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Application of Physiologically Based Pharmacokinetic Modeling to Support Bioequivalence Evaluation of Mesalamine Delayed Release Tablets

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INTRODUCTION

The product-specific guidance for mesalamine delayed release (DR) tablet recommends a fasting pharmacokinetic (PK) bioequivalence (BE) study, and a fed PK BE study and comparative three-stage dissolution studies with stage 3 at four different pH (6.5, 6.8, 7.2, and 7.5). For this case example, dissolution studies showed differences between test and reference listed drug (RLD) with f2 less than 50 at pH 6.5 and 6.8 buffer conditions for stage 3 of dissolution testing. The purpose of this study is to use physiologically based pharmacokinetic (PBPK) modeling to evaluate the risk of bioinequivalence for the test product at the site of action.

METHOD

PBPK model using GastroPlus 9.8.2 (Simulations Plus, Inc., Lancaster, CA) was developed in house for Mesalamine DR tablet. Intravenous PK data obtained from the literature were used to estimate disposition parameters. Three-stage dissolution data with stage 1 in 0.1N HCl for 2 hours, stage 2 in pH 6.4 phosphate buffer for 1 hour and stage 3 in pH 7.2 (or pH 6.8, pH 6.9 or pH 7.0) phosphate buffer for 8 hours was incorporated to inform the absorption parameters. pH-dependent solubility data were incorporated in the model. The intestinal transit time was optimized to mimic most drug absorption in the colon and no drug absorption in stomach and early small intestine (duodenum and jejunum) since the formulation shows delayed pH-dependent drug release. The validated model was then used to evaluate whether the three-stage dissolution data with stage 3 at multiple pH is biopredictive. Population simulation was conducted to compare percentage of drug absorbed in the colon between test product and RLD to support BE assessment.

RESULTS

Dissolution profile at pH 6.8 for stage 3 was not biopredictive for the systemic exposure of test product with percent prediction error (PE%) for Cmax and AUC ≥30%. Dissolution profiles at pH 6.9, pH 7.0, and pH 7.2 (as stage 3) are biorelevant/biopredictive to the PK profiles with %PE < 22% (Table 1). The predicted amount of mesalamine in colon was found to be similar between RLD and test product at pH 6.9 and above as shown in Table 2. Further, model population simulations (n=25) showed that amount of drug in the colon is similar between RLD and test (Table 3).

PBPK modeling with integration of biopredictive dissolution for GI locally acting product

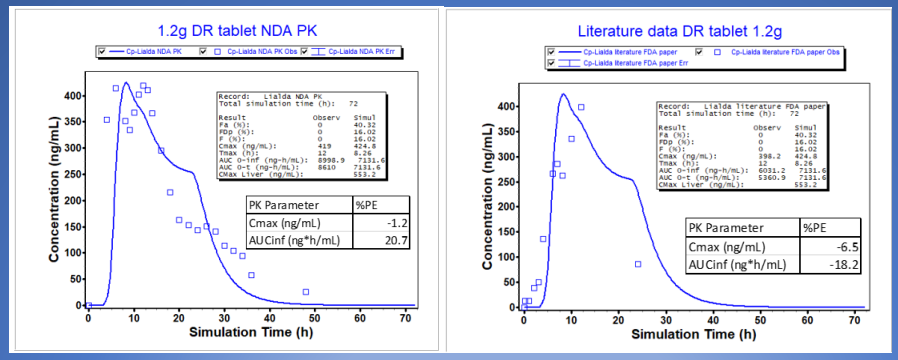

Fig 1. Model prediction versus observed PK data of RLD

	Percent Prediction Error			
PK Parameter	**stage 3 pH 6.8**	**stage 3 pH 6.9**	**stage 3 pH 7.0**	**stage 3 pH 7.2**
Cmax (ng/mL)	**34.5**	20.1	19.9	20.5
AUCinf (ng*h/mL)	**30.6**	17.6	12.7	11.3
AUCt (ng*h/mL)	**30.6**	17.6	12.7	11.3
AUC4-48 (ng*h/mL)	10.7	0.2	1.8	2.4

Table 1. Prediction error from incorporating stage 3 dissolution data at multiple pH conditions.

