Physiologically Based Pharmacokinetic Absorption Modeling to Support Bioequivalence Assessment for BCS Class III Drug Products

2024 Simulations Plus Webinar

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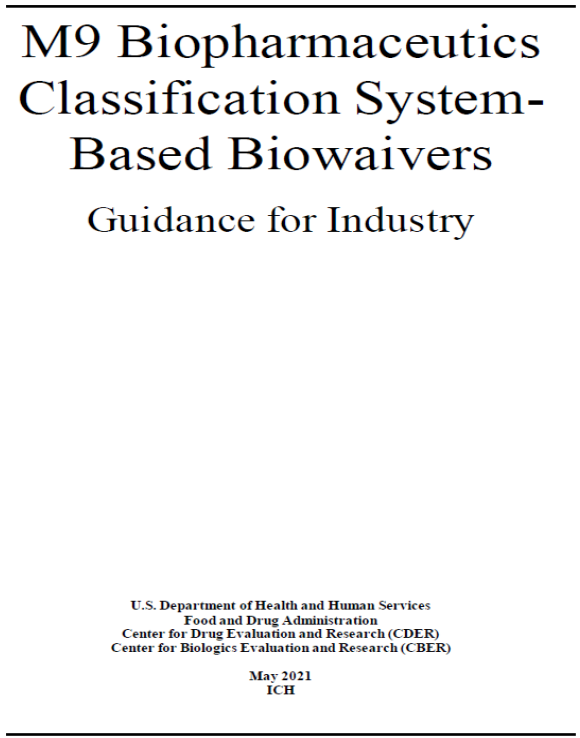
Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Guidance for BCS-based Biowaivers

For BCS Class III drug products, the following should be demonstrated:

- The drug substance is highly soluble
- The drug product (test and reference) is very rapidly dissolving (≥85% for the mean percent dissolved in ≤15 minutes)
- All of the excipients should be qualitatively (Q1) the same and quantitatively (Q2) similar.


M9 Biopharmaceutics Classification System-Based Biowaivers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH

Link: M9 Biopharmaceutics Classification System-Based Biowaivers | FDA

BCS: Biopharmaceutics Classification System

Product-Specific Guidance (PSG)

- Drug is classified and eligible
  - Agency generally recommends BCS-based biowaiver as one option for BE demonstration in PSG
- Drug is not classified or ineligible
  - BCS-based biowaiver option is not in the PSG
  - Many immediate-release (IR) drugs with high solubility are potentially eligible for BCS-based biowaiver (I or III) with **sufficient supportive data**

BE: bioequivalence

Biowaiver for BCS Class 3 Generic Drugs

PSG for Oseltamivir Phosphate Oral Capsule

I. BCS Class III-based biowaiver option

- "A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution, and the test product formulation is qualitatively the same and quantitatively similar"

In December 2009, FDA issued a draft product-specific guidance for industry on oseltamivir phosphate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient:	Oseltamivir phosphate
Dosage Form; Route:	Capsule; oral
Recommended Studies:	Two options: (1) Biopharmaceutics Classification System (BCS)-based biowaiver or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints

I. Option 1: BCS Class III-based biowaiver

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, very rapid dissolution, and the test product formulation is qualitatively the same and quantitatively similar as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[a] is submitted in the application. A decision

PSG: Product-Specific Guidance

Link: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021087.pdf.

Case Example 1: PBPK Modeling to Support Expanding BCS Based Waiver to Non-Q1/Q2 Drug Product

