Current limitations in producing a fully mechanistic PBPK model for a highly soluble orally inhaled drug product that exhibit slow lung absorption

2021 Generic Drug Science and Research Initiatives Public Workshop
Danny Brinkley, Director, Global Inhalation, Teva Pharmaceuticals
23rd June 2021

Disclaimer

The opinions expressed in this presentation are those of the presenter and not necessarily those of Teva Pharmaceutical Industries Ltd. or its affiliates (collectively "Teva").

This presentation has been prepared for discussion purposes only. Neither Teva nor any of its employees or representatives make any representation or warranty, express or implied, as to the accuracy or completeness of any information contained herein. The information and examples presented originate from individual experience and may not represent the full scope and/or examples of Teva.

Nothing contained within the presentation is, or should be relied upon as, a promise or representation as to the future and Teva expressly disclaims any obligation to update the information if it should change.

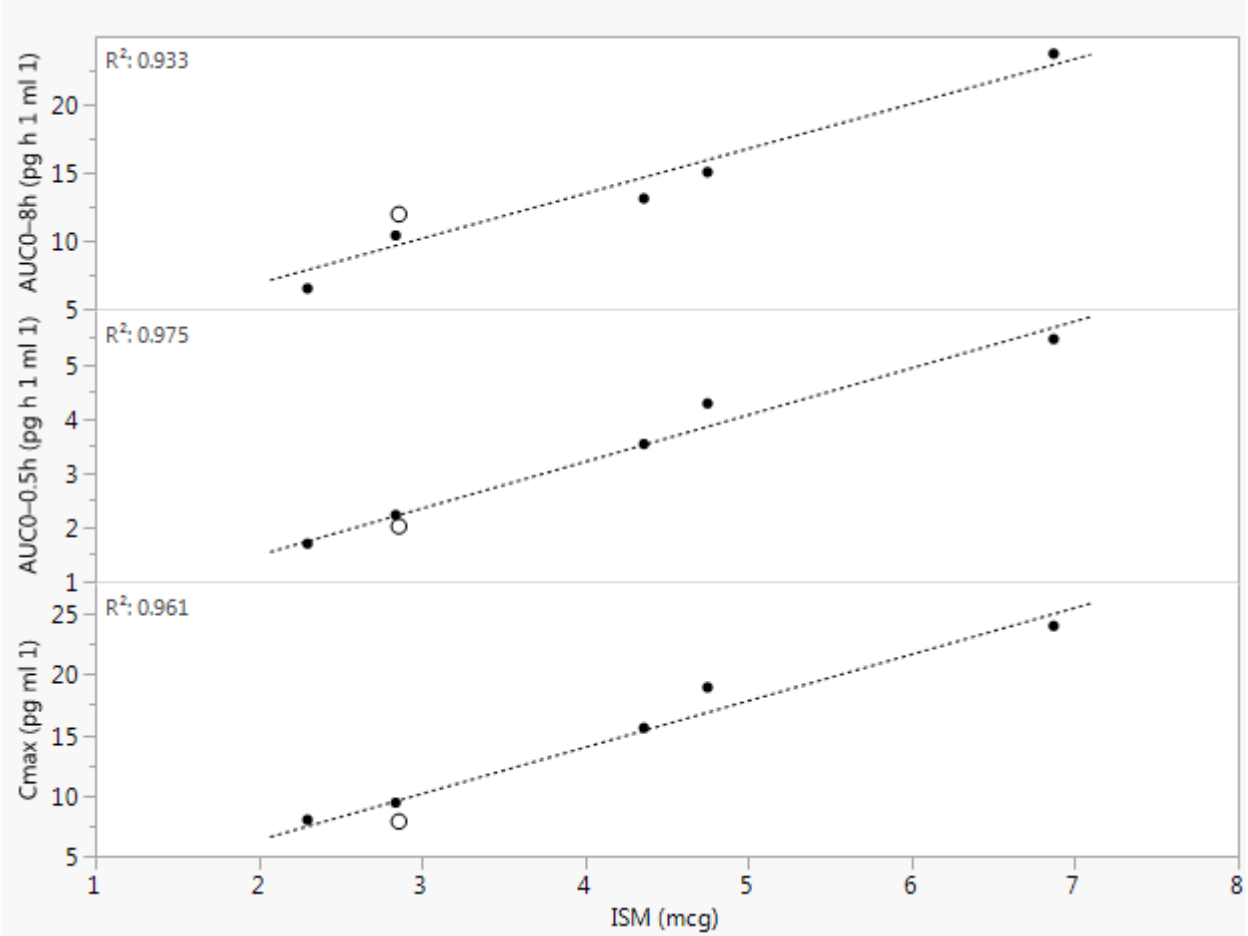
