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Aerodynamic characteristics of dry powder inhaler (DPI) single-dose combination of budesonide with formoterol *in vitro* study validation

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Background: The aerodynamic properties of dry powder inhalers are essential for drug efficacy. Despite the availability of several devices, few studies have measured aerodynamic characteristics of the drug delivery using their proper device.
Aim: To describe the aerodynamic characteristics of the combination dry powder inhaler (DPI) Alenia® single-dose AeroCaps®(AA), which contains budesonide (BUD) and formoterol fumarate (FF) when compared with Foraseq® Aerolizer®(FA) as the reference combination drug.
Methods: They were assessed using quantitative sample analysis by high pressure liquid chromatography (HPLC), dose uniformity sampling apparatus (DUSA) and Andersen cascade impactor (ACI) to confirm the presence of active ingredients as well as the uniformity of released dose and the aerodynamic diameter of particles produced by their proper devices.
Results: Table 1 summarize the experiments.

Experiment	Alenia® BUD	Alenia® FF	Foraseq® BUD	Foraseq® FF
HPLC %	111.41	103.80	110.59	104.51
Sampling Uniformity mcg	293.24 (12.91)	10.23 (0.47)	353.04 (11.48)	11.07 (0.60)
Emitted dose delivered from the mouthpiece under specified in vitro	92,69–109,25%	89,63–108,01%	91,31–107,14%	91,32–111,83%
Mass (%) aerodynamic diameter <5 micra (ACI)	140,67 (44,71)	6,18 (56,13)	181,53 (53,56)	5,46 (52,05)

Experiments recommended by European Pharmacopoeia.

Alenia showed microbial quality control within acceptable<100CFU/g and the water container were normal of 4.76% by Karl Fischer test.
Conclusions: Alenia® and Foraseq® had active ingredients, dose uniformity and appropriate aerodynamic diameter to their respective dry powder inhalers.
Funded by Aché Laboratórios.

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Consider the turbulent energy not inhalation flow when patients use dry powder inhalers (DPIs)

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During an inhalation the formulation of a DPI is de-aggregated by a turbulent energy created by the interaction between the DPI's internal resistance and the patient's inhalation flow. We have measured the inhalation profiles of asthmatic children (CHILD; n=16; FEV_1 79% predicted), asthmatic adults (ADULT; n=53, FEV_1 72%) and COPD (n=29, FEV_1 42%) when they inhale through an Aerolizer (AERO), Accuhaler (ACC), Turbuhaler (TBH) and Easyhaler (EASY) using their 'real life' DPI inhalation technique. These are low, medium, medium/high and high resistance DPIs. A summary of the inhalation characteristics is presented below.

Mean (SD) data

	AERO	ACC	TBH	EASY
Child				
PIF (L/min)	71.4 (21.5)	53.3 (24.2)	44.8 (16.0)	45.5 (13.2)
P (kPa)	2.37 (1.33)	2.10 (1.70)	2.55 (1.79)	5.26 (2.89)
Accel (kPa)	7.2 (6.7)	5.4 (5.5)	6.7 (5.9)	11.7 (9.4)
IV (L)	1.22 (0.68)	1.19 (0.76)	1.00 (0.73)	1.00 (0.46)
Ti (sec)	1.69 (0.38)	1.50 (0.46)	1.52 (0.17)	1.62 (0.23)
Adult				
PIF (L/min)	93.7 (25.9)	76.3 (23.8)	60.2 (17.0)	58.3 (14.4)
P (kPa)	4.05 (2.19)	3.96 (2.39)	4.44 (2.39)	8.48 (4.13)
Accel (kPa)	12.6 (9.8)	11.0 (8.8)	13.2 (13.0)	20.9 (15.0)
IV (L)	1.96 (0.77)	1.91 (0.73)	1.63 (0.74)	1.68 (0.81)
Ti (sec)	1.54 (0.34)	1.61 (0.56)	1.63 (0.45)	1.55 (0.47)
COPD				
PIF (L/min)	81.8 (25.4)	62.0 (22.4)	50.9 (15.3)	49.6 (15.0)
P (kPa)	3.13 (1.88)	2.68 (1.80)	2.94 (1.9)	6.29 (3.55)
Accel (kPa)	8.68 (6.78)	6.74 (7.28)	8.51 (6.66)	14.0 (9.0)
IV (L)	1.71 (0.83)	1.79 (0.87)	1.50 (0.80)	1.52 (0.80)
Ti (sec)	1.71 (0.46)	1.53 (0.24)	1.57 (0.20)	1.68 (0.60)

PIF, peak inhalation flow; P, peak turbulent energy; Accel, acceleration rate; IV, inhalation volume; Ti, duration of inhalation.

