Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate

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Introduction

- For orally inhaled drug products (OIDPs), charcoal block pharmacokinetics (PK) studies are intended to quantify PK due to lung dose (i.e., total lung deposition [TLD]).
- Can charcoal block PK studies be used to quantify ***regional*** deposition?
- Physiologically based pharmacokinetic (PBPK) modeling was used to predict systemic PK following administration of a suspension-based metered dose inhaler (MDI) with the generic name budesonide; formoterol fumarate dihydrate inhalation metered aerosol.
- Sensitivity analyses explored potential relationships between systemic PK and regional deposition.

Methods

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- GastroPlus® 9.8.3 (Simulations Plus, Inc., Lancaster, CA, USA)
  - Pulmonary Compartmental Absorption & Transit (PCAT™)
- Model parameters determined based on literature search.
  - Intravenous (IV) PK data not available for formoterol fumarate dihydrate.
- For inhalation PK simulations, input parameters for dissolution, particle size distribution (PSD), and extrathoracic deposition were based on pooled aerodynamic particle size distribution (APSD) data.
  - Collected for Contract 75F40119C10154 by the University of Florida and Emmace Consulting AB, using three realistic mouth-throat (MT) models produced by the Oropharyngeal Consortium (OPC) and Virginia Commonwealth University (VCU) and three breathing profiles
- A central-to-peripheral deposition ratio (C/P) of 1 and exhaled fraction of 0.6% were assumed for the purposes of model development (Usmani et al. [2021]).

Usmani O, Roche N, Wahab E, Israel S, Jenkins M, Trivedi R, Dorinsky P, Aurivillius M. A scintigraphy study of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in patients with moderate-to-very severe chronic obstructive pulmonary disease. Respir Res 2021, 22: 261.

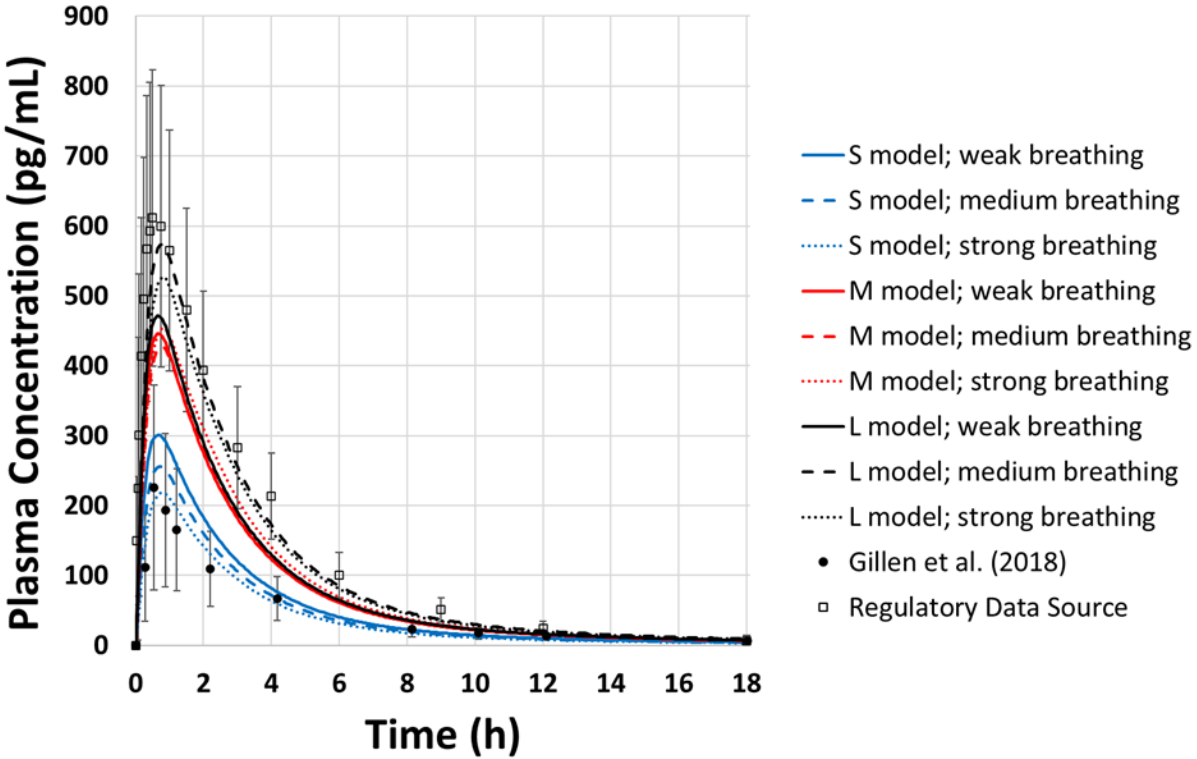
Input Deposition Fraction (DF) Parameters – Budesonide

