Assessment of In Vivo Bioperformance of Enalapril Maleate in Co-Renitec Tablets Manufactured at Two Facilities via Deconvolution Analysis and PBBM

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Abstract

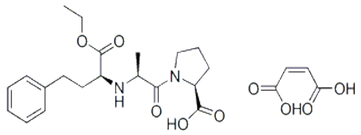
Co-Renitec is a fixed-dose combination of enalapril maleate and hydrochlorothiazide. To support a sourcing change from Merck manufacturing site A to site B, dissolution profiles were generated on batches of product from both sites. Dissolution comparison of 20 mg/12.5 mg tablets manufactured at these 2 sites was performed using USP2 apparatus at 50 rpm in 900 mL water. A slower dissolution of the formulations from site B was observed for enalapril maleate, resulting in F2 failure in 3 versus 3 batches comparison between the formulations of these 2 sites.

To explore the clinical relevance of this observation, the absorption of enalapril was characterized based on data from a definite bioavailability study, using both Physiologically Based Biopharmaceutics Modeling (PBBM) and a "rate of absorption" analysis. Physiologically-based absorption models of enalapril were established in GastroPlus using available clinical data. The deconvolution approach analyzing the rate of dissolution and absorption were explored, which required fewer model assumptions than PBBM.

Based on the M&S results from both PBBM and deconvolution analysis, any minor dissolution differences at earlier timepoints (eg, 15 min) are not considered of physiological relevance. Since the dissolution of batches from both manufacturing sites are complete within 30 min, a clinical bioequivalence study is not deemed necessary.

BACKGROUND

- Enalapril maleate physicochemical properties
  - CLogP: 2.45 (Enalapril) (Loftsson et al., 2010)
  - pKa: 3.0 and 5.4 (NDA package)
- pH-solubility profile: >25 mg/mL across physiological pH
- Dose: 5 mg, 10 mg, 20 mg, and 40 mg
- Oral absorption of the drug: 59~73% according to Vasotec NDA package, with an average of 64% from 5~40 mg oral doses
- Based on the estimation of fraction absorbed, enalapril maleate can be classified as a BCS III compound – human Jejunal Permeability: 1.57×10^{-4} cm/s (Lennernas et al., 2007)



MW: 376.447 (Enalapril)

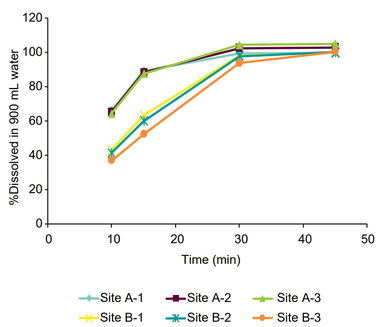
PROBLEM STATEMENT AND OPTIONS

- Co-Renitec (VASORETIC) is a fixed-dose combination of enalapril maleate and hydrochlorothiazide
- As part of the overall manufacturing strategy, Merck had proposed to switch the manufacturing of Co-Renitec formulations from site A to site B, to supply the market of geographic location of site A
- Dissolution comparison of 20 mg/12.5 mg tablets manufactured at these 2 commercial sites was performed (USP2, 50 rpm, 900 mL water)
- Slow down of dissolution of the formulations from site B was observed for enalapril maleate, resulting in failure of F2 in a comparison of 3 versus 3 batches
- IVIVC was not established previously

Options to support filing of this manufacturing site change:

- Run a clinical **bioequivalence study**
- Generate a **biopharm impact report** that the differences in the disso profile are not expected to impact bioavailability including a **M&S analysis** in the report

Dissolution of Enalapril Maleate for 20 mg/12.5 mg Co-Renitec Tablets



Note: F2 values of 34, 32, 28, 36, 33, 29, 36, 34, 29 in 3 versus 3 batches comparison between the formulations of these two sites.

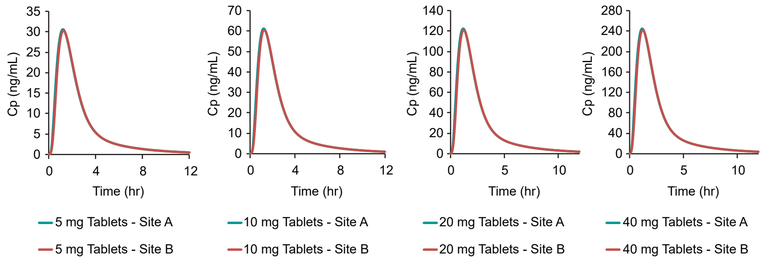
OPTION 1: PBBM ANALYSIS

- To use physiologically based absorption modeling on characterization of enalapril absorption based on the data from an absolute bioavailability study to provide evidence as related to the irrelevance of dissolution difference between batches on in vivo bioperformance of enalapril maleate
- Simulations were conducted in GastroPlus v8.5
- Dissolution settings: Apply average of in vitro dissolution profiles of site A and site B batches into the models for each dose
- FPE (First pass extraction): The difference of oral and IV bioconversion of MK-0421 (18%) was believed to be the first pass effect (Irvin et al., 1984). The oral absorption of the drug was determined as ~64% (average of %Fa from 5 ~40 mg doses). Therefore the FPE was set as 28% in the model (0.18/0.64)
- The **regional absorption settings** (ASF) in PBBM:
  - Enalapril maleate is believed to be a substrate of oligopeptide substrate (eg, PepT1/SLC15A1) and the expression of SLC15A1 is believed to be regional dependent, with significantly lower mRNA expression in lower gut (ie. colon) (Englund et al., 2006; Meier et al., 2007)
  - Baseline model – assuming regional absorption from duodenum and jejunum and low to no absorption in rest of the regions
  - Other regional absorption models also explored in PBBM (data not shown)

