414. Drug delivery and pharmacokinetics II

P3971

Safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) of GSK573719 inhalation powder in healthy subjects

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Introduction: GSK573719 is a new long-acting muscarinic antagonist offering sustained 24-hour bronchodilation in development for the treatment of chronic obstructive pulmonary disease (COPD).
Objectives: To investigate the safety, tolerability, PD and PK of single inhaled doses of GSK573719.
Methods: This double-blind, placebo-controlled, crossover, dose-escalation study randomised 20 ipratropium-responsive healthy male subjects to GSK573719 (10–350μg), tiotropium bromide (TB; 18μg) and placebo.
Results: Eighteen subjects completed all 5 treatment periods. Adverse events (AEs) were mainly mild-to-moderate; no serious AEs were reported. One severe non-drug related AE was reported (increased creatine phosphokinase). 95% confidence intervals were assessed for statistical significance of PD data. Significantly higher specific airways conductance (sG_{aw}) was observed, versus placebo, for GSK573719 100 and 250μg at 12h, and for GSK573719 350μg and TB at 12h and 24h. FEV_1 values were also significantly greater than placebo for GSK573719 100 and 350μg at 12h and 24h and for TB at 24h. GSK573719 plasma C_{max} (maximum plasma concentration) occurred at a median t_{max} of 5min, followed by a rapid decline to below the lower limit of quantification by 6h. Between subjects C_{max} variability was moderate-to-high (38–57%).
Conclusion: In this first-in-human study, GSK573719 demonstrated adequate safety, tolerability and prolonged bronchodilation, suggesting the potential for once-daily administration in COPD.
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P3972

Safety, tolerability and pharmacokinetics (PK) of repeated doses of GSK573719 inhalation powder, a new long-acting muscarinic antagonist, in healthy adults

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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 PK of repeated once-daily doses (14 days) of GSK573719 dry powder inhalation (DPI).
Methods: In this single-centre, double-blind, parallel-group study, 36 healthy adults were randomised 3:1 to GSK573719 (250μg, Cohort 1; 750μg, Cohort 2; 1000μg, Cohort 3) or placebo as DPI once daily for 14 days.
Results: Most adverse events (AEs) were mild and all resolved during the study; the most frequent drug-related AEs were headache and pharyngolaryngeal pain (0–2 subjects per group). No clinically relevant abnormalities or changes were seen in laboratory results or vital signs. There were no clinically significant ECG abnormalities or heart rate changes. Although 41–67% of plasma PK samples were non-quantifiable, available data showed a median t_{max} of 5–15min, mean $t_{\frac{1}{2}}$ (Day 14) of 26–28h (25–35h from urine PK). Although visual assessment of Ctau data suggested that steady state was achieved following 6 to 8 days of dosing, there was large data variability. Urinary excretion of unchanged GSK573719 was 1–1.5% of the total dose on Day 1 and 3.9–4.5% at steady state. Accumulation (Day 14:Day 1) was 1.5–3x based on plasma PK (3–4.5x on urine PK). There was no correlation between GSK573719 systemic exposure and pharmacodynamic variables.
Conclusion: GSK573719 was well tolerated by all subjects and no safety concerns were identified even at the highest dose, supporting the continued development for COPD.
Funded by GSK (AC4106889; NCT00475436)

P3973

The pharmacokinetics (PK) and pharmacodynamics (PD) of repeat inhaled administration of fluticasone furoate (FF) in healthy Caucasian, Chinese, Japanese and Korean subjects

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Introduction: FF is an ICS still active at 24h, being developed as once daily (OD) inhaled treatment in combination with vilanterol (VI) a long-acting $beta_2$-agonist, for asthma and COPD. Early data suggested that FF systemic exposure might be higher in Japanese subjects than in Caucasians.
Objective: To evaluate and compare the PK and systemic PD effects of FF in Caucasian (Ca), Chinese (Ch) Japanese (J) and Korean (K) subjects when delivered via a novel dry powder inhaler.
Methods: Open-label, randomised, two-way crossover study. Healthy male and female Ca, Ch, J and K subjects [20/group] received OD inhaled FF (200mcg (7 days) then 800mcg (7 days)) and single i.v. 250mcg FF. PK was obtained on Day (D) 1 and/or D7 and PD (cortisol) data on D7 at 200mcg only.
Results: FF Cmax and AUC values were consistently higher in Ch, J and K subjects compared with Ca subjects (Mean ratio: Cmax; 1.35-1.78 and AUC; 1.27-1.75). Repeat inhaled FF 200mcg showed no difference in serum cortisol 0-24h weighted mean between Ca and Ch or K subjects but this was 22% (90% CI:12-30) lower in J subjects compared to Ca subjects. All treatments were safe and well tolerated with no quantitative or qualitative differences in safety endpoints between ethnic groups.
Conclusion: FF systemic exposure was higher (< 2-fold) in Chinese, Japanese and Korean subjects compared to Caucasians. Lowered serum cortisol was only seen in Japanese subjects and was without any clinical consequence. Further clinical