Inhalation flow should not be considered in isolation. The turbulent energy and acceleration rate of the inhalation were the greatest for the DPI with the highest resistance.

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The effect of airway alkalization by nebulized sodium bicarbonate on airway blood flow

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Background: The airway acidifies in a variety of inflammatory lung diseases as measured by exhaled breath condensate (EBC). We have demonstrated in vitro that alkalization improves absorption of cationic bronchodilators, such as albuterol and tiotropium, both in airway epithelia and smooth muscle cells; however, the rationale of airway alkalization therapy is not fully understood.
Objective: The purpose of the study was to determine the effect of nebulized sodium bicarbonate ($NaHCO_3$) solution on airway vascular smooth muscle function.
Methods: Ten healthy non-smoker volunteers participated in the study. To assay airway pH, EBC was collected pre- and post-administration of 4.2% $NaHCO_3$ (pH=8.4). $NaHCO_3$ induced CO_2 production was evaluated with a real-time mass spectrometer gas analyzer by measuring Phase 1 and end-tidal CO_2 levels during normal breathing, and breath-hold maneuvers for 5 and 15 sec. Airway vascular smooth muscle responses were assessed by measuring airway blood flow (Q_{aw}).
Results: After $NaHCO_3$ administration for 15 min using a heated ultrasonic nebulizer, EBC pH increased from 7.54±0.2 to 8.07±0.09 units ($p<0.05$). Pre- and post-treatment exhaled CO_2 levels during normal breathing, and breath-hold maneuvers for 5 and 15 sec were not significantly different, suggesting no excessive CO_2 generation from the breakdown of inhaled $NaHCO_3$. $NaHCO_3$ nebulization resulted in an increase of mean Q_{aw} from 33.9±3.8 to 48.7±5.5 µl/min/ml ($p<0.05$).
Conclusion: Nebulized $NaHCO_3$ can increase airway pH without significant effects on exhaled CO_2 levels in healthy subjects. $NaHCO_3$ induced increase in Q_{aw}, together with elevated airway pH, could improve absorption of inhaled cationic bronchodilators.

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The investigation of inhalation continuous duration for dry powder inhalers in asthmatic patients

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Background: Dry powder inhalers (DPIs) have been important for management of asthmatic patients. And instruction for use of inhaler devise was effectively for control of asthma. Although inhalation technique of DPIs that inhaling fast with maximum force from start to stopping was reportedly important, effective inhalation continuous duration was unknown. In this study, we evaluate effect of instruction considering inhalation continuous duration in asthmatic patients.
Methods: One hundred and thirty nine asthmatic patients who use fluticasone propionate discus or budesonide turbuhaler were studied. Insufficient peak inspiratory flow rate (PIF) and length of inspire continuous time were evaluated by discus-trainer or turbuhaler-tester or In-Check. Of 139 patients, 22 without sufficient PIF were omitted from the study. Instruction considering inhalation continuous time was done for 117 patients and effects for forced expiratory volume in one second (FEV1.0) and peak expiratory flow rate (PEF) was evaluated.
Results: In all patients groups distinguished by inhalation continuous duration before instruction, significant increase of inhalation continuous duration was found after instruction (p value of all groups were $p<0.01$). And Significant improvement of FEV1.0 and PEF was found after instruction in patients group with inhalation continuous time less than one second (both of FEV 1.0 and PEF, $p<0.01$).
Conclusion: In control of asthmatic patients, instruction considering inhalation continuous duration was useful and instructing not only inhale fast and forcefully, adding "continue inhalation with deeply breath more than one second" is considered to be recommend from our results.

