasal application with a high exit velocity from the applicator system might dry out the nasal mucosa by means of convection. Prenasal oxygen application with the Oxynasor device might obviate the need for humidification and therefore might simplify application and reduce therapy cost.

P838

Objective measurement of inhalation profiles in patients using metered dose inhalers (MDIs)

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Subjective assessments of inhaler technique suggest that patients have problems using MDIs (Crompton et al. Respir Med 2006). To expand on this problem we have electronically measured inhalation profiles of patients when they use a MDI using their normal technique. Children with asthma (CHILD; n=20), adults with asthma (ADULT; n=60) and chronic obstructive airways disease (COPD; n=31) completed the study. We have measured their peak inhalation flow (PIFR), inhalation volume (IV), length of inhalation (Ti) and the time between actuation and the start of an inhalation (TsIn). The results are shown in the table below.

Table 1. Mean (SD) [range]

	Child	Adult	COPD
Age (years)	8.8 (3.4)	49.0 (16.4)	64.9 (11.9)
FEV_1 (% pred)	78.4 (18.8)	70.6 (17.8)	51.2 (22.4)
PIFR (L/min)	67.9 (38.5) [14–166]	100. (47.5) [12–234]	70.9 (28.1) [16–142]
IV (L)	0.89 (0.73) [0.02–2.73]	1.67 (0.91) [0.03–4.2]	1.06 (0.56) [0.14–2.67]
TI (sec)	1.39 (0.74) [0.49–3.84]	1.77 (1.04) [0.28–1.73]	1.44 (0.65) [0.35–2.72]

Using a PIFR <90L/min for slow flow with a TsIn of 0-0.2 seconds for good co-ordination only 3 CHILD, 4 ADULT and 6 COPD demonstrated a good inhalation technique. The PIFR of 15 CHILD was <90L/min, 26 ADULT and 24 COPD. 9 CHILD actuated too early, 4 too late and 2 did not actuate. 17 ADULTS actuated too early, 27 were too late and 5 did not actuate. 9 COPD actuated too early and 14 too late. The mean (SD) ADULT ACQ was 2.04 (1.00) with no difference between slow and fast PIFR and co-ordination. ACQ for those with a good (n=4) and poor technique (n=56) was 1.07 (0.36) and 2.08 (1.02). As expected MDI co-ordination (TsIn) was poor and most PIFRs were too fast. The low IV and short Ti reveal that patients need to exhale more and prolong their inhalation time.

P839

In-vitro nebulised dose emission characteristics of a tobramycin solution (75mg/ml) using an I-Neb (I-NEB) and a pari LC+ driven by a TurboBoy compressor (PARI) nebuliser

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In practice solutions are nebulised by the equipment that is available rather than that recommended in the Summary of Product Characteristics (SPC). We have compared the in-vitro aerodynamic droplet characteristics of Bramitob when 4ml was nebulised by PARI (Pari, GmbH), recommended in the SPC, and an I-NEB (Philips Respironics, UK) with a 300μl cup. We have previously adapted the compendial methodology for nebulisers (Adelrahim & Chrystyn, J Aerosol Med 2009) and modified this to incorporate breath simulation (BS, tidal volume of 500ml and an inspiration: expiration ration of 1:3) for use with I-NEB. The schematic design of our methodology is shown in figure 1.
The mean (SD) aerodynamic droplet characteristics of tobramycin nebulised using PARI until sputtering and I-NEB until dryness are summarised in Table 1.
From the I-NEB data the fine particle dose (FPD) is 8.3mg. Separate determinations using PARI and compendial methodology provided a FPD of 17.5mg. The in-vitro droplet emission characteristics suggest that 2 separate doses of Bramitob

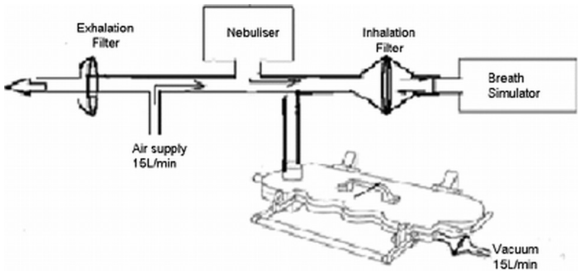

Figure 1

Table 1

	PARI	I-NEB
Residual amount (mg)	202.8 (37.2)	5.5 (2.4)
Total emitted dose (mg)	119.1 (20.8)	15.5 (2.4)
Fine particle fraction (%)	64.9 (4.5)	53.3 (9.9)
Mass Median Aerodymanic Diameter (μm)	3.8 (0.3)	4.4 (0.2)

nebulised using an I-Neb with a 300μl cup could be comparable to 4ml nebulised by a Pari LC+.