studies in Japanese subjects to evaluate the safety and efficacy of FF 100 and 200mcg are underway.
Funded by GSK (HZA113477; NCT01000597)

P3974

The pharmacokinetics (PK) of fluticasone furoate (FF) in healthy Caucasian, Chinese, Japanese and Korean subjects

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Introduction: FF is an ICS still active at 24h, being developed as once daily (OD) treatment in combination with vilanterol (VI) a long-acting beta$_2$-agonist, for asthma and COPD. Early data suggested that FF systemic exposure might be higher in Japanese subjects than in Caucasians.
Objective: To evaluate and compare FF PK in Caucasian (Ca), Chinese (Ch) Japanese (J) and Korean (K) subjects following FF administration via a novel dry powder inhaler and i.v. infusion.
Methods: Open-label, randomised, two-way crossover study. Healthy male and female Ca, Ch, J and K subjects [N=20/group], randomised to receive OD inhaled FF (200mcg (7 days) then 800mcg (7 days)) and single i.v. 250mcg FF dose. PK data were obtained on D1 and/or D7.
Results: The inherent PK characteristics of i.v. FF were similar in Ca, Ch, J and K subjects, consistent with similar CYP3A4 activity in each population. Inhaled FF systemic exposure was higher at both doses (AUC ratio: 1.27 to 1.75) in Ch, J and K subjects, compared with Ca subjects, reflecting higher bioavailability (800mcg D7: 14.3% to 16.3% v 10.4%, respectively). Deconvolution analysis suggested that inhaled FF resided in the lungs of Ch, J and K subjects for longer than in Ca subjects, a likely reason for seeing greater bioavailability. All treatments were safe and well tolerated with no marked quantitative or qualitative differences in safety endpoints between the ethnic groups.
Conclusion: Following inhaled FF there was higher (< 2-fold) systemic exposure in Chinese, Japanese and Korean subjects compared with Caucasian subjects, although there were no safety or tolerability consequences.
Funded by GSK (HZA113477; NCT01000597)

P3975

Glycopyrrolate MDI demonstrates comparable efficacy and safety to tiotropium DPI in a randomized, double-blind, placebo-controlled phase 2b study in patients with COPD

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Rationale: Anticholinergics (LAMAs) are central to the management of patients with COPD. Tio (Spiriva® Handihaler® 18 μg), is a LAMA approved as a dry powder inhaler (DPI) for the treatment of COPD. The availability of a LAMA in an MDI formulation could provide a needed alternative method of administration. Pearl Therapeutics' proprietary porous particle technology allows the formulation of glycopyrrolate in an MDI format (GP-MDI). In a previous single-dose, Phase 2a study, GP-MDI showed comparable efficacy and safety to Tio. Based on these findings, Pearl evaluated GP-MDI compared to Tio in a chronic dosing study.
Methods: In a randomized, double-blind, customized, unbalanced, incomplete block, crossover study conducted in patients with moderate to very severe COPD, GP-MDI 36 μg was compared to placebo (PL) and Tio (open-label). GP-MDI and PL were administered BID for 1 week; Tio was administered QD for 1 week. The primary efficacy endpoint was FEV_1 $AUC_{0\text{-}12}$ on Day 7 relative to pre-dose baseline at the start of treatment. Secondary endpoints included peak FEV_1, morning trough FEV_1, and safety assessments.
Results: GP-MDI 36 μg and Tio were superior to PL for the primary endpoint (189 and 195 mL respectively, P<0.0001 all comparisons). GP-MDI 36 μg was non-inferior to Tio for this endpoint (mean difference = -6 mL, 95% CI: -49, +38 mL). Secondary endpoints confirmed the overall efficacy of GP-MDI and Tio. GP-MDI 36 μg was safe and well tolerated with a similar safety profile to Tio.
Conclusion: Pearl's GP-MDI 36 μg demonstrated comparable efficacy and safety to Tio, supporting further development in patients with COPD.