P2145

Pharmacokinetics (PK) of single doses of mometasone furoate (MF) delivered via the Breezhaler® (BH) and Twisthaler® (TH) devices in healthy subjects

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Background: QMF149 is being developed as a fixed dose combination of the long-acting β_2-agonist indacaterol and the inhaled corticosteroid MF for treatment of asthma and COPD. Indacaterol is approved in the single dose dry power inhaler (DPI), BH for treatment of COPD (Onbrez® Breezhaler®). MF is approved in the multiple-dose DPI, TH for treatment of asthma (Asmanex® Twisthaler®). Due to its low oral bioavailability, systemic exposure after inhalation of MF reflects the amount of drug delivered to and absorbed from the lung.
Objective: To evaluate the PK of single doses of MF administered by oral inhalation via BH and to compare the systemic exposure to MF delivered via BH and TH devices.
Methods: This open-label, single-dose, crossover study recruited 24 healthy subjects to sequentially receive MF TH (400µg) and escalating doses of MF BH (50, 100, 200, 400µg). PK data were obtained up to 72h post-dose.
Results: Twenty subjects completed all treatments. Dose-normalized AUC_{last} for MF was 1.8 to 1.9-fold higher when delivered via BH compared to TH. AUC and C_{max} of MF increased in a dose proportional manner over the dose range 50-400µg for MF BH. Median T_{max} was reached earlier for all doses of MF BH (0.375-2 h) compared to MF TH 400µg (3h). The terminal half-life was similar for all treatments (mean $T_{1/2}$:12-13h).
Conclusion: Systemic exposure of MF increased in a dose proportional manner over the dose range 50-400µg for the MF BH. The estimated average dose of MF BH expected to provide systemic exposure comparable to the approved MF TH dose of 400µg was 195µg [(90% CI: (175, 215)].

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An open-label trial to investigate the dose delivery and tolerability of inhaled dry powder mannitol (IDPM) using low output and high output Orbital™ inhalers across defined flow rates in healthy volunteers

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Introduction: Current dry powder inhalers (DPIs) typically deliver up to 30mg as the emitted powder mass. The Orbital™ DPI is a disposable, single-use, pre-filled product being developed to deliver 400mg of mannitol to the lung via a number of inhalations. The assessment of emitted powder mass and tolerability is the focus of this trial.
Methods: Open-label trial in healthy subjects >18 years with baseline FEV_1 >70% of predicted to determine the tolerability and dose delivery of IDPM across two defined flow rates using low and high output Orbital DPIs. Subjects who completed a full inhalation at any flow rate at Visit 1 progressed to Visit 2 at which time up to a maximum dosage of 400mg of IDPM was administered by sequential inhalations.
Results: The single inhalation shot weights from the sequential assessments are shown in Table 1. For the Visit 2 procedure, the mean number of inhalations required to empty the DPI was 7.5 (SD 1.76; Range 5-12). The mean shot weight per inhalation was 43mgs, mean cumulative shot weight after 5 inhalations was 300mgs (SD 36).

Visit 1 shot weights (mgs)

	45 L/min Low Output	45 L/min High Output	60 L/min Low Output	60 L/min High Output
N	21	21	20	21
Mean (SD)	36 (12)	59 (18)	54 (25)	75 (26)
Median	33	53	58	71
Min, Max	18, 68	32, 94	2, 106	38, 118

Conclusion: Compared to convential DPIs, the Orbital DPI is capable of delivering many-fold greater masses of dry powder over repeated inhalations. Further development is warranted to investigate the upper limits of dose delivery and to examine the utility of the device with other engineered particles.

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Lung bioavailability of beclometasone dipropionate and formoterol fumarate fixed dose combination administered using a pMDI or a novel DPI: NEXThaler®

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Introduction: NEXThaler® is a novel, easy to use, dry powder inhaler (DPI) containing the fixed combination of beclometasone dipropionate (BDP) 100 µg and formoterol fumarate (FF) 6 µg, formulated for extrafine delivery. This will provide physicians and patients with an alternative inhaler device for treatment of asthma able to ensure delivery of the drugs to the lungs especially in patients with poor hand-breath coordination.
Objective: To compare the lung bioavailability of beclometasone monopropionate B17MP (active metabolite of BDP) and FF after administration of the fixed combinations using NEXThaler® or the pMDI Foster®.
Methods: An open-label, two-way crossover, single-dose design was used. Activated charcoal was administered to block gastrointestinal absorption and pMDI use was optimized via spacer device. Adult asthmatic patients (n=24) were randomized to undergo two single dose treatment clinic visits, separated by a 7-day wash-out period. At each treatment visit, blood samples were collected over 24h for pharmacokinetic evaluation.
Results: The ratios (and 90% CI) for AUC_{0-t} of B17MP and FF when comparing NEXThaler® to pMDI fell entirely within the bioequivalence region of 80-125%, showing that the lung bioavailability of both components was equivalent. No clinically significant trend to change in blood pressure or heart rate after dosing with either NEXThaler® or pMDI was observed.
Conclusions: BDP and FF lung bioavailability using the fixed dose combination NEXThaler® and pMDI was equivalent in the target population. Furthermore, treatment with NEXThaler® was well tolerated with no safety concerns.

