M1130-01-05

Evaluating Influence Of Critical Quality Attributes Of Metronidazole Topical Gel On Bioequivalence Using The Dermal Virtual Bioequivalence (VBE) Module In Simcyp Simulator

K. C. Telaprolu[1], S. Arora[1*], J. Clarke[1], **Y.Dancik[1#]**, E Tsakalozou[3], P. Ghosh[3], K. Alam[3], M.S. Roberts[4], S. Polak[1, 2]

[1]Certara UK Ltd, Simcyp Division, Sheffield, UK;

[2]Faculty of Pharmacy, Jagiellonian University Medical College, Poland

[3]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Silver Spring, MD, USA

[4]Therapeutics Research Centre, Diamantina Institute, University of Queensland, Brisbane, Queensland, Australia

*Present address - Janssen Pharmaceutical, Companies of Johnson & Johnson, Turnhoutseweg 30, 2340 Beerse, Belgium.

#Presenting author

CONTACT INFORMATION: krishna.chaitanyatelaprolu@certara.com

PURPOSE

The purpose of this work was to virtually evaluate the bioequivalence of a generic metronidazole gel (applied to the skin) against its reference standard under various study designs by using a dermal physiologically based pharmacokinetic (PBPK) modelling approach for population predictions. An additional aim was to use the Virtual Bioequivalence (VBE) module in the Simcyp simulator to evaluate the influence of differences in the Critical Quality Attributes (CQAs) of the metronidazole gel formulation on the BE outcomes for metronidazole exposure in the systemic compartment (plasma) and in different skin layers.

METHODS

PBPK models for each formulation, reference standard (NDC Cod: 66993-962-45, 0.75% w/w) and the generic product (NDC Code(s): 51672-4116-2, 51672-4116-5, 51672-4116-6, 0.75% w/w), were developed and verified using the Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML MechDermA) within Simcyp simulator (V20) (Certara, NJ, USA) [1]. The PBPK model utilized the experimentally obtained critical quality attributes (CQA): apparent viscosity, formulation pH and evaporation profile as described in the published paper [1]. To carry out the VBE simulations, compound files for the reference standard and a generic product were developed containing the empirical drying profile for each. Apparent viscosity was available for the reference standard, but unknown for test, therefore the sensitivity of this parameter was assessed. Table 1 lists both VBE and formulation parameters including number of individuals, proportion of females and age of population details used in the simulations. Bioequivalence between these formulations was evaluated using various available BE design options such as crossover design, crossover design with within subject variability (WSV), crossover design with multiple-dosing scenario, and parallel design. In the absence of literature to parametrize within subject variability for skin physiology parameters, a scenario of assuming WSV is equal to between subject variability (BSV) like in the study explored by Bego et al. for oral administration [3]. For this scenario zero percent for dermis blood flow and 7.2% and 7.4% for skin surface pH was used as WSV. An additional case scenario using upper limit of 30% CV for skin pH and dermis blood flow scalar has been explored here. Global sensitivity analysis was carried out on formulation quality attributes and apparent viscosity was identified as a critical parameter for drug permeation to the systemic compartment and local skin layers. Therefore, apparent viscosity was modified for the generic formulation to generate “microstructural (Q3) variants” and the simulations were conducted as explained above exploring the impact of this CQA on BE outcomes. Bioequivalence was assessed using the non-compartmental analysis and the BE modules in Phoenix WinNonLin version 8.3 (Certara USA Inc.). For BE evaluation, plasma PK parameters such as maximum plasma concentration (Cmax) [mg/mL], Area Under the Concentration versus Time Curve extrapolated to infinity (AUCINF) [mg/mL·h], and local tissue PK parameters such as maximum amount (Amax) (mg), AUCINF (mg·h) in stratum corneum (SC), viable epidermis (VE) and dermis, were compared between simulated generic (“Q3 variants”) and reference formulations by average BE.