P3976

The absolute bioavailability of fluticasone furoate (FF) and vilanterol (VI) trifenatate following inhaled administration in combination in healthy subjects

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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.
Objective: To determine the absolute bioavailability of FF and VI when administered in combination as FF/VI from a novel dry powder inhaler in healthy subjects.
Methods: In this open-label, non-randomised, three-way crossover, single-dose study, male and female subjects [N=16] received (in order) a single inhaled dose of FF/VI 800/100mcg (4 inhalations of 200/25mcg), a single 250mcg intravenous (i.v.) dose of FF and a single 55mcg i.v. dose of VI. FF and VI pharmacokinetic data were obtained up to 48h post-dose.
Results: The average absolute bioavailability of FF when inhaled as FF/VI relative to i.v. FF was 15% (90% CI: 13, 18). The average absolute bioavailability of VI when inhaled as FF/VI relative to i.v. VI was 27% (90% CI: 22, 35). Both FF and VI were rapidly cleared and widely distributed following i.v. dosing. FF showed longer retention in the lung than VI following inhaled administration with the time for 90% of the total to be absorbed from the lung on average, 35.2h and 3.8h, respectively. All treatments were safe and well tolerated even though this study evaluated multiples of the likely inhaled therapeutic dose (200/25mcg).
Conclusion: In healthy adult subjects the absolute bioavailability of FF was 15% and for VI was 27% following a single inhaled dose of FF/VI delivered via a novel dry powder inhaler.
Funded by GSK (HZA102934, NCT01299558)

P3977

No pharmacodynamic (PD) and pharmacokinetic (PK) interaction of riociguat (BAY 63-2521) and aspirin

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Objectives: Riociguat, an oral soluble guanylate cyclase (sGC) stimulator, is a new candidate for treatment of pulmonary hypertension (PH). Riociguat increases cGMP production through a novel dual mode of action: direct NO-independent stimulation of sGC; and increasing sensitivity of sGC to low levels of NO. Riociguat and aspirin are likely to be used together in PH. This randomized, open-label, crossover study investigated potential PD and PK interactions between the 2 drugs.
Methods: Participants took 2.5 mg/day riociguat, two morning doses of 500 mg aspirin, or both treatments concomitantly.
Results: Eighteen healthy men (mean age 34.8 years) were enrolled. Six of 17 participants in the safety evaluation reported ≥1 treatment-emergent adverse event (AE). All AEs were mild except 1 case of moderate headache following riociguat administration. Fifteen participants were valid for PD/PK analysis. Riociguat PK were independent of aspirin coadministration. One hour after coadministration of riociguat and aspirin, the mean increase in fraction unbound was 19% for riociguat and 24% for its metabolite M-1 (BAY 60-4552) indicating mild displacement by salicylic acid, the main aspirin metabolite. Effects of aspirin on bleeding time, platelet aggregation and plasma thromboxane B_2 were not affected by concomitant riociguat. Riociguat alone had no effect on PD variables.
Conclusion: Riociguat demonstrated no clinically relevant PD or PK interaction with aspirin. Coadministration of riociguat and aspirin does not require dose adjustment. Phase 3 randomized controlled trials are investigating riociguat in chronic thromboembolic pulmonary hypertension or pulmonary arterial hypertension.

P3978

How can we improve patient use of inhaler devices in COPD?