P2148

Comparative *in vitro* performance of a new re-usable breath-actuated nebulizer (BAN) with other high performance systems intended for domiciliary use – 2: Portable battery-compressor

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Rationale: Treatments with home based compressor/nebulizer systems can of-

fer very different delivery characteristics. We evaluated a new, reusable BAN (AeroEclipse-XL®, Trudell Medical International) in breath-actuated mode with its portable (Ombra®) battery-compressor.
Methods: The nebulizer-on-test (n=5/group) was filled with 2.5-mL, 1.0 mg/mL albuterol (Ventolin®, GSK Canada Inc.), and connected to a breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA) mimicking adult tidal breathing (V_t= 600-mL; duty cycle = 33%; rate = 10 cycles/min). Emitted aerosol was captured on a filter at the mouthpiece, replaced at minute intervals until onset of sputtering, defining run time. Recovery/assay of salbutamol was undertaken by HPLC-UV spectrophotometry. Fine droplet fraction (FDF<4.7μm) and mass median droplet diameter (MMD) were determined by laser diffractometry. Total fine droplet mass ($FDM_{<4.7\mu m}$) was the product of total mass and $FDF_{<4.7\mu m}$. Comparative measurements were made with the Sprint® (PARI, Germany) and MicroPlus® (Philips-Respironics, Germany) nebulizers using PARI BOY® Mobile S® and Inspiration Micro Elite® portable compressors respectively.
Results: See Table

Mean ± SD	BAN	Sprint	Sidestream
FDF<4.7μm (%)	68.1±0.9	52.0±0.7	52.8±2.8
MMD (μm)	3.53±0.04	4.55±0.05	4.46±0.23
FDM<4.7μm (μg)	474±32	344±20	297±20
Run time (min)	12	9	11

Conclusions: The BAN/Ombra® system provided highly respirable aerosol with $FDM_{<4.7\mu m}$ substantially greater than the benchmark systems. Its run time reflects the fact that aerosol is only delivered during inhalation and not wasted to the environment.

P2149
The absorption, distribution, metabolism and excretion (ADME) of single oral doses of AZD5069, a novel CXCR2 antagonist, in healthy male volunteers
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Background: AZD5069 is a CXC chemokine receptor-2 (CXCR2) antagonist with potential as a novel COPD treatment. Initial studies have indicated an acceptable safety profile for AZD5069. This study characterised the ADME of a single oral dose of AZD5069.
Methods: In this phase I, open-label, non-comparative, single centre study, healthy male volunteers received a single oral dose of 120 mg [^{14}C]AZD5069. Blood and urine samples (for radioactivity analysis, metabolite profiling, identification and bioanalysis of AZD5069) and faeces samples (for radioactivity analysis and metabolite profiling) were collected. Safety and tolerability were also assessed.
Results: Subjects (n=6) were white males (aged 50–65 years, mean BMI 25.6 kg/m^2). The mean recovery of radioactivity in urine and faeces was 100% (range 98–103% [65% in urine, 35% in faeces]). 6.7% of the AZD5069 dose was recovered unmetabolised in urine. AZD5069 was rapidly absorbed and the apparent terminal elimination half-life was 10 hours. There were no deaths, serious adverse events (AEs) or withdrawals due to AEs. Four subjects reported 6 AEs, with headache the most commonly observed event. There were no clinically significant safety and tolerability findings, other than the expected reversible reduction in circulating neutrophil numbers.
Conclusion: Absorption of AZD5069 was rapid. Complete recovery of radioactivity was attained, with the majority being excreted in the urine. Only a small fraction was renally excreted as parent drug, suggesting that metabolism is the primary route of elimination. No safety concerns were identified.