RESULTS

Results in Figure 2 show that mean percent ratio of test (generic) least square mean (LSM) to reference standard LSM values (Ratio_%Ref) and 90% confidence interval (CI) of metronidazole plasma Cmax and AUCINF, Amax in various layers of skin under various VBE trial design setups; the generic product was found to be bioequivalent to the reference standard under most of the explored study designs with certain exceptions. The scenarios in which BE criteria were not met include: in the dermis under crossover design with 30% WSV (Cmax) and in the plasma and the SC in the parallel design with multiple dosing condition (AUCINF). A sensitivity analysis of apparent viscosity was carried out for plasma and local tissue exposure data using parallel design BE setup. The “safe space” for apparent viscosity, a critical parameter based on its impact on AUCINF and Cmax, was found to extent between 6390 (2-fold lower than the reference standard) to 15974 (1.25-fold higher than the reference standard) cPs as shown in Figure 3. For metronidazole products, pH was shown to be an insensitive parameter in the developed gel formulation model, this is due to the drug being mostly unionized at the pH of the formulations which is close to skin surface pH. Therefore, skin surface pH was used to estimate fraction of unionized drug at skin surface.

Table 1: VBE trial design setup and the formulation parameters.

Parameter	Value	Comment
Bioequivalence Trial Setup		
BE design	Crossover 2Trials 2Period 2Sequence, Parallel Design	NA
No of Subjects in each trial	50	Default
Total duration of study (h)	24	As this formulation is applied twice in a single day
Duration of application (h)	12	Details from Prescribing Information [2]
No of doses in Multiple dose study	2	Details from Prescribing Information [2]
Proportion of Females	0.5	Default (assumed)
Age of Population	20 to 50	Default (assumed)
Treatment Dosage Regimen (same for both treatments)		
Metronidazole dose (mg)	4.5	Prescribing Information [2]
Area of product application (cm²)	60	Drug product dose applied: 10 mg/cm2
Product thickness (cm)	0.01	Drug product dose applied: 10 mg/cm2 [1]
Sampling plan (h)	0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 18, 20, 22, 24	Assumed
Formulation Parameters		
Evaporation Profile	User input	Measured Profile [1] as shown in Figure 1
Apparent viscosity (centipoise)	12779	Measured for reference product and assumed to be same for generic product.

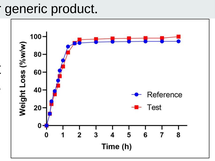


Figure 1: Drying profile of reference versus test product plotted as weight loss versus time measured using gravimetrical analysis [1].

Figure 2 Mean ± 90% Confidence Interval (CI) (n= 50) percent ratio of test least square mean (LSM) to reference standard LSM values (Ratio_%Ref) of PK parameter for (a) Plasma AUCINF, Cmax (mg/L) parameters; (b) SC AUCINF, Amax (mg) parameters; (c) VE AUCINF, Amax parameters and (d) Dermis AUCINF, Amax under various BE study designs. *WSV (Within Subject Variability), BSV (Between Subject Variability), SC (Stratum Corneum), VE (Viable Epidermis), AUCINF (*Area Under the Concentration versus time Curve extrapolated to infinity), *Cmax (*maximum plasma concentration), *Amax* (*maximum amount)*