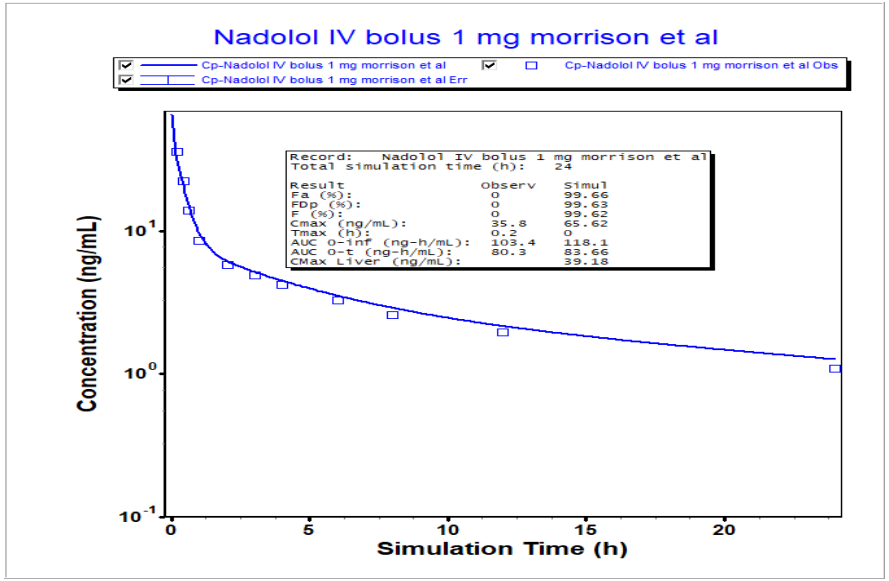
Background for nadolol oral tablets

- Nonselective β-blocker and approved for managing hypertension and angina
- PSG recommends fasting and fed PK BE studies

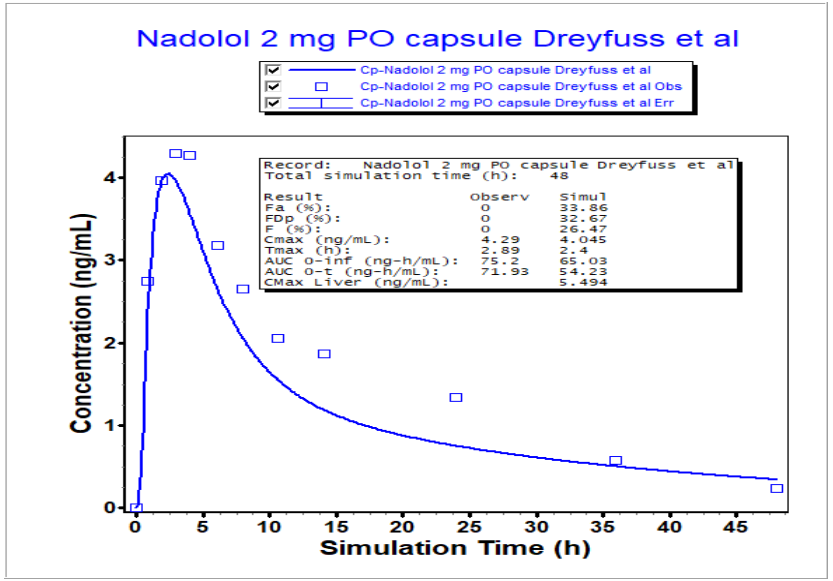
Research Question: Can PBPK modeling support expanding BCS-based biowaiver to non-Q1/Q2 drug products?

PBPK: Physiologically Based Pharmacokinetic; PK: Pharmacokinetics; BE: Bioequivalence
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Nadolol_tab_18063_RC5-09.pdf

Development of Nadolol PBPK Model (Fasted State)