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P2151
The pharmacokinetics (PK) and pharmacodynamics (PD) of the fluticasone furoate (FF) and vilanterol (VI) combination in subjects with severe renal impairment
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Introduction: A combination of the novel corticosteroid FF and long-acting beta$_2$ agonist VI (FF/VI) is being developed as a once-daily inhaled treatment for asthma and COPD.
Objectives: To investigate the effect of severe renal impairment on FF and VI PK and PD.
Methods: Open-label, parallel group study of repeat dose once-daily FF/VI 200/25mcg (7 days) in 9 subjects with severe renal impairment (CrCl<30mL/min) and 9 matched control healthy subjects (by gender, ethnicity, age (±5 years) and BMI (±15%)). FF and VI PK parameters were assessed on Day 7. PK parameter point estimates (90% confidence interval [CI]) were constructed for the ratio of geometric means (renally impaired:healthy subjects). Non-inferiority was to be concluded if the upper 90% CI for the ratio was <2 for the Day 7 comparison. Systemic PD effects of FF (0–24h serum cortisol) and VI (0–4h heart rate and serum potassium) were assessed on Day 7.
Results: For FF AUC(0–24) and Cmax the geometric mean ratio [90% CI] for renal:healthy was 0.91 [0.60, 1.38] and 0.96 [0.57, 1.61], respectively. For VI AUC(0–24) and Cmax the geometric mean ratio [90% CI] for renal: healthy was 1.56 [1.27, 1.92] and 0.70 [0.49, 1.00], respectively. Administration of FF/VI 200/25mcg to subjects with severe renal impairment did not result in significantly greater effects on serum cortisol, heart rate or serum potassium compared with healthy subjects.
Conclusions: There was no evidence of clinically relevant increases in FF or VI systemic exposure or systemic pharmacodynamic effects in subjects with severe renal impairment compared with healthy subjects.
Funded by GSK (HZA113970; NCT01266980).

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P2153

Absorption, distribution, metabolism, and elimination (ADME) of umeclidinium (UMEC) in healthy adults

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Introduction: Umeclidinium (UMEC; GSK573719) is a new, long-acting muscarinic antagonist in development for treatment of chronic obstructive pulmonary disease (COPD).
Objectives: Evaluate the absorption, distribution, metabolism and elimination (ADME) of UMEC following single IV and oral doses of [^{14}C]-UMEC.
Methods: This was an open-label, non-randomised ADME study of 6 healthy male subjects. There were two dosing periods: (1) a 65mcg IV dose of [^{14}C]-UMEC (7.1mcCi) infused over 30min, and (2) a 1000mcg dose of [^{14}C]-UMEC (50mcCi) administered orally. The dosing periods were separated by a washout of $\geq$28 days. Total radioactivity was measured in plasma, urine and faeces for 7–10 days following each dosing period.
Results: Following IV administration, the derived area-under-the-curve (0–∞) demonstrated that only $\sim$20% of total radioactivity in plasma was parent UMEC, suggesting the predominance of UMEC metabolites. The geometric mean volume of distribution of IV UMEC was 86L, suggestive of tissue compartmentation. By day 8, approximately 58% and 22% of IV UMEC-associated radioactivity was excreted in the faeces and urine, respectively. Oral UMEC is poorly absorbed with $<$1% of administered parent drug detected in plasma (all concentrations non-quantifiable). Following oral administration, total radioactivity in the faeces and urine was 92% and $<$1% of the administered oral UMEC dose respectively, confirming negligible gut absorption.
Conclusions: Oral UMEC bioavailability is negligible. Intravenous UMEC is mainly removed from plasma by metabolism and subsequent biliary secretion, and to a lesser extent by urinary excretion.
Funded by GSK (AC4112014; NCT01362257).