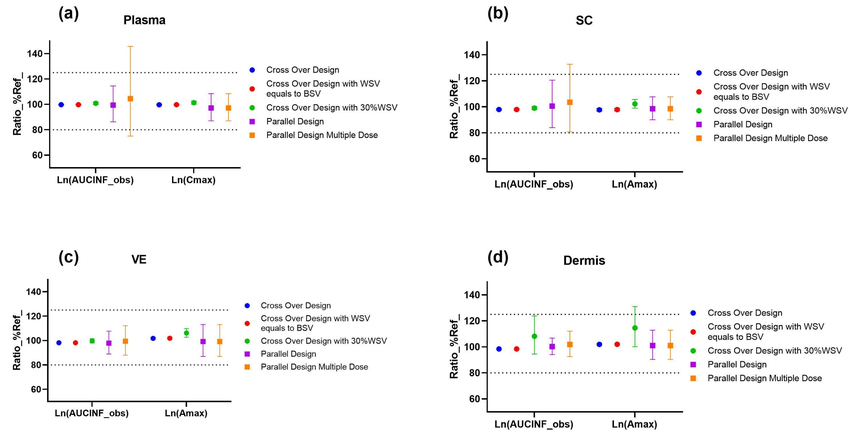
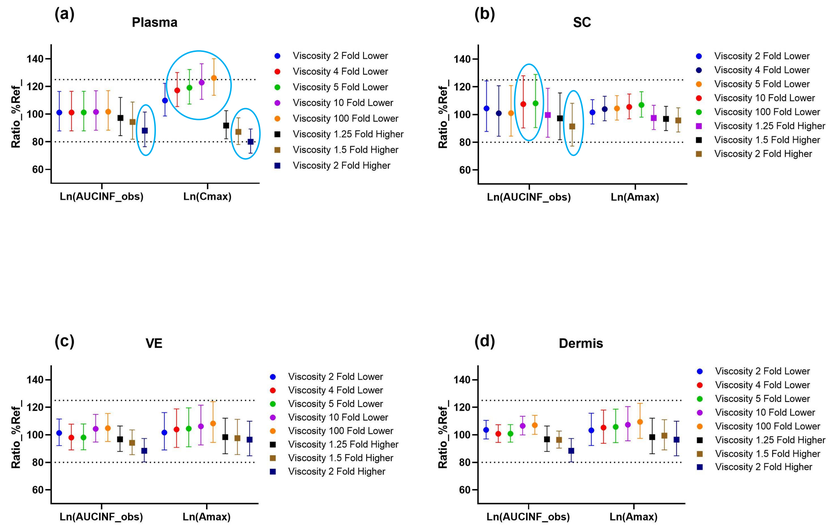


Figure 3: Mean ± 90% Confidence Interval (CI) (n= 50) percent ratio of test least square mean (LSM) to reference standard LSM values (Ratio_%Ref) PK parameter for (a) Plasma AUCINF, Cmax (mg/L) parameters; (b) SC AUCINF, Amax parameters; (c) VE AUCINF, Amax parameters and (d) Dermis AUCINF, Amax by varying apparent viscosity of generic formulation in BE testing. SC (Stratum Corneum), VE (Viable Epidermis), AUCINF (Area Under the Concentration versus time Curve extrapolated to infinity), Cmax (maximum plasma concentration), Amax (maximum amount)



CONCLUSIONS

Using the VBE module with metronidazole gel formulations as a case example, model capabilities in terms of simulating different BE trial design setups and accounting for WSV for crossover study designs has been shown. Here, the VBE module in the Simcyp Simulator/Phoenix was used to evaluate VBE between a reference standard and a generic product applied on the skin for relevant PK metrics in the plasma and various skin layers. In addition, changes in apparent viscosity, a CQA, was explored via simulation for its impact on systemic and local tissue exposure leading to BE failures. In addition, this module can be used understand the influence of CQAs on VBE outcomes which may be different across the skin layers and plasma as shown here. Coupled with PBPK modelling, this methodology can be used to identify a ‘safe space’ for CQAs.

REFERENCES

1. Arora, S., et al., Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model. Mol Pharm, 2022. https://doi.org/10.1021/acs.molpharmaceut.2c00229

2. Prasco Laboratories Prescribing Information, Metronidazole Topical Gel, 0.75%. 2019. DailyMed - METRONIDAZOLE TOPICAL GEL- metronidazole gel (nih.gov)

3. Bego, M., et al., Proof of Concept in Assignment of Within-Subject Variability During Virtual Bioequivalence Studies: Propagation of Intra-Subject Variation in Gastrointestinal Physiology Using Physiologically Based Pharmacokinetic Modeling. AAPS J, 2022. 24(1): p. 21.

This project was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award [FAIN] U01FD006522 totalling $250,000 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.