MT Model(s)	Breathing Profile	Extra-thoracic DF (%)	Tracheo-bronchial DF (%)	Bronchiolar DF (%)	Alveolar-Interstitial DF (%)
VCU and OPC pooled small	Weak	71.0	14.200	7.100	7.100
	Medium	75.1	12.150	6.075	6.075
	Strong	78.4	10.500	5.250	5.250
VCU and OPC pooled medium	Weak	55.7	21.850	10.925	10.925
	Medium	55.5	21.950	10.975	10.975
	Strong	51.1	24.150	12.075	12.075
VCU and OPC pooled large	Weak	53.2	23.100	11.550	11.550
	Medium	39.0	30.200	15.100	15.100
	Strong	42.8	28.300	14.150	14.150

Input DF Parameters – Formoterol Fumarate Dihydrate

MT Model(s)	Breathing Profile	Extra-thoracic DF (%)	Tracheo-bronchial DF (%)	Bronchiolar DF (%)	Alveolar-Interstitial DF (%)
VCU and OPC pooled small	Weak	66.0	16.700	8.350	8.350
	Medium	65.0	17.200	8.600	8.600
	Strong	77.4	11.025	5.513	5.513
VCU and OPC pooled medium	Weak	51.0	24.200	12.100	12.100
	Medium	48.8	25.300	12.650	12.650
	Strong	41.0	29.200	14.600	14.600
VCU and OPC pooled large	Weak	41.7	28.850	14.425	14.425
	Medium	30.2	34.600	17.300	17.300
	Strong	34.1	32.650	16.325	16.325

Validation – Budesonide



- Plasma concentration predictions in a single subject intended to represent the population mean
- Two inhalations of the 0.16 mg/inh; 0.0045 mg/inh strength of the reference listed drug (RLD) product without a charcoal block
- Compared with in vivo PK data from Gillen *et al.* (2018) (n = 49) and a regulatory data source (n = 96)
- Model inputs based on realistic APSD data collected with small (S), medium (M), and large (L) MT models under various breathing conditions, taken from Contract 75F40119C10154.

Gillen M, Forte P, Svensson JO, Lamarca R, Burke J, Rask K, Nilsson UL, Eckerwall G. Effect of a spacer on total systemic and lung bioavailability in healthy volunteers and in vitro performance of the Symbicort®(budesonide/formoterol) pressurized metered dose inhaler. Pulm Pharmacol Ther 2018, 52: 7-17.