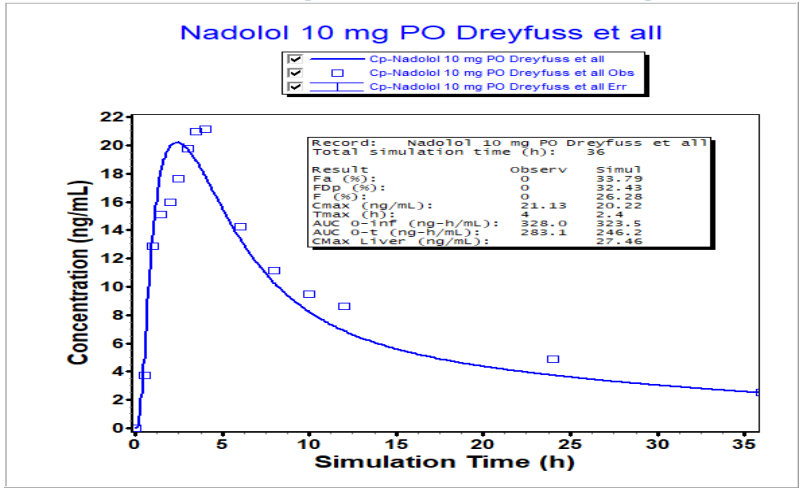


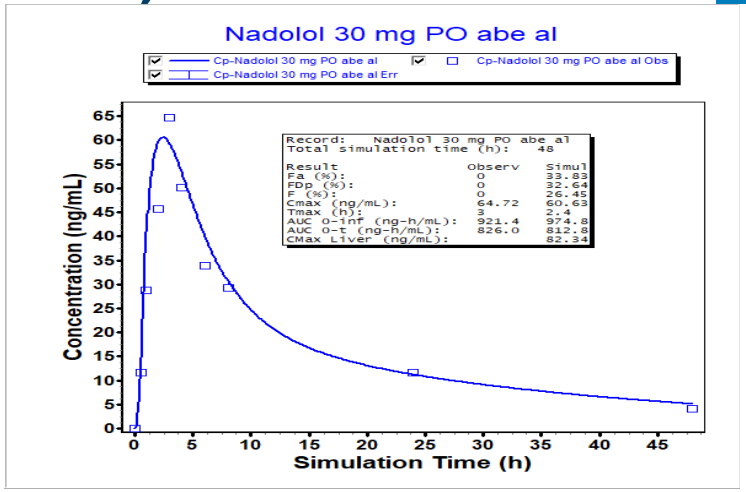
Morrison et al. Eur J Clin Pharmacol,1988



Dreyfuss et al. J Clin Pharm, 1979

Validation of Nadolol Oral PBPK Model
10 mg and 30 mg Oral Tablets, Fasted State





	Observed	Predicted	%PE
C_{max} (ng/ml)	21.13	20.22	-4.3
AUC_{0-t} (ng-h/ml)	283.1	246.2	-13.0
AUC_{0-inf} (ng-h/ml)	328.0	323.5	-1.4

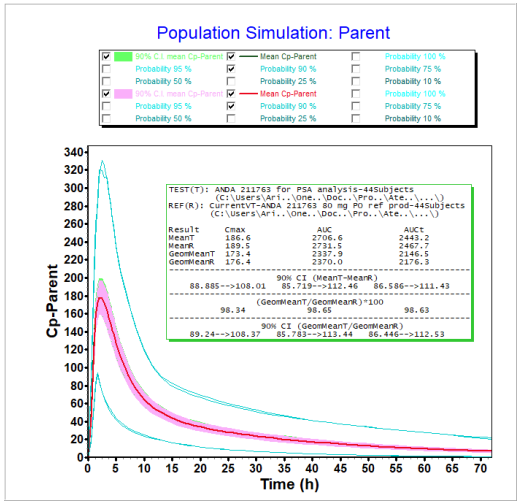
Dreyfuss et al. J Clin Pharm, 1979

	Observed	Predicted	%PE
C_{max} (ng/ml)	64.72	60.63	-6.3
AUC_{0-t} (ng-h/ml)	826.0	812.8	-1.6
AUC_{0-inf} (ng-h/ml)	921.4	974.8	5.8

Abe et al. Eur J Clin Pharmacol, 2018

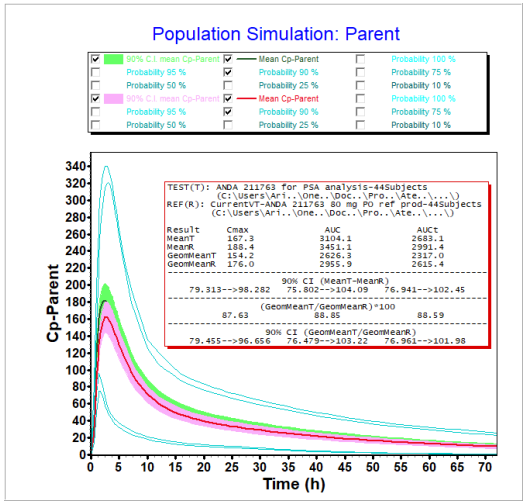
Model Application: Fasted state
Effect of Z-factor on VBE of Nadolol and Safe Space

Reference VS Test
(about 10% Decreased Z-factor)

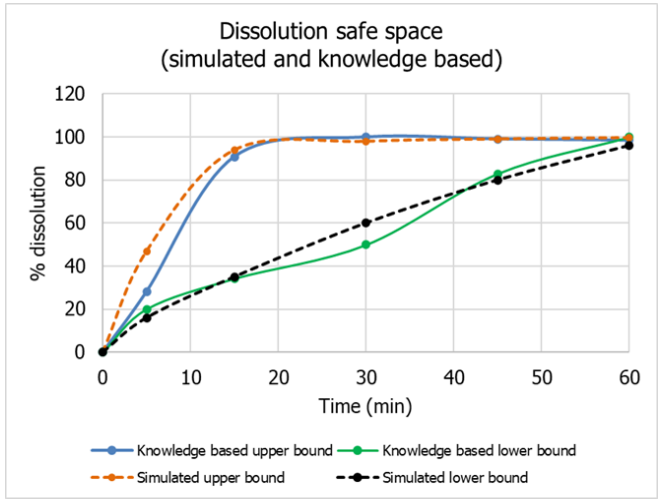


BE Scenario

Reference VS Test
(about 60% decreased Z-factor)