PBBM RESULTS

Calculated pharmacokinetics parameters (left) and simulated PK profiles (right) of enalapril after 5 mg, 10 mg, 20 mg, and 40 mg oral dosage of enalapril maleate via PBBM

	Predicted $AUC_{0\text{-}12hr}$ (ng hr/mL)	Predicted C_{max} (ng/mL)	AUC Ratio (Site B/Site A)	C_{max} Ratio (Site B/Site A)
Site A (5 mg)	77.9	30.6	/	/
Site B (5 mg)	76.3	30.3	0.98	0.99
Site A (10 mg)	156	61.2	/	/
Site B (10 mg)	152	60.5	0.97	0.99
Site A (20 mg)	312	122	/	/
Site B (20 mg)	305	121	0.98	0.99
Site A (40 mg)	623	245	/	/
Site B (40 mg)	610	242	0.98	0.99



- Based on the PBBM results, **comparable exposure** (less than 5% difference in exposure) is expected for batches from both sites at 5 mg ~ 40 mg doses
- However, a couple of key assumptions have to be taken to establish the current model, which could potentially impact the argument with agency using PBBM approach:
  - There is no means to validate the predictions of the model (ie, an external validation that would be required for an IVIVC) for a slow batch as these data do not exist
  - In order to fit the available clinical oral PK data, the models explored in the report had to assume a different combination of regional absorption scenarios with low permeability values in ileum with no means to verify or defend the regional absorption model
- "Fewer" assumptions are better for regulatory argument – which leads to **Option 2**

OPTION 2: "RATE OF ABSORPTION" APPROACH

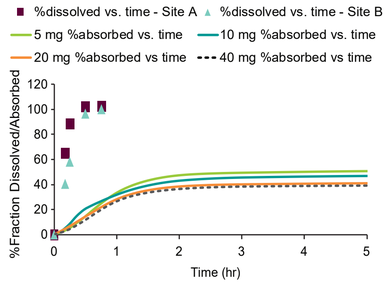
- A deconvolution approach analyzing the **rate of absorption and dissolution**
- The PK data of enalapril (MK-421) for individual subjects after 5 mg IV dose of enalapril maleate or 5 mg, 10 mg, 20 mg, and 40 mg oral doses of enalapril maleate tablets were obtained and calculated from the absolute bioavailability study. A first-order 2-compartment PK model was used to describe the PK profiles following IV administration of 5 mg enalapril maleate
- From that the unit impulse response (UIR) functions were calculated for all subjects. Macro PK constants (A, B, α, β) were calculated and PK profiles of enalapril (MK-421) for individual subjects after 5 mg IV dose of enalapril maleate were fitted
- Cumulative %fraction inputs of enalapril as a function of time were estimated using deconvolution for individual subjects. The average cumulative inputs of enalapril as a function of time were calculated from the data from individual subjects at different doses (5 mg, 10 mg, 20 mg, and 40 mg)
- All deconvolution were conducted in Phoenix WinNonlin v6.3

DECONVOLUTION ANALYSIS RESULTS

Calculated pharmacokinetics macro constant (UIRs) of enalapril for individual subjects after 5 mg intravenous dose of enalapril maleate using a first-order 2-compartment PK model

Subject ID	A (ng/mL)	A_CV%	Alpha (1/hr)	Alpha_CV%	B (ng/mL)	B_CV%	Beta (1/hr)	Beta_CV%
1	256.51	37.27	2.04	24.42	6.91	63.1	0.14	56.22
2	261.78	21.88	2.07	19.67	18.72	53.3	0.4	21.33
3	303.53	56.52	2.57	48.68	24.39	58.3	0.26	28.79
4	144.48	61.56	2.17	64.35	35.58	69.04	0.64	13.31
5	173.44	32.98	1.81	19.24	2.17	66.64	0.11	73.07
6	586.31	137.81	7.53	72.11	42.64	35.29	0.5	11.27
7	632.66	127.59	5.02	86.6	76.73	43.6	0.59	11.19
8	257.08	14.41	1.72	8.98	4.11	29.32	0.11	33.23
9	298.2	37.99	1.82	26.01	11.22	70.75	0.28	30.23
10	205.76	27.03	1.57	19.42	5.31	55.35	0.09	73.99

Overlay of average deconvolution output (percent in vivo absorption versus time) at 5 mg, 10 mg, 20 mg, and 40 mg oral doses with in vitro dissolution profiles of enalapril for site A and site B formulation batches



- For all studied enalapril doses, the absorption followed typical approximately first order kinetics, and the calculated in vivo absorption reaches a plateau around 2~3 hours post dosing, which is in line with the BCS III classification of the compound (based on 60%~70% fraction absorbed)
- The timeframe of absorption is much longer than the observed dissolution time in simple aqueous media where complete dissolution is achieved within 30 min for all batches tested
- Therefore any differences in dissolution within that timeframe between different batches are not expected to have an impact on pharmacokinetics

CONCLUSIONS

- To explore the clinical relevance of dissolution slow-down for formulation from manufacturing site A to site B, the absorption of enalapril was characterized based on data from a definite bioavailability study, using both PBBM and deconvolution based analysis assuming 1:1 translation of in vitro to in vivo dissolution
- Based on the M&S results from both models, any minor dissolution differences at earlier timepoints (eg, 15 min) are not considered of physiological relevance
- Since the dissolution of batches from both manufacturing sites are complete within 30 min, a clinical bioequivalence study is not deemed necessary

Acknowledgment

The author would like to acknowledge Henry Wu, David Storey, and the Co-Renitec RA CMC team for their contributions and helpful discussions of this project.

Presented at the 4th FDA/PQRI Conference on Advancing Product Quality; Rockville, MD, USA; April 9-11, 2019.