Validation – Formoterol Fumarate Dihydrate

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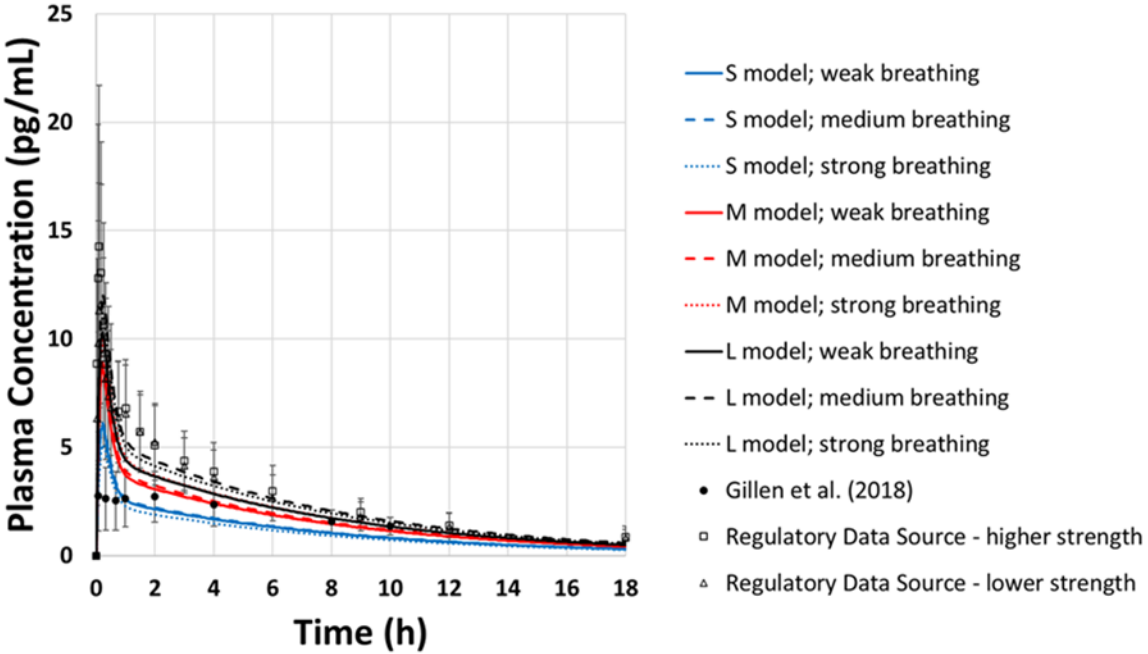

- Same conditions as for budesonide
- In studies "Regulatory Data Source - lower strength" and "Regulatory Data Source - higher strength" the amount of formoterol fumarate dihydrate is the same for both strengths

Sensitivity Analyses

Predicted values of maximum plasma concentration (C_{max}), area under the plasma concentration time curve from time 0 to time t (AUC_{0-t}), and area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) in a single subject intended to represent the population mean when a one-to-one inverse correlation is between C/P and TLD is assumed.

Active Ingredient	C/P	TLD	C_{max} (pg/mL)	AUC_{0-t} (pg-h/mL)	$AUC_{0-\infty}$ (pg-h/mL)
Budesonide	0.8	1.2	241.1	811.5	864.8
	1	1	197.0	662.1	705.5
	1.25	0.75	144.8	485.9	517.8
Formoterol Fumarate Dihydrate	0.8	1.2	6.3	16.3	24.7
	1	1	5.1	13.2	19.9
	1.25	0.75	3.7	9.5	14.5

Conclusions

1. Model validation showed that by using parameter inputs based on in vitro realistic APSD data, simulation results reflected in vivo systemic PK data reasonably well for both active ingredients.

2. A one-to-one inverse correlation was assumed between C/P and TLD, where predicted PK metrics following product administration with a charcoal block showed sensitivity to the combined effect on regional lung deposition.

Conclusions (cont'd)

3. However, to apply these conclusions for regulatory purposes, further research is needed to address the remaining scientific gaps, which includes experimental verification of the assumed reverse relationship between C/P and TLD for budesonide and formoterol fumarate dihydrate under in vivo conditions as well as uncertainty with respect to the sources of PK variability.

4. Regional deposition modeling is expected to be a useful means of better understanding the actual relationships between C/P and TLD for each active ingredient.

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