Title: Sub-microgram dose formulations for dose ranging studies with long acting bronchodilators and their fixed dose combination using metered dose inhalers (MDIs)

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Body: Preliminary safety and efficacy studies with glycopyrrolate (GP; Reisner C, et al. Eur Respir J 2010; 36: Suppl. 54, 829s), formoterol fumarate (FF; Orevillo C, et al. Eur Respir J 2010; 36: Suppl. 54, 829s), and their fixed dose combination (GFF MDI, PT003), suggested the need to assess GP and GFF at sub-microgram levels before an appropriate dose for further evaluation in long term trials could be identified. Dose proportional and stable MDIs were prepared over a 120 fold dose range for GP, and 60 fold for GFF, with nanogram level precision using a novel cosuspension technology. Methods: GP MDIs from 300 ng to 18 µg/actuation, FF MDIs from 480 ng to 9.6 µg, and GFF MDIs with GP doses of 600 ng to 18 µg/actuation at fixed FF dose of 4.8 µg/actuation, were prepared by cosuspending drug crystals in hydrofluoroalkane with spray-dried distearoyl-phosphatidylcholine porous particles. Aerodynamic particle size distribution (aPSD) and delivered dose uniformity (DDU) were tested at 30 L/min air flow. Robustness was tested by thermal cycling (-5.0°C to +40°C every six hours for 4 weeks), and isothermal storage at various temperatures. Results: The in vitro drug delivery and aPSD for GP, in mono and combination MDIs with FF, were found to be linearly dose proportional (r² > 0.99) over the entire dose range, with stable aPSD and DDU. Similar performance was observed for FF MDIs. Conclusions: Pearl’s novel cosuspension platform generates dose proportional and stable MDIs even with sub-microgram doses. Clinical studies evaluating an unprecedented dose range allowed for a complete benefit-risk assessment of GFF MDI, GP MDI and FF MDI.