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Introduction: "Ease of use" is traditionally seen as a key factor in COPD inhaler choice. Our aim was to assess patient and healthcare professional (HCP) needs and problems with inhalers and to assess options to satisfy these needs, enabling better patient adherence with maintenance inhalers.
Methods: 1008 HCPs and 490 patients (≥18 yrs) participated in an online survey. Sawtooth Software's ACA and CBC products were used to collect, randomize and measure relative impact of features in utility values (positive vs. negative choice impacts).
Results: Overall, with current devices, patients indicate a lack of full certainty that they have taken the full dose correctly (rating of only 4.3 for Asthma, 5.3 for COPD; 1–7 scale). HCPs place far more importance on increasing patient satisfaction and demand than other attributes, reasoning this aids adherence. Similarly, patients want ease of use and features to aid adherence (a dose reminder and improvements over dose counters) to address their primary unmet need of uncertainty in inhaling

all doses fully. Device type (MDI, DPI, multidose, singledose) has little impact in HCP choice (COPD HCP utilities: patient satisfaction and demand +92, multidose DPI –6, dose counter –3).
Conclusion: Issues such as dose counters and multidose vs. singledose have little impact on physician demand. Satisfying patient need for true dose confirmation can drive patient satisfaction and adherence. Patients need devices that assure them that they have taken the full dose to be more adherent, and HCPs need devices that drive patient demand and adherence.

P3979
Patient assessments of ease of use of Genuair® versus Aerolizer® and HandiHaler®
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Introduction: The Genuair®* inhaler, a multidose, dry powder inhaler, has been developed to provide reliable and effective delivery of inhaled medications including aclidinium bromide, which is in clinical development for the treatment of chronic obstructive pulmonary disease (COPD).
Aim: To report data from two Phase II studies that included patient assessments of the convenience of Genuair® versus Aerolizer® and HandiHaler®, respectively.
Methods: Both studies were randomised, double-blind, double-dummy, cross-over trials in patients with moderate to severe COPD. In the first study, 79 patients received treatment over seven-day periods via Genuair® and Aerolizer®. In the second study, 30 patients received treatment over 15-day periods via Genuair® and HandiHaler®. At the end of the studies, patients were asked to evaluate their impressions of inhaler conveniences.
Results: Patient assessments of the different inhalers are presented in Table 1.

	Patients (%)		
	Inhaler 'very easy' to use	Dose 'very easy' to prepare	'Definitively preferred' inhaler
Study 1			
Genuair®	65	73	63
Aerolizer®	24	19	6
Study 2			
Genuair®	80	83	30
HandiHaler®	53	47	7

Conclusions: Patient assessments of convenience were higher for the Genuair® inhaler versus the Aerolizer® or HandiHaler®.
These studies were supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc, New York, USA.
*Genuair® is a registered trademark of Almirall S.A.

P3980
Comparison of the bronchoprotective effects of two salbutamol suplphate HFA pMDI using methacholine challenge testing
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Background: Clinically, methacholine challenge has been widely used for the detection and quantitation of bronchial responsiveness. This study assessed the bronchoprotective effects of two salbutamol HFA pMDI formulations using methacholine challenge.
Aim: The aim of this study was to evaluate equivalence between Salbutamol sulphate HFA pMDI (Cipla Ltd, India: test product) and Ventolin Evohaler HFA pMDI (Allen & Hanburys, UK: reference product) in terms of bronchoprotective effect against the methacholine challenge.
Methods: This was a randomised, double blind, double dummy, four period, crossover study. At each treatment visit patients administered either one puff (100 μg) or two puffs (200 μg) of either the test or the reference product. On each of the treatment days, two methacholine challenge tests were performed, one before dosing & one 10 minutes after dosing.
Other safety parameters (serum potassium, blood glucose, tremor and ECG) were also assessed at each treatment visit.
Results: Out of 57 randomised patients 52 were included in the ITT & 46 in the PP population. The estimated mean difference in the PP population between the high dose (200 μg) of the two formulations was 0.2081 (95% CI -0.2400,0.6561) and between the low dose (100 μg) of the two formulations was -0.2362 (95% CI -0.6809, 0.2085). For both doses, the 95% CI was within clinically relevant equivalence limits of ± 1 DD.
Conclusion: The bronchoprotective effect of salbutamol sulphate HFA pMDI (Cipla Ltd, India) against methacholine induced bronchoconstriction was equivalent to salbutamol sulphate HFA pMDI (Ventolin Evohaler, Allen & Hanburys, UK). Both the products were safe and well tolerated.

