Methods We performed a randomised, cross-over trial in 21 mild-to-moderate persistent asthmatics receiving ICS with elevated FeNO (>30ppb) that increased further (>10ppb) after ICS wash-out. Patients were randomised to 2 weeks of either fluticasone propionate 50µg twice-daily (FP100) or 250µg twice-daily (FP500). The primary outcome was response in diurnal domiciliary FeNO levels. Secondary outcomes included: mannitol challenge; serum eosinophilic cationic protein (ECP); blood eosinophil count; and asthma control questionnaire (ACQ).

Results We found significant dose-related reductions of diurnal FeNO compared to baseline - morning FeNO: baseline=71ppb (95%CI:61–83ppb); FP100=34ppb (95%CI:29–40ppb), $p<0.001$; FP500=27ppb (95%CI:22–33ppb), $p<0.001$; and significant dose separation for morning, $p<0.05$, and evening, $p<0.001$. Time series FeNO displayed exponential decay (Figure 1): FP100 $R^2=0.913$, half-life=69hrs (95%CI:50–114hrs); FP500 $R^2=0.966$, half-life=55hrs (95%CI:45–69hrs); as well as diurnal variation. ACQ showed significant improvements exceeding the minimal important difference (>0.5) with values in keeping with controlled asthma (<0.75) after each dose: FP100=0.48 (95%CI:0.24–0.71), $p=0.004$; FP500=0.37 (95%CI:0.18–0.57), $p=0.001$. All other secondary inflammatory related outcomes (mannitol, ECP and eosinophils) showed significant improvements from baseline but no dose separation.

Conclusions There is a significant dose-response of diurnal FeNO to ICS in asthmatics with an elevated FeNO phenotype, which translates into well-controlled asthma. Further interventional studies are warranted using domiciliary FeNO in this specific phenotype.

S7 INFLUENCE OF BETA-2 ADRENOCEPTOR GENOTYPE ON RESPONSE TO REGULAR RACEMIC OR LEVOSALBUTAMOL IN STEROID TREATED ASTHMATICS

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Background Asthmatic patients receiving inhaled corticosteroids often take frequent add-on therapy with albuterol despite on-demand prescription. We wished to evaluate trough methacholine

airway hyper-responsiveness (the primary outcome) following regular treatment with racemic salbutamol and levosalbutamol compared to placebo, in steroid treated asthmatics stratified according to beta-2 adrenoceptor 16 genotype.

Methods We performed a randomised, double-blind, placebo-controlled, triple crossover trial comparing 2 weeks of regular therapy with inhaled racemic salbutamol (200µg qid); levosalbutamol (100µg qid); or placebo on methacholine PC₂₀ 6 hours post dose in 30 persistent asthmatics (15 homozygous Arg16 and Gly16) receiving inhaled corticosteroids.

Results There was no rebound worsening of trough airway hyper-responsiveness to methacholine after chronic exposure to either racemic ($p=0.53$) or levosalbutamol ($p=0.84$) compared to placebo; nor between genotypes - as doubling dilution (dd) difference in methacholine PC₂₀ from placebo (Figure 1): salbutamol/Arg16=0.36dd (95% CI: -0.43, 1.15); salbutamol/Gly16=0.01dd (95% CI: -0.47, 0.49); levosalbutamol/Arg16=-0.01dd (95% CI: -0.89, 0.87); levosalbutamol/Gly16=0.28dd (95% CI: -0.22, 0.77). Both active treatments improved morning PEF in Gly16 ($p=0.04$) but not Arg16 patients ($p=0.50$); while evening PEF improved in both Gly16 ($p<0.001$) and Arg16 patients ($p=0.006$).

Conclusions Chronic exposure to either racemic or levosalbutamol added to inhaled corticosteroids did not cause rebound worsening of airway hyper-responsiveness at trough compared to placebo; with no difference seen between beta-2 adrenoceptor 16 genotypes.

S8 CAN EOSINOPHIL AND NEUTROPHIL MIGRATION BE THE KEY TO PHENOTYPING ASTHMA?

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Introduction To date, our knowledge of in vivo migration of neutrophils and eosinophils in homeostasis and disease states is based on granulocytes. Here we present a pilot study using purified human eosinophils or neutrophils and demonstrate their differential in vivo kinetics in asthmatic and healthy volunteers. **Methods:** On two separate occasions 100 ml of blood was obtained from eight human

Time series morning and evening exhaled tidal nitric oxide (FeNO) values and one-phase exponential decay curves. FeNO values displayed as geometric means at each sequential time point for each group. R^2 = coefficient of determination (goodness of fit) of exponential decay curves to each data set. $t_{1/2}$ = half-life of exponential decay. ppb = parts per billion.

Abstract S6 Figure 1