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Title: A dual-acting muscarinic antagonist, ß$_2$-agonist [MABA] molecule (GSK961081) improves lung function in COPD. A randomised trial

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Body: Introduction GSK961081 is a dual pharmacophore demonstrating both muscarinic antagonist and beta agonist activities in one molecule (MABA). Recent COPD treatment guidelines have recommended that combining bronchodilators with different mechanisms may increase the degree of bronchodilation for equivalent or lesser side effects (GOLD 2010). Methods This was a 4 week, multicentre, randomised, double blind, double dummy, placebo and salmeterol controlled parallel group study. Dose ranging across three twice-daily (BD) doses and three once-daily (QD) doses were assessed in moderate and severe COPD subjects. Trough FEV_1 at day 29 was the primary endpoint. Other efficacy endpoints, included serial FEV1 over 24h, FVC, and rescue salbutamol use. Safety endpoints included heart rate, glucose and QTc Results The study recruited 436 subjects. GSK961081 showed statistically and clinically significant differences from placebo in all doses and regimens for FEV_1 trough on day 29 (155-277ml $p<0.001$). The optimal daily dose was 400mcg, either as once (400mcg QD) or as twice a day (200mcg BD) dosing with an improvement in Day 29 trough FEV_1 of 215ml (95%CI) (140,290) $p<0.001$ and 249ml (170,320) $p<0.001$ respectively. Other efficacy endpoints including FVC and rescue salbutamol also showed improvement. The molecule showed no effects on glucose, potassium, heart rate, blood pressure and no dose response effect on QTc elongation. Conclusion This study showed that GSK961081 is an effective bronchodilator in moderate and severe COPD subjects. GSK961081 was safe and well tolerated. Clinical Trials Register number NCT01319019. Study code MAB115032 and was funded by GlaxoSmithKline.