Tiotropium Bromide

Attributes influencing systemic absorption via the lung

Parameter	Value	*Reference*
Formula	$C_{19}H_{22}BrNO_4S_2$	*DrugBank*[1]
Molecular weight	392.512 g/mol	*DrugBank*[1]
LogP	-1.8	*DrugBank*[1]
Solubility in simulated lung fluid, PBS at pH 7.4	35 mg/m	*Teva*[2]
Physiological Charge	+1	*DrugBank*[1]
Permeability in Caco-2 cells at pH 7.4	3.5 nm/s	*Teva*[2]
Plasma unbound drug fraction, Fup	0.28	*Eriksson (2018)*
Unbound concentration, Vu	3.87 ml/g	*Bäckström (2016)*
Tissue to plasma partition coefficient, Kp (Vu*Fup)	1.08 ml/g	Calculated
Dissociation rate for M1, M2 and M3 receptors ($t_{1/2off}$)	876 / 88 / 3308 min	*Starck (2008)*

Tiotropium Total Lung Dose - PK Correlation

Linear regression of impactor size mass (ISM) and PK C_{max} and AUC_t for five spray-dried tiotropium formulations and Spiriva Handihaler



- ○ Spiriva Handihaler
- • Spray dried tiotropium formulations

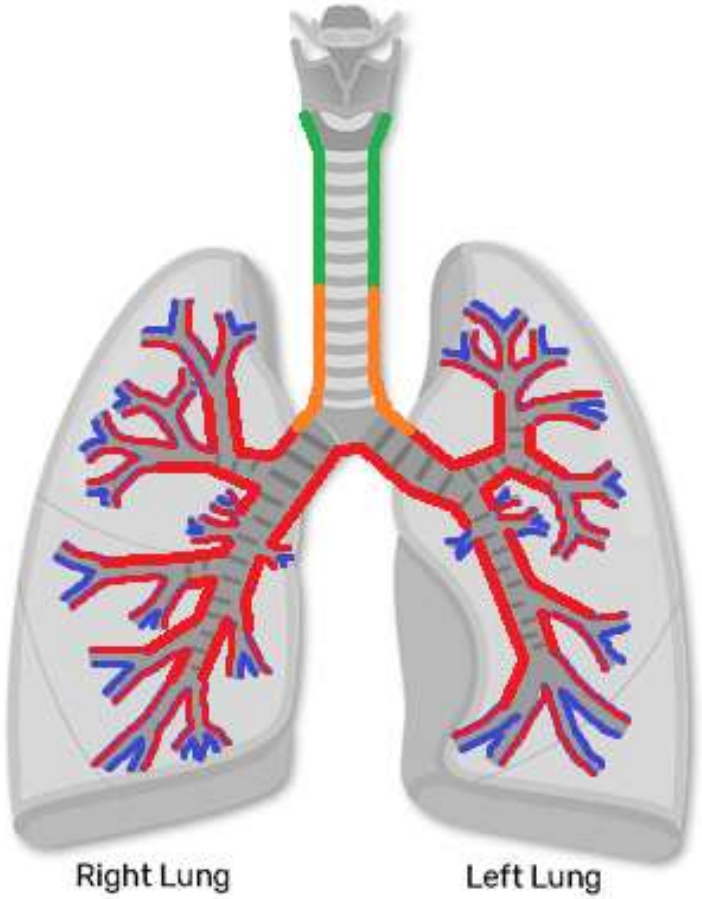
Data sourced from Perry *et al* (2019).

Impactor sized mass (ISM) measured using next generation impactor and Alberta Idealized Throat (AIT).