P3981
Preference of the inhaler device and assessment of the technique among the asthmatic and COPD patients
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Different inhaler devices (IDs) are available for delivering treatments to patients with asthma & COPD. They have different technique which can easily confuse patients, resulting in incorrect use. The aim of this study was to evaluate the preference of the IDs and assessment of inhaler technique among the asthmatic and COPD Patients. 300 patients (117 male&183 female) included in this study. Their mean (SD) age was 44.6 (16.9) years. Manly three different inhaler devices; Metered dose inhaler (MDI), Accuhaler (ACH) and Turbuhaler (TUR) were used. 205 patient preferred the ACH while 82 & 13 preferred the TUR & MDI respectively. The assessment of inhaler technique according to the manufacturer instruction shows that 156 patients were having a good technique when using MDI, while 278 and 210 patients were having a good technique when using TUR & ACH respectively. Table 1 highlights that some patients were inhaling with either very low or very high rates.

Table 1. The range of patients inhalation flow rates through the MDI, ACH and the TUR using the In-Check Dial

ID/Flow rate	<30 L/min	30–60 L/min	60–90 L/min	>90 L/min
MDI	0	4	13	283
ACH	1	26	127	146
TUR	2	77	190	31

Thus they need to be trained but this may not be successful, because studies have shown that patient soon revert back to the pre counselling technique. Even after counselling some patients may not have sufficient inspiratory effort to achieve the most desirable inhalation rate for the DPI they have been prescribed. From the results obtained we can conclude that the ACH is the most desirable ID by the patients followed by the TUR & MDI. All patients were using MDI, where nearly all of them having a high flow rate through it.

P3982
Pharmacokinetic evaluation of two HFA pMDI formulations of salmeterol xinafoate administered through a spacer in healthy subjects
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Background: No pharmacokinetic studies of salmeterol HFA pMDI with a spacer device have been published. In this study comparative bioavailability of two salmeterol HFA pMDI formulations administered through a spacer device was evaluated using pharmacokinetic endpoints.
Aim: To compare the rate and extent of absorption of the test product Salmeterol xinafoate HFA pMDI (Cipla Ltd.) with that of the reference product Serevent Evohaler (supplied by Allen & Hanburys, UK), both administered using a spacer.
Methods: This was a balanced, open label, randomised, two-period, single dose, crossover comparative bioavailability study in 24 healthy subjects. Eligible subjects were randomly assigned to receive a single dose of 100μg of both test and reference product administered with a spacer in a crossover manner on two treatment days. The two treatment days were separated with a washout period of 1 week. The blood samples were collected upto 24 hrs. Safety assessments including ECG, tremor assessment, serum potassium and blood glucose were also done at predefined time points. The primary endpoints were C_{max} and AUC_{0-t}.
Results: The plasma concentration–time profile of the test product (T) was similar in shape to that of the reference product (R). The T/R ratio of the geometric mean for C_{max} and AUC_{0-t} was 94.54 (90% CI 87.11-102.61) and 90.68 (90% CI 83.87–98.03) respectively. The CI limits for C_{max} and AUC_{0-t} was well within the bioequivalence range of 80 – 125%.
Conclusion: The bioavailability of the two HFA formulations of salmeterol when administered with a spacer was comparable and both the treatments were safe and well tolerated.

P3983
The aerodynamic particle size of mometasone furoate 100 μg and 200 μg dry powder formulations
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Background: Regional lung deposition of inhaled particles depends on aerody-

namic particle size, as well as inspiratory flow rate and other factors. Inhaled particles of aerodynamic sizes of approximately 2 μm have been found to deposit most efficiently in the alveolar region across a broad range of inspiratory flow rates. In vivo studies of mometasone furoate (MF) delivered by the Twisthaler® showed mean peak inspiratory flow rates at satisfactory levels in adult/adolescent patients aged ≥12 years (69 L/min), children aged 9–12 years (>60 L/min), and children aged 5–8 years (>50 L/min).
Objective: We report aerodynamic particle size findings from an in vitro study analyzing the mass median aerodynamic diameter (MMAD) of MF.
Methods: Twelve inhalers each of the 100 and 200 μg strengths were tested in vitro at the beginning and end of unit lives at a 60 L/min flow rate. Aerosolized MF was collected by cascade impaction for 2 inhalations from the 100 μg strength and 1 inhalation from the 200 μg strength, thereby providing similar particle masses.
Results: The average MMAD of the 100 μg strength for beginning and ending inhalations (n=24) was 2.0 μm (range, 1.9–2.1 μm), while the 200 μg strength for beginning and ending inhalations (n=24) was 2.2 μm (range, 2.0–2.4 μm).
Conclusion: Average MMAD values of MF for both strengths measured in vitro at a clinically relevant flow rate, together with in vivo particle-size efficiency deposition models, suggest that the aerodynamic particle size of MF is optimal (~2 μm) for efficient alveolar deposition when administered via the Twisthaler®.

