Name of Sponsor/Company
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Title of Study
A proof of concept study to evaluate rebound trough airway hyper-responsiveness after single and chronic dosing with levosalbutamol and racemic salbutamol in persistent asthmatics

Investigators
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Study centre(s)
Asthma & Allergy Research Group

Publication (reference)
ANDERSON WJ, SHORT PM, WILLIAMSON PA, MORRISON AE, PALMER CAN, TAVENDALE R, LIPWORTH BJ. Proof of concept evaluation of trough airway hyper-responsiveness following regular racemic or levosalbutamol in genotype-stratified steroid-treated persistent asthmatics. Clin Sci 2014;126:75-83

Date of first enrolment
02.09.2008

Date of last completed
24.04.2012

Objectives
To directly compare racemic and levosalbutamol after regular exposure at trough (i.e. 6 h post final dose) as add-on therapy to pre-existing ICS treatment; and to perform the same comparison in patient groups stratified *a priori* by B2ADR 16 genotype.

Methodology
We performed a randomized, double-blind, placebo-controlled, triple crossover, proof of concept trial comparing 2 weeks of regular therapy with inhaled racemic salbutamol [200 μg q.i.d. (four times daily)], levosalbutamol (100 μg q.i.d.) or placebo on trough methacholine PC_{20} [provocative concentration causing 20% fall in FEV_1 6 h post-dose in 30 persistent asthmatic patients (15 who were Arg16 homozygous and 15 who were Gly16 homozygous) all receiving ICS.

Number of patients planned
Sufficient numbers to complete 30.

Number of patients analysed
30

Diagnosis and main criteria for inclusion
Homozygous Arg16 and Gly16, mild-to-moderate persistent asthma, aged 18–65 years, $\leq$2000 μg/day ICS (BDP equivalent), methacholine PC_{20} <8 mg/ml who demonstrated >1 dd (doubling dilution) increase in methacholine PC_{20} after inhaling 200 μg of racemic salbutamol.

Test product dose

Treatment A
Racemic salbutamol (200 μg q.i.d.)

Treatment B
Levosalbutamol (100 μg q.i.d.)

Treatment C
Placebo (q.i.d.)

Duration of treatment
6 weeks (3 treatment periods of 2 weeks)

Reference therapy
None

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Criteria for evaluation

Primary Endpoint
DD shift in methacholine PC_{20} 6h after the final dose of each randomised treatment

Secondary Endpoints
Spirometry, FeNO, domiciliary PEF, asthma symptoms scores, reliever use.

Statistical methods
A power calculation indicated that 30 patients would detect a 1 dd difference (minimum important difference) in methacholine PC20 between treatments with >90% power. The treatment–genotype interaction was powered at 80% to show the same 1dd difference. Non-Gaussian data were logarithmically transformed to achieve normality before analysis. If normality of distribution could not be achieved then we used equivalent non-parametric analyses. Comparisons between treatments were performed using repeated measures ANOVA, including sequence effect, with Bonferroni correction for multiple pairwise tests to avoid confounding the overall alpha error (significance level $P<0.05$, two tailed). Comparisons between genotypes were performed using Student's *t* test for independent samples. IBM SPSS Statistics version 20 was used for all analyses.

Summary Conclusions

Results
There was no worsening of AHR (airway hyper-responsiveness) at trough to methacholine after 2 weeks regular exposure to either racemic ($P=0.53$) or levosalbutamol ($P=0.84$) compared with placebo, nor between genotypes – as dd (doubling dilution) difference in methacholine PC_{20} from placebo [salbutamol/Arg16 =0.36 dd [95% CI, −0.43, 1.15]; salbutamol/Gly16 =0.01 dd (95% CI, −0.47, 0.49); levosalbutamol/Arg16= −0.01 dd (95% CI, −0.89, 0.87); and levosalbutamol/Gly16 =0.28 dd (95% CI, −0.22, 0.77)]. Both active treatments improved morning PEF (peak expiratory flow) in Gly16 ($P=0.04$ overall) but not Arg16 ($P=0.50$ overall) patients, whereas evening PEF improved in both Gly16 ($P<0.001$ overall) and Arg16 ($P=0.006$ overall) patients.

Conclusion
The regular exposure to either racemic or levosalbutamol for 2 weeks added to ICSs did not cause worsening of AHR at trough compared with placebo; with no difference seen between B2ADR 16 genotypes.

Date of the report: 12.05.16