Physiological Based Pharmacokinetic Model & Simulation (PBPK)

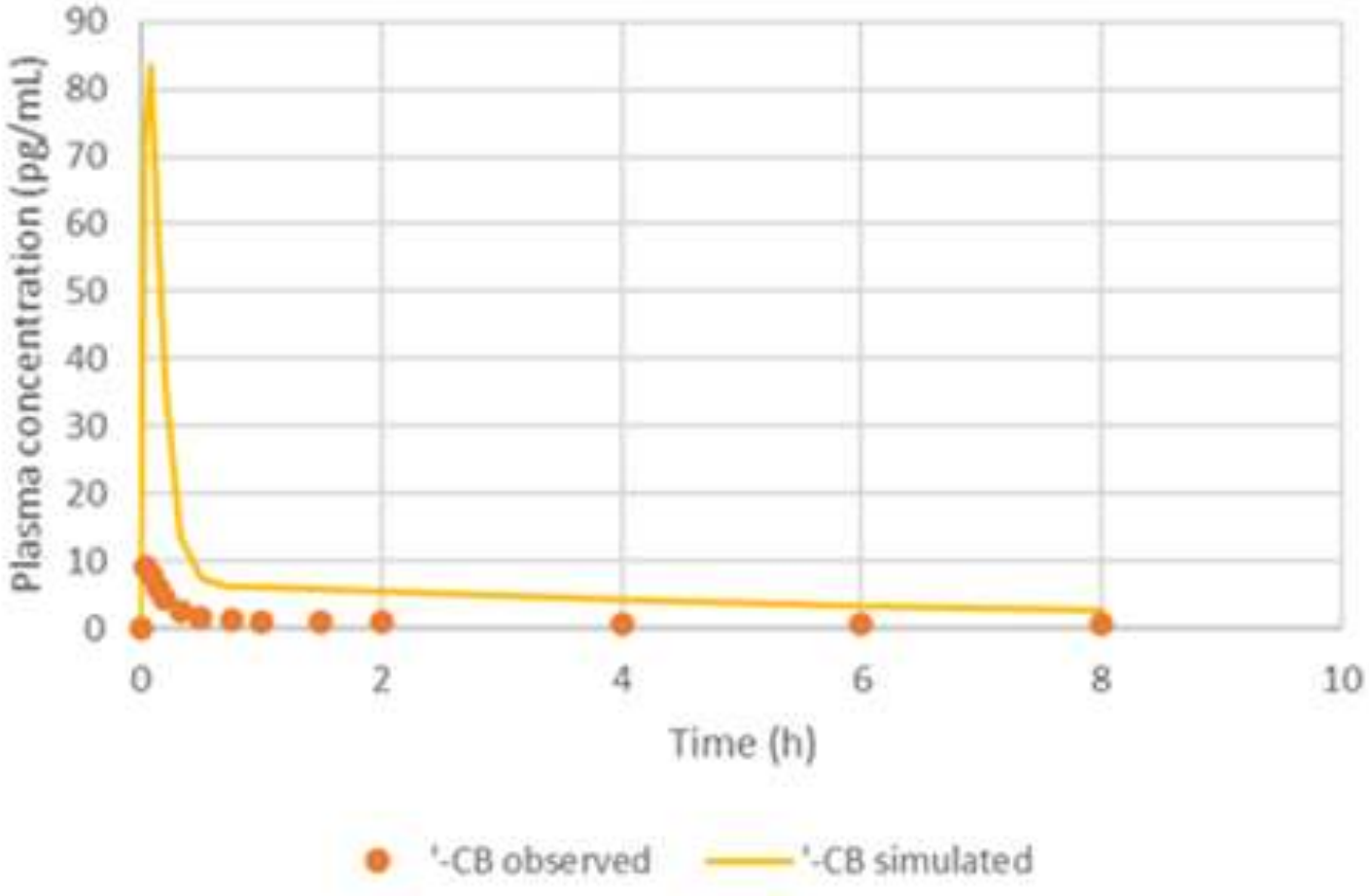
Spiriva Handihaler PBPK simulated in Mimetikos Preludium™