P3984
Safety and tolerability of single doses of AZD5069 in healthy volunteers
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Background: AZD5069 is a small molecule CXC chemokine receptor 2 (CXCR2) antagonist in development as a novel oral treatment for chronic obstructive pulmonary disease. The safety and tolerability of single ascending doses (SAD) of AZD5069 have been investigated in a first time in human Phase I, randomised, double-blind, parallel group, placebo-controlled study in healthy male and female adult volunteers (NCT00953888).
Methods: 69 volunteers were randomised in cohorts of up to 9 to receive either a single dose of AZD5069 (n=45) or placebo (n=24) after an overnight fast. Doses of AZD5069 were 0.1 mg, 0.5, 1.65, 5.45, 17.99, 60, 120 or 200 mg. Each volunteer was dosed only once.
Results: Reversible dose-related reductions in circulating neutrophil counts were observed by 8 hours post-dose, consistent with reported literature on CXCR2 inhibition. The reduction reached a plateau, beyond which increasing exposure had no further effect, but recovering by 96 hours post-dose, at all doses. The reductions were approximately dose related, but a direct relationship with drug concentration could not be confirmed from these data. The pharmacokinetics of AZD5069 were linear, approximately dose proportional and predictable up to 200 mg. Biomarker assay responses were +ve at 4 hrs post dose at > 5.45 mg, maximal at 120 mg.
AZD5069 was well tolerated. A total of 33 adverse events (AEs) was reported [23 AZD5069, 10 placebo], all of which were of mild-to-moderate intensity, except for one severe AE in the placebo group. Four AEs were considered drug-related: dry mouth (AZD5069 0.5 mg), nausea (AZD5069 120 mg), dysuria and headache (placebo).
Conclusion: AZD5069 was generally well tolerated in SAD in healthy volunteers.

P3985
No significant clinical drug-drug interaction potential with indacaterol
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Background and aim: Indacaterol is an inhaled, long acting beta2 agonist, that is metabolized by UGT1A1 and cytochrome P450 enzymes, mainly CYP3A4. In vitro studies showed indacaterol to be a low affinity substrate for the efflux transporter Pgp. Four studies evaluated whether co-administration of drugs that inhibit CYP3A4 and/or Pgp may result in elevated systemic concentrations of indacaterol.
Method: All studies had open-label, two period, crossover designs in which a single inhaled 300μg dose of indacaterol was first given alone and then in the presence of steady-state concentrations of the orally administered inhibitor. Serum indacaterol was quantified using a sensitive LC/MS/MS method. The key PK parameters were Cmax, AUC0-24h and AUClast.
Results: Verapamil was used as the prototype inhibitor of Pgp and resulted in 1.5- to 2-fold increase in AUC and 1.5-fold increase in Cmax. Erythromycin (CYP3A4 inhibitor) resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2-fold for Cmax. Combined inhibition of Pgp and CYP3A4 by the strong dual inhibitor ketoconazole caused 1.9 to 2-fold and 1.3-fold increases in AUC and Cmax, respectively. Concomitant treatment with another dual inhibitor of CYP3A4 and Pgp, ritonavir, resulted in a 1.7- to 1.8-fold increase in AUC, whereas Cmax was unaffected.
Conclusion: Systemic clearance of indacaterol is influenced by modulation of both Pgp and CYP3A4. The 2-fold AUC increase caused by ketoconazole reflects the impact of maximal combined inhibition. As indacaterol has demonstrated good overall safety at daily doses of up to 600μg over a year, the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses up to 300μg.