P2154

Not all antistatic valved holding chambers have equivalent performance: An example why each valved holding chamber (VHC)-inhaler combination should be considered unique

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Rationale: Electrostatic charge mitigation by the use of charge dissipative materials with VHCs is common, since initial pre-washing can be avoided. We compared "antistatic" VHCs; Optichamber® Diamond® (OD), Phillips Healthcare with AeroChamber Plus® Flow-Vu® (AC Flow-Vu) Trudell Medical International) (n=4 devices/group), to determine suitability for patients delaying inhalation post-actuation.
Methods: An abbreviated Andersen impactor that determined fine particle mass $<$4.7 µm at 28.3 L/min ($FPM_{<4.7\mu m}$) was used with an apparatus simulating 2, 5 and 10 s delay intervals following pMDI actuation (Flovent®, GSK plc, 125 µg/actuation fluticasone propionate (FP)). This approach conforms to guidance from European authorities that testing of VHCs should simulate delayed inhalation. Assay for FP was undertaken by HPLC-UV spectrophotometry. Measurements without delay were undertaken to assess mass recovery for FP, validating the procedure. All values are mean±SD.
Results: Mass recoveries (131.5±2.9 and 130.7±3.8 µg/actuation for the OD and ACPlus VHCs respectively) were close to label claim, validating system suitability. The variation of $FPM_{<4.7\mu m}$ with delay interval is shown in the Table.

Relative depletion of FPM$<$4.7µm

VHC	Delay (s)		
	2	5	10
AC Flo-Vu	42.2±3.1	39.7±1.3	35.7±2.0
OD	35.0±3.2	29.2±1.7	23.0±2.8

The ratio $FPM_{<4.7\mu m\text{-}ACPlus}/FPM_{<4.7\mu m\text{-}OD}$) increased from 1.2 (2-s) to 1.4 (5-s) and to 1.6 (10-s), demonstrating faster depletion of the therapeutically beneficial medication from the OD.
Conclusion: Not all VHCs manufactured from anti-static materials provide optimum performance for patients who have poor coordination.

P2155

Design and implementation of a multi-part, flexible protocol to assess the tolerability and pharmacodynamic effects of PUR118 in healthy subjects and COPD patients

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Background: PUR118, an inhaled cationic airway lining modulator (iCALM), is a simple host-targeted therapy to prevent and control respiratory exacerbations. An innovative protocol was developed to establish single and multi-dose tolerability and early pharmacodynamic/efficacy data for this therapy.
Objective: To develop and conduct a flexible clinical protocol to obtain maximum data to support the further investigation of PUR118.
Methods: Data required to progress PUR118 development were identified and structured into a 4 part dose-ranging protocol in healthy subjects (HS) and COPD patients (COPD):
1. Crossover safety and tolerability of 3 single dose levels vs. placebo (12 HS)
2. 3 ascending dose 14-day safety and tolerability vs placebo (24 HS)
3. Parallel 3 dose level multi-dose safety and tolerability plus exploratory assessment of inflammatory biomarkers (sputum, serum, exhalation) in COPD
4. Impact of ascending of single dose vs. no treatment on mucociliary clearance velocity by gamma scintigraphy

The design was flexible to allow dose escalation or de-escalation. Selection of exploratory biomarkers was adaptive and not pre-determined in the protocol.
Results: A highly-flexible 4 part protocol was designed, submitted to and approved by the MHRA and EC in 27 days. Parts 1 and 2 in HS are complete, Parts 3 and 4 are ongoing. Preliminary results show PUR118 is well tolerated in HS and subjects with COPD.
Conclusions: This multi-part dose- ranging protocol, developed and implemented in the UK, demonstrates its regulatory framework embraces innovative, highly flexible, multi-part trials in early clinical development strategies.

P2156

Drug product stability of aclidinium bromide in Genuair®

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Introduction: Aclidinium bromide is a novel, long-acting inhaled anticholinergic bronchodilator developed for the treatment of COPD. It is administered using a novel multidose dry powder inhaler called Genuair®, designed with an intuitive feedback system. The following studies were performed to evaluate the stability of the drug product (DP: Aclidinium bromide 400µg formulation & inhaler).
Methods: The stability of commercial scale batches were tested (Appearance, identity, purity, content of active, delivered dose (DD), fine particle dose (FPD) and microbial purity) as follows:
1) Packed DP: $\leq$24 months storage in 2 orientations at different climatic conditions.
2) Opened DP:
– *In use:* 12 months packed storage at different climatic conditions, then open storage, without the protective cap during the in use period.
– *Effect of moisture:* 4 weeks open storage at 20°C/34%R.H. versus 25°C/75% R.H.
3) Stability under extreme stress conditions was tested:
– *Temperature cycling study:* 2 weeks storage at -10°C to 40°C (alternating every 24 h).
– *Vibrational stability:* stressed at 50 Hz, amp. 1 mm using 3 durations.
4) Photostability evaluated according to ICH conditions.
Results: All tested samples and parameters confirmed the excellent stability of the packed and unpacked DP. Especially, the data for the pharmaceutical parameters DD (mean values: 362.4µg - 385.7µg) and FPD (mean values: 138.7µg - 164.3µg) were consistent and remained unchanged independent of storage time and conditions.
Conclusion: The advanced design and technological features of the Genuair® combined with the Aclidinium bromide inhalation powder guarantee a stable and robust product under various climatic, mechanical, and light radiation stress conditions.