- Aerosol deposition in human respiratory tract calculated:
  - ET: Mouth-Throat
  - BB: Tracheobronchial
  - bb: Bronchiolar
  - AI: Alveolar Interstitial
- Post deposition effects simulated.
  - Lung and systemic properties
  - Compound and formulation properties



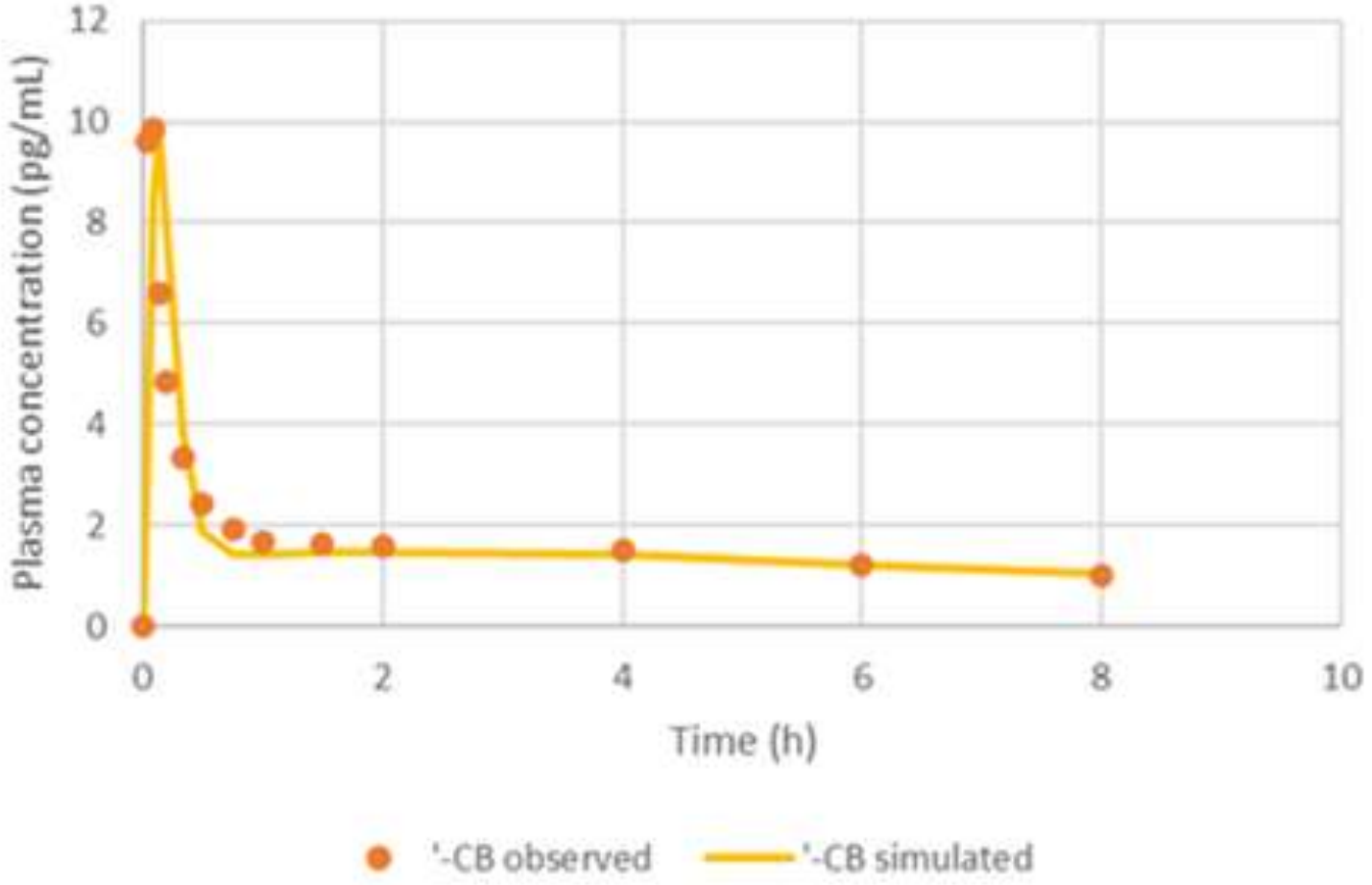
PBPK Model v1

Observed versus simulated PK profile (without charcoal block, -CB) overestimated tiotropium uptake rate