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Fluticasone propionate/formoterol fumarate combination therapy is equally effective and well-tolerated when administered with or without a spacer device to patients with asthma
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Background: Phase 3 studies involving a new asthma therapy combining fluticasone (FLUT) and formoterol (FORM) in a single aerosol inhaler (FLUT/FORM; *flutiform*®) either used a spacer or did not. This is the first comparison of the efficacy and tolerability of treatment with or without the use of a spacer device.
Methods: Adults and adolescents with mild, moderate or moderate-severe asthma were treated with FLUT/FORM 100/10μg or 250/10μg b.i.d. delivered either with (N=195) or without (N=532) a spacer in 6 randomised, double-blind and open-label, parallel group studies. The endpoint was non-inferiority between spacer and non-spacer groups (concluded if the lower bound of the 95% CI was ≥-0.2L) in terms of changes in morning pre-dose FEV_1 and morning pre-dose to 2h post-dose FEV_1 over 12 weeks. The incidence of adverse events (AEs) was analysed over 8 weeks.
Results: FLUT/FORM was consistently as effective when delivered with or without a spacer at all dose strengths and asthma severities. From baseline to end of study, the LS mean treatment difference in morning pre-dose FEV_1 was 0.067L greater without spacer (95% CI: -0.149, 0.015) and in morning pre-dose to 2h post-dose FEV_1 was 0.015L greater with spacer (95% CI: -0.051, 0.081). AEs were reported with similar frequency both with and without a spacer (nasopharyngitis: 14 (2.1%) vs 34 (3.2%); asthma: 12 (1.8%) vs 17 (1.6%) patients; cough: 4 (0.6%) vs 10 (0.9%); dysphonia: 5 (0.7%) vs 7 (0.7%)).
Conclusions: Pooled analysis showed that fluticasone/formoterol may be given with or without a spacer device with both approaches providing similar efficacy and tolerability.

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Effects of steady-state female hormones on single-dose pharmacokinetics of roflumilast and roflumilast N-oxide
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Background/Rationale: Roflumilast (ROF) is an oral, selective phosphodiesterase 4 (PDE4) inhibitor licensed for the treatment of severe COPD. It is mainly metabolised by cytochrome P450 (CYP) 1A2 and 3A4 to roflumilast N-oxide (RNO), which mediates >90% of ROF total PDE4 inhibitory activity (tPDE4i), and is then mainly cleared by CYP3A4. Female hormones such as ethinyloestradiol and gestodene can inhibit the metabolism of CYP1A2 and 3A4 substrates; the pharmacokinetic (PK) effects, safety and tolerability of their coadministration with ROF were therefore investigated.
Methods: In a phase I, open-label, two-period PK study, 20 women received a single dose of ROF 500μg with/without concomitant oral administration of a daily fixed dosing to steady state of gestodene 0.075mg plus ethinyloestradiol 0.03mg. Blood samples were taken for the analysis of ROF and RNO over 120 hours after ROF dosing.
Results: After coadministration, total systemic exposure for ROF (AUC_{inf}) increased to 151% (90% CI 122, 187%) of reference, and peak concentration (C_{max}) increased to 138% (90% CI 121, 158%). For RNO, the AUC_{inf} was 114% (90% CI 96.6, 134%) after coadministration, while C_{max} decreased to 87.6% (90% CI 80.4, 95.5%). The tPDE4i rose to 117% (90% CI 98.8, 138%). The combination of ROF and female hormones was well tolerated and there were no safety concerns.
Conclusions: No clinically relevant interaction between ROF/RNO and gestodene plus ethinyloestradiol was observed. These results suggest that ROF may be used without dose adjustments with other exogenous female hormones, including those used in hormone replacement therapy.

P3988
Lack of effect of mild and moderate hepatic impairment or UGT1A1 genotype on the pharmacokinetics of inhaled indacaterol
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Introduction and aim: Indacaterol (IND) is an inhaled long acting beta2 agonist

for once-daily treatment of COPD. IND is highly protein bound and metabolized by CYP450 and UGT1A1. Therefore, hepatic impairment or low UGT1A1 activity (Gilbert Syndrome genotype) could potentially alter clearance of IND through changes in metabolic capacity and/or altered protein binding. Two open label studies were conducted to investigate these potential effects.

Methods: The first study was a single centre, parallel group, single dose (IND 600μg) study in hepatically impaired and matched healthy subjects. The second was a parallel 14 day repeat dose study (IND 200μg once-daily) in healthy subjects with different UGT1A1 genotypes – the fully functional [(TA)6,(TA)6] (6/6) genotype and the low activity [(TA)7,(TA)7] (7/7) genotype (Gilbert syndrome). IND was determined in serum and urine (only first study) using a sensitive LC/MS/MS method. IND pharmacokinetics were compared to the respective control group, i.e. patients with mild and moderate impairment to matched healthy subjects, and UGT1A1 (7/7) to (6/6) genotype, with ratios of >1 indicating higher values in the test group.