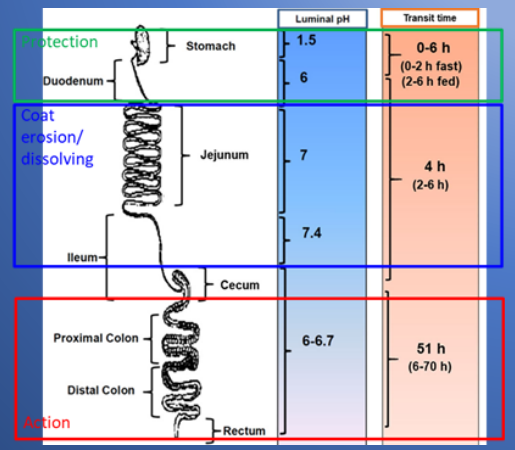

Fig 3. pH of GI tract and release mechanism of mesalamine DR tablets (*Hua et al. 2015*)

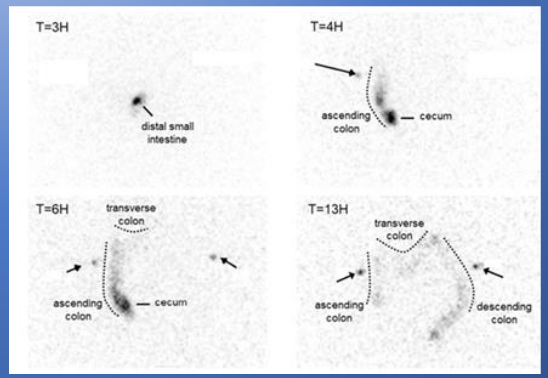

Fig 4. Gamma scintigraphy imaging of mesalamine DR tablet disintegration in GI tract (*Varum et al. 2022*)

Table 2. Predicted PK parameters Cmax (mg) and AUCt (mg*h) for amount of drug in colon from the single simulation results.

pH at Stage 3 Dissolution	PK Parameter	Predicted for Colon for RLD	Predicted for Colon for Test
7.2	Cmax (mg)	157.7	152.4
	AUCt (mg*h)	2592	2609
7	Cmax (mg)	156.6	153.6
	AUCt (mg*h)	2580	2567
6.9	Cmax (mg)	157	153.2
	AUCt (mg*h)	2521	2422

Table 3. Predicted percentage of drug absorbed in the colon based on population simulations (n=25)

Stage 3 pH	T/R Ratio	90% CI lower	90% CI upper
pH 7.2	99.71	99.21	100.20
pH 7.0	101.58	98.06	105.10

Mesalamine DR tablet will start the erosion of enteric coating and release of mesalamine in the ileum (pH is about 7.4) and continued release and absorption in the colon (pH is about 6-6.7) as seen in Figures 3 and 4. Drug release from the tablet core is not expected to be different between R and T at pH 6.8 based on the release mechanism, which is consistent with PBPK modeling results that the dissolution at pH 6.8 for stage 3 did not predict well of the in vivo PK.

CONCLUSION

PBPK modeling results were used to conclude that the risk of bioinequivalence at site of action (colon) is low for the test product compared to RLD. PBPK modeling supported that:

- By incorporating the biopredictive dissolution data with stage 3 at pH 6.9 and above, the PBPK predicted that the local amount of mesalamine in colon is similar between test product and RLD.
- Population simulations showed that the percentage of drug absorbed in the colon is similar between the RLD and test product with the 90% CI of the T/R ratio falling within 80-125%.

Disclaimer: This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

References:

1. Hua et al. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue Nanomedicine: Nanotechnology, Biology, and Medicine. 2015;11:1117–32.
2. Varum F et al. Targeted colonic release formulations of mesalazine – A clinical pharmaco-scintigraphic proof-of-concept study in healthy subjects and patients with mildly active ulcerative colitis. Int J Pharm. 2022; 625:122055.