Non-BE Scenario

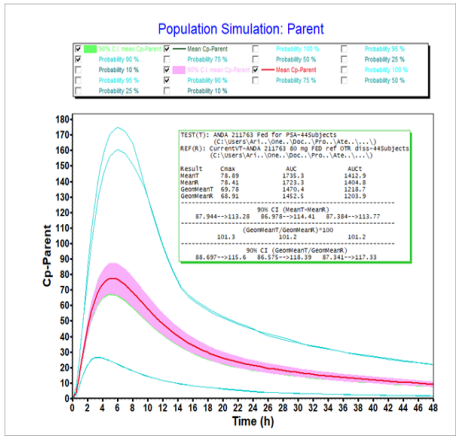


Dissolution safe space

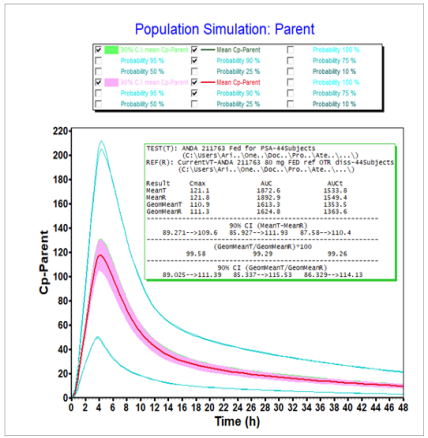
VBE: Virtual Bioequivalence

Model Application: Fed state
Effect of Z-factor on VBE of Nadolol and Safe Space

Reference VS Test
(10% Decreased Z-factor)

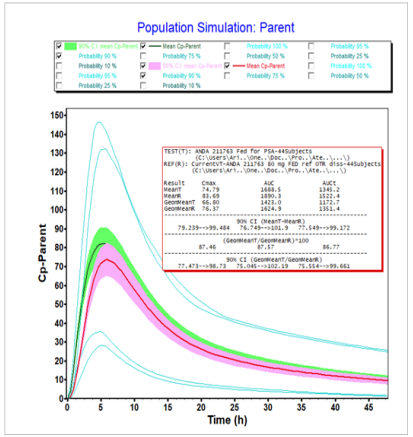


Reference VS Test
(60% decreased Z-factor)

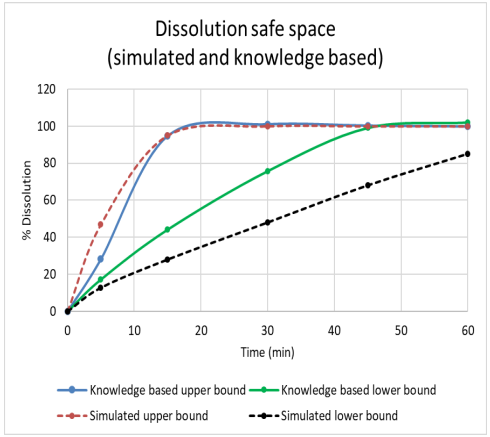


BE Scenarios

Reference VS Test
(85% decreased Z-factor)



Non-BE Scenario



Dissolution safe space

Summary

- Nadolol generic drug products, which are NOT Q1 the same/ Q2 similar and not very rapidly dissolved, don't qualify for BCS-based waiver per ICH M9 guidance.
- Nadolol PBPK model under fasting and fed condition has been developed and validated.
- Parameter Sensitivity Analysis (PSA) showed that the PBPK model under fasted condition is sensitive enough to discriminate dissolution differences.
- With VBE simulations, we established dissolution safe space and demonstrated that the product with dissolution falling in safe space are of low risk for non-BE under fasting and fed conditions.
- This exercise could help expanding biowaiver options for non Q1 / Q2 and non-very rapidly dissolved BCS III drug products.