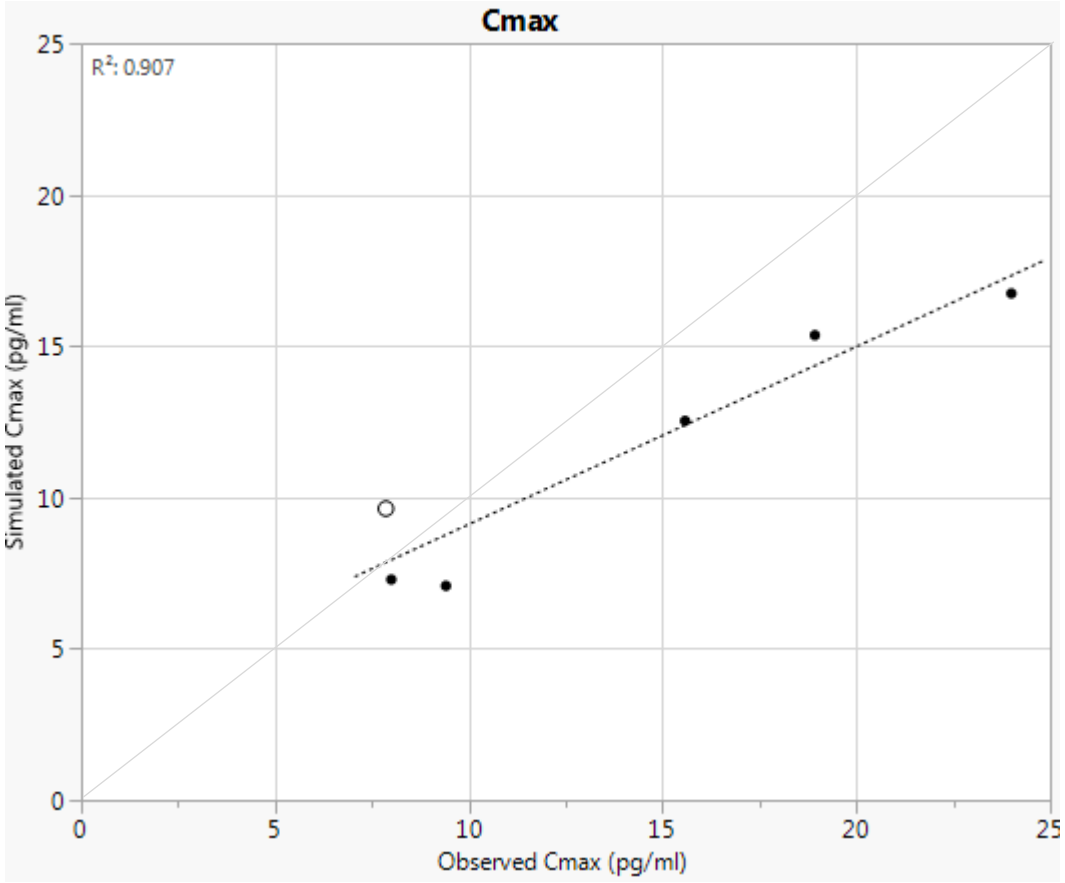
PBPK Model v2

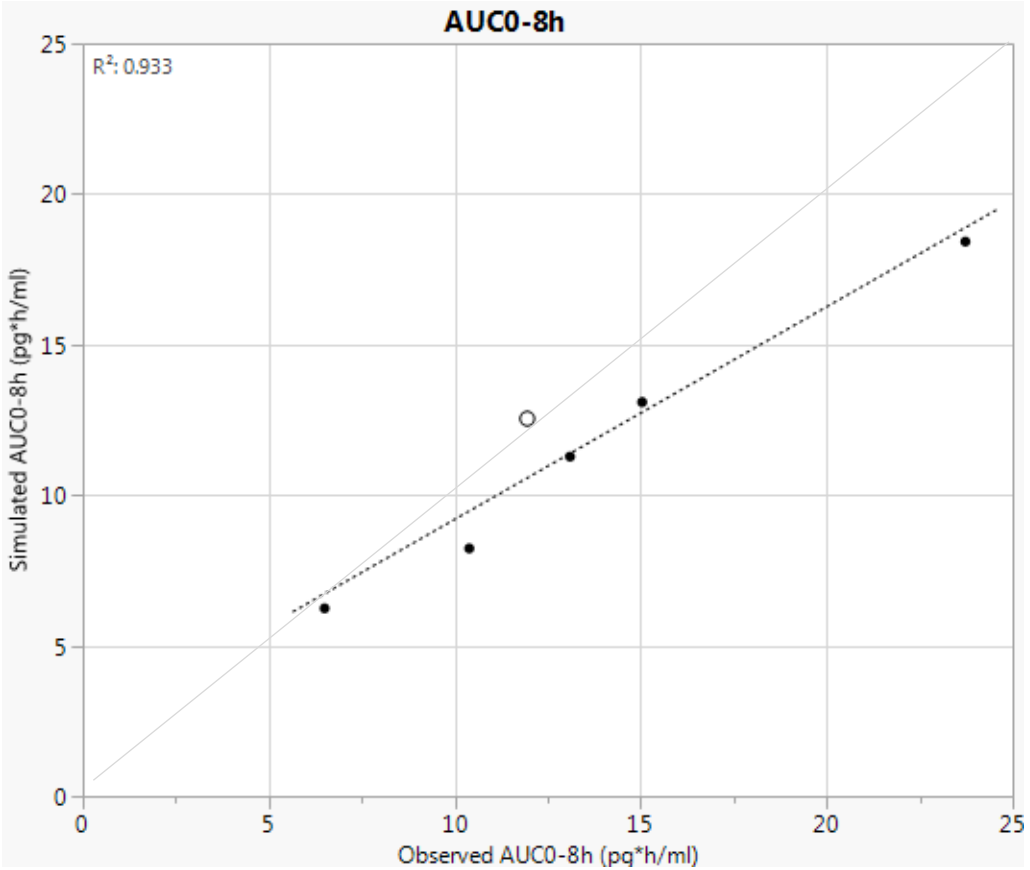
Good correlation for Spiriva Handihaler observed versus simulated PK profiles when parameters fitted for a putative deep tissue compartment and reduced permeability