Results: For hepatically impaired subjects the ratios (impaired vs. controls) for AUC, C_{max} and Ae (amount excreted in urine) ranged from 0.77–1.01; no change in *ex-vivo* protein binding was noted. In the comparison of UGT1A1 (7/7) to the (6/6) genotype, the ratios for AUC and C_{max} on Day 1 and Day 14 ranged from 0.89–1.18.

Conclusions: Taken together the pharmacokinetics of indacaterol are not significantly affected by mild and moderate hepatic impairment or UGT1A1 genotype.

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

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The OptiChamber Diamond (Diamond; Philips Respironics) VHC is a compact, anti-static device designed to facilitate effective pMDI aerosol delivery. This study compared aerosol characteristics from an HFA albuterol sulfate pMDI (ProAir HFA, 90 μg albuterol, Teva Specialty Pharmaceuticals LLC) alone and with an anti-static preproduction Diamond VHC, an anti-static AeroChamber Plus Z-Stat (Z-Stat; Monaghan Medical Corp.) VHC, and a conventional AeroChamber Plus (AC+; Monaghan Medical Corp.) VHC.

Six of each VHC brand were washed and air dried and six pMDIs were primed before use. For each run (n) the pMDI was actuated into the VHC or straight into the next generation impactor (NGI) (for pMDI alone - run before and after VHC tests), followed by 20 s extraction at 30 L/min, repeated 10 times. Drug deposits from the NGI were analyzed by HPLC. The Emitted Dose (ED; drug entering 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. Means (Standard Deviation)

Device	ED (μg)	FPD (μg)	FPF (%)	MMAD (μm)
pMDI alone (n=12)	90.7 (1.3)	57.8 (4.0)	63.7 (4.2)	2.35 (0.02)
pMDI with Diamond VHC (n=6)	69.7 (3.8)	61.2 (3.7)	87.8 (1.5)	2.41 (0.02)
pMDI with Z-Stat VHC (n=6)	72.3 (5.3)	61.1 (6.2)	84.4 (2.7)	2.40 (0.05)
pMDI with AC+ VHC (n=6)	68.5 (4.3)	58.1 (4.7)	84.8 (1.7)	2.39 (0.04)

The aerosol characteristics from the three VHCs were substantially equivalent and all removed significant potential throat deposition compared to use of the pMDI alone.

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Fluticasone propionate/formoterol fumarate combination therapy has superior efficacy to both fluticasone and formoterol alone

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Background: A new combination of fluticasone propionate and formoterol fumarate (FLUT/FORM; *flutiform*®) in a single aerosol inhaler has been developed. This study investigated the efficacy and safety of a low dose of FLUT/FORM compared with its individual components administered alone.

Methods: Patients aged 12 years or older (N=357) with mild to moderate asthma were evenly randomized to 12 weeks twice daily treatment with FLUT/FORM (100/10 μg b.i.d.) in a single inhaler, fluticasone (FLUT; 100 μg b.i.d.) or formoterol (FORM; 10 μg b.i.d.) in a double-blind, parallel group, multicentre study. The co-primary endpoints were the change in forced expiratory volume in the 1st second (FEV_1) from morning pre-dose at baseline to pre-dose at Week 12 compared with FORM and the change in FEV_1 from morning pre-dose at baseline to 2 hours post-dose at Week 12 compared with FLUT.

Results: Statistically significant differences in the co-primary endpoints were recorded for FLUT/FORM compared with FLUT and FORM. FLUT/FORM showed significantly greater improvements in change in pre-dose FEV_1 compared with FORM (full analysis set; least squares (LS) mean difference: 0.118 L; 95% Confidence Interval (CI): 0.034, 0.201; p=0.006) and post-dose FEV_1 compared with FLUT (LS mean difference: 0.122 L; 95% CI: 0.040, 0.204; p=0.004). Sensitivity analyses supported the co-primary analyses. The safety profiles of FLUT/FORM and its components were comparable.

Conclusions: Fluticasone/formoterol was safe and showed statistically superior efficacy for the co-primary endpoints compared to FLUT and FORM administered alone in adolescents and adults with mild to moderate asthma.