

specifically discusses effects on urinary cortisol. We acknowledge the limitations of urinary cortisol assessment; however, as outlined in the online supplement, the urinary cortisol population in our study specifically excluded subjects with an incomplete urine collection and/or 24-h urinary creatinine levels below the lower limit of the threshold range. Thus, our data are not confounded by incomplete collections. We also acknowledge that patients were receiving inhaled corticosteroid (ICS) at baseline; however this represents an asthma population who would be eligible for an ICS/long-acting beta2 agonist combination product. We do not consider that our data give a false impression of the lack of effect of FF on cortisol particularly when considered in the context of other published data on the effect of FF at therapeutic doses on serum or urine cortisol in subjects with asthma. For example, the effects of FF/VI 100/25 and 200/25 µg on the hypothalamic-pituitary-adrenal (HPA) axis were assessed in a 6-week placebo-controlled study in corticosteroid-free adult and adolescent subjects with asthma.² There was no effect on 0–24 h weighted mean serum cortisol or on 0–24 h urine cortisol. In an 8-week study in subjects with asthma who were not receiving ICS controller therapy at baseline, neither FF 100 nor 200 µg demonstrated an effect on 24-h urine cortisol.³

The relationship between FF $AUC_{(0-24)}$ and both 24-h serum cortisol and 24-h urine cortisol is well established. The estimated FF area under the curve values that produced 50% of the maximum effect on cortisol (AUC_{50}) were 1556 and 1686 pg.h/mL, respectively.⁴ These values are several times higher than the average FF $AUC_{(0-24)}$ values observed at the highest clinical dose of FF (FF 200 µg), 495 pg.h/mL.⁴ Therefore, despite the high lipophilicity of FF and long half-life, the systemic exposure is far below levels that would affect the HPA axis.

Nevertheless, we agree that there will be individuals who may demonstrate increased susceptibility to the systemic effects from inhaled corticosteroids. Likewise, it is recognised that lack of an effect on the HPA axis does not preclude the existence of systemic effects (eg, growth suppression). For these reasons, we acknowledge that vigilance regarding the development of systemic adverse effects is warranted for all patients receiving inhaled corticosteroids.

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Authors' reply to 'Safety and tolerability of fluticasone furoate/vilanterol'

We thank Dr Lipworth for his response to our article on the safety and tolerability of fluticasone furoate/vilanterol (FF/VI) combination in asthma,¹ in which he

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