Observed versus Simulated PK Parameters

Calculated ratios for observed/simulated samples range from 1.0 to 1.4

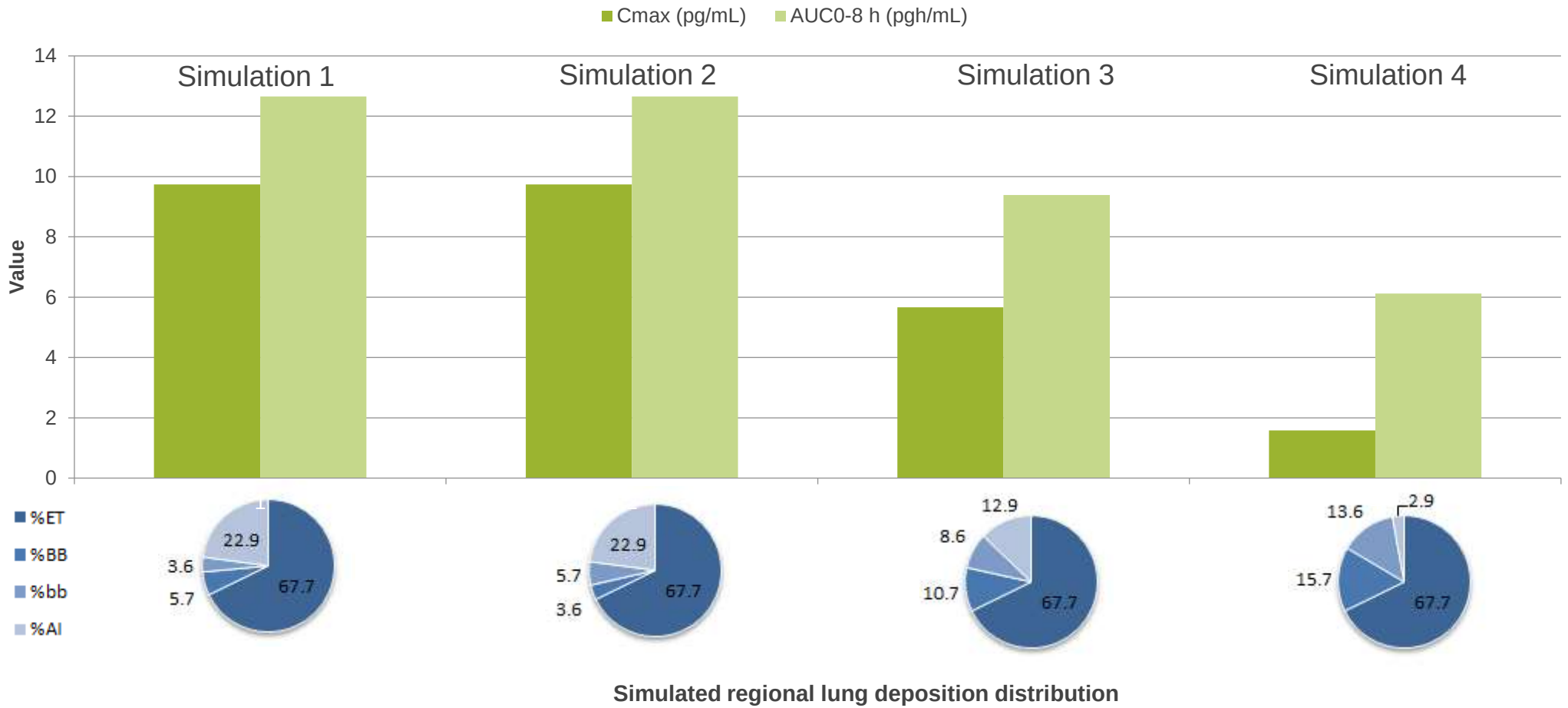




○ Spiriva Handihaler • Spray dried tiotropium formulations

PK Simulations for Variations in Regional Lung Deposition

Alveolar interstitial (AI) deposition appears to be driving C_{max}



Simulated regional lung deposition distribution

Conclusions

- PBPK for highly soluble OIPs that exhibit a slow lung absorption component present a unique modelling challenge.
- Slow lung absorption component meant only a partial mechanistic model was possible with fitted parameters required for a putative deep tissue compartment.
- This model produced a simulated PK profile consistent with the observed profile for Spiriva Handihaler.
- The model indicated AI region significantly influences PK C_{max}.
- Further research on the mechanisms determining this slow absorption component will help in creating a fully mechanistic-model.

Acknowledgments

The content of this presentation is based on a collaborative effort of those acknowledged below:

Alan Thompson, Amanda Valente, Bradley Bath, Chris Edlin, Clare Butler, Elizabeth Rody, Julian Blair, Mangubhai Rohit, Marc Kelly, Mark Stanford, Praful Deshpande.

EMMACE Consulting AB

References

1. https://www.drugbank.ca/drugs/DB01409
2. Values derived from in house testing.
3. Eriksson, A., *et al*. *Pulmonary absorption - estimation of effective pulmonary permeability and tissue retention of ten drugs using an ex vivo rat model and computational analysis*. Eur J Pharm Biopharm (2018) 124:1-12
4. Bäckström, E., *et al*. *Development of a Novel Lung Slice Methodology for Profiling of Inhaled Compounds. J Pharm Sci (2016) 105(2):838-845*
5. Starck, J.P., *et* al. *Alkyne–quinuclidine derivatives as potent and selective muscarinic antagonists for the treatment of COPD*. Bioorganic & Medicinal Chemistry Letters 18 (2008) 2675–2678

- Perry, J., *et al*. *Particle size and gastrointestinal absorption influence tiotropium pharmacokinetics: a pilot bioequivalence study of PUR0200 and Spiriva HandiHaler.* Br J Clin Pharmacology (2019). 85 580–589.

Thank you.