Case Example 2: Support BCS Waiver for BCS Class III Drugs with Degradation

- Cladribine tablets is considered as BCS III drug per European Public Assessment Report: Mavenclad. European Medicines Agency; 2017
- Degradation of the drug substance in acidic environments observed in *in vitro* studies
  - Significant degradation (>10%) can be concerning per M9 guidance
- Question: Is BCS-based waiver option applicable for cladribine tablets?
  - Use PBPK model to evaluate whether BCS waiver is applicable for cladribine tablets with degradation

Development of Cladribine PBPK Disposition Model

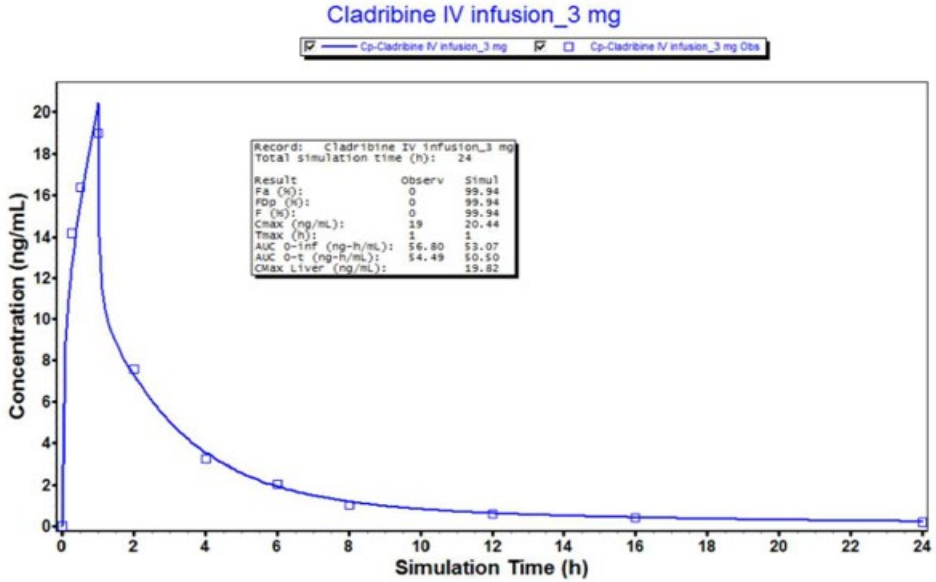
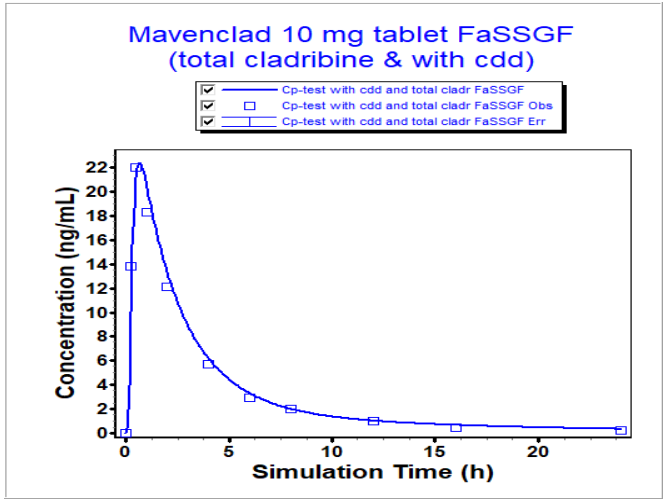


Figure. Observed vs predicted plasma concentration profile of cladribine after intravenous (IV) infusion (3 mg)

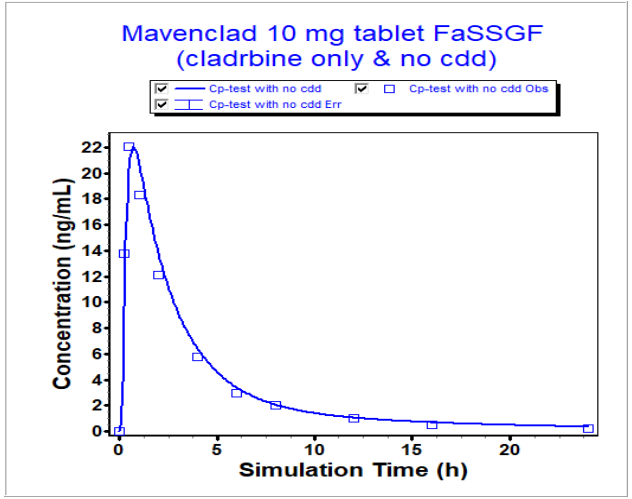
- IV data from literature (Hermann R et al. Clinical Pharmacokinetics, 2019) was used to obtain disposition parameters

Development of Cladribine PBPK Absorption Model

A



B