P2157

The pharmacokinetics (PK) and pharmacodynamics (PD) of the fluticasone furoate (FF) and vilanterol (VI) combination in subjects with hepatic impairment

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Introduction: A combination of the novel corticosteroid FF and long-acting beta$_2$ agonist VI (FF/VI) is being developed as a once-daily inhaled treatment for asthma and COPD.
Objectives: To investigate the effect of hepatic impairment (HI) on FF and VI PK and PD.

Methods: Open-label, repeat dose (7 day) study in subjects with mild, moderate or severe HI (Child-Pugh classification) and healthy subjects (HS) (matched with moderate HI). Subjects received FF/VI 200/25mcg or 100/12.5mcg (severe HI) once daily. FF and VI PK (Day 7) parameter point estimates and 90% confidence intervals (CIs) were constructed for the ratio of geometric means (HI:HS). Systemic PD effects of FF (0–24h weighted mean serum cortisol) and VI (0–4h heart rate and serum potassium) were assessed on Day 7.
Results: There was no effect of HI on dose-normalised VI Cmax or AUC(0–24) and no clinically relevant effects of FF/VI on heart rate or serum potassium compared with HS. Dose-normalised FF systemic exposure (AUC(0–24); Day 7) was higher in subjects with mild, moderate and severe HI (ratio vs. HS [90% CI]: 1.34 [0.82, 2.20], 1.83 [1.11, 2.99] and 1.75 [1.05, 2.91], respectively. Serum cortisol was only reduced in subjects with moderate HI (average 34% reduction (90% CI: 11%, 51%) compared with HS. A similar effect would be predicted in severe HI with FF/VI 200/25mcg.
Conclusions: In subjects with HI there was no increase in VI systemic exposure or systemic effects. FF exposure was increased by ≤3-fold in subjects with HI and was associated with a reduction in serum cortisol of approximately 30%.
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P2158
No relevant drug-drug interaction between inhaled NVA237 and oral cimetidine
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Introduction: NVA237 (glycopyrronium bromide) is a once-daily long-acting muscarinic antagonist for the treatment of COPD. Renal clearance is a major elimination pathway of NVA237 and active tubular secretion in the kidneys contributes to this process. This study investigated the effect of inhibition of the organic cation transport in the kidneys on NVA237 disposition. Cimetidine was used as a probe inhibitor.
Methods: 20 healthy volunteers participated in this two-sequence crossover study. They inhaled a single 100 µg dose of NVA237 via the Breezhaler® device on two occasions, i.e. alone (Treatment A) and on the 4th day of a 6-day treatment regimen with cimetidine 800 mg twice-daily (Treatment B). Treatments were separated by a washout period of 7 to 10 days. Plasma concentrations and urinary excretion of NVA237 were determined after each NVA237 dose. The primary PK parameters were plasma peak concentration (Cmax), AUC up to the last measured concentration (AUClast) and renal clearance (CLr) of NVA237. Trough plasma concentrations of cimetidine were determined throughout cimetidine dosing.
Results: Cimetidine trough concentrations indicated that the inhibitor drug had reached PK steady state prior to NVA237 inhalation in Treatment B. The concomitant administration of cimetidine resulted in an increase of total systemic exposure (AUClast) of NVA237 by 22%. This exposure increase correlated with a slight decrease of 23% in CLr. Cmax was not affected. Both treatments were safe and well tolerated.
Conclusion: Based on the magnitude of the PK changes, no relevant drug interaction is expected when NVA237 is co-administered with cimetidine or other inhibitors of the organic cation transport in the kidneys.

P2159
Drug-drug interactions in hospitalized patients with chronic obstructive pulmonary disease
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Aim: Chronic obstructive pulmonary disease (COPD) patients are treated with several drugs for their primary disease and comorbidity, which carries the risk of clinically relevant drug-drug interactions (DDIs). We aimed to evaluate DDI in hospitalized COPD patients.
Methods: This retrospective study included COPD patients hospitalized from January 2011 to July 2011 in a tertiary care clinic. Pharmacological therapy at admission and discharge was evaluated for DDI with electronic Lexi-Comp database: C- monitor therapy; D- consider therapy modification; X- avoid combination.
Results: We included 196 patients (68% male, age 71*m*9 years). The average number of prescribed drugs was significantly lower at hospital admission than at discharge (6±3 vs. 7±2, p<0.01). Overall, more than 90% of patients had at least one interaction and Table 1 summarizes type C, D, and X interactions at hospital admission and discharge. The most prevalent type C interaction was between two β_2-agonists (10% of cases) and the most prevalent type D interaction between β-blocker and α-blocker (9%). There were 15 type X interactions recorded at discharge, among which the most common was between non selective β-blocker and β2-adrenoreceptor agonist (8 cases)
Conclusion: DDI are common in hospitalized patients with COPD but few carry clinically relevant risk. Most type X interactions were between non-selective β-blocker and β2-adrenoreceptor agonist which likely was indicated and should be safe in COPD patients.

Table 1. Number of patients with at least one interaction (percentage)

Type of interaction	Hospital admission	Hospital discharge	p-value (McNemar test)
C	177 (90)	180 (92)	0.648
D	39 (20)	47 (24)	0.243
X	4 (2)	12 (6)	p<0.05

P2160
Aerosol deposition in asthmatic subjects breathing helium-oxygen vs. air
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Introduction: Helium-oxygen (He/O_2) mixtures are known to facilitate breathing due to their low density compared to air, and therefore, may be valuable to treat obstructive lung diseases such as asthma.
Objectives: The objective is to study the effect of air vs. He/O_2 on the aerosol deposition of a nebulized radiolabel in stable, moderate asthmatic subjects.
Methods: 16 evaluable male subjects (6 asthmatics, 10 healthy volunteers) were studied. Each subject performed two inhalations which differed by a single controlled parameter (particle size, ventilation, or carrier gas). 2 of the asthmatics inhaled aerosols with either air or He/O_2 (78%He/22%O_2), and aerosol deposition was imaged with 3D-SPECT.
To characterize the sites of aerosol deposition, the 3D Central to Peripheral ratios, C/P, were calculated for right and left lungs.
Results: The effect of He/O_2 on aerosol deposition was very visible for one of the asthmatic subjects (A06) with a large decrease in central deposition (Right C/P=4.91 and Left C/P=5.58 for air, vs. 1.32 and 1.37 for He/O_2) when He/O_2 was used to drive the nebuliser, but the other asthmatic did not respond to the change in carrier gas (Right C/P=3.87 and Left C/P=6.66 for air, vs. 3.87 and 7.53 for He/O_2).

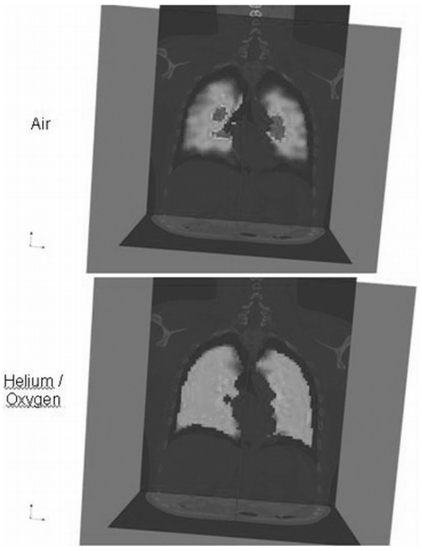

Figure 1. 3D-SPECT images of aerosol deposition superimposed with HRCT for subject A06 inhaling either air (top) or helium/oxygen mixture (bottom).

Conclusion: These results suggest that He/O_2 can reduce aerosol deposition in central airways and increase deposition in peripheral airways in some asthmatic patients, but this response is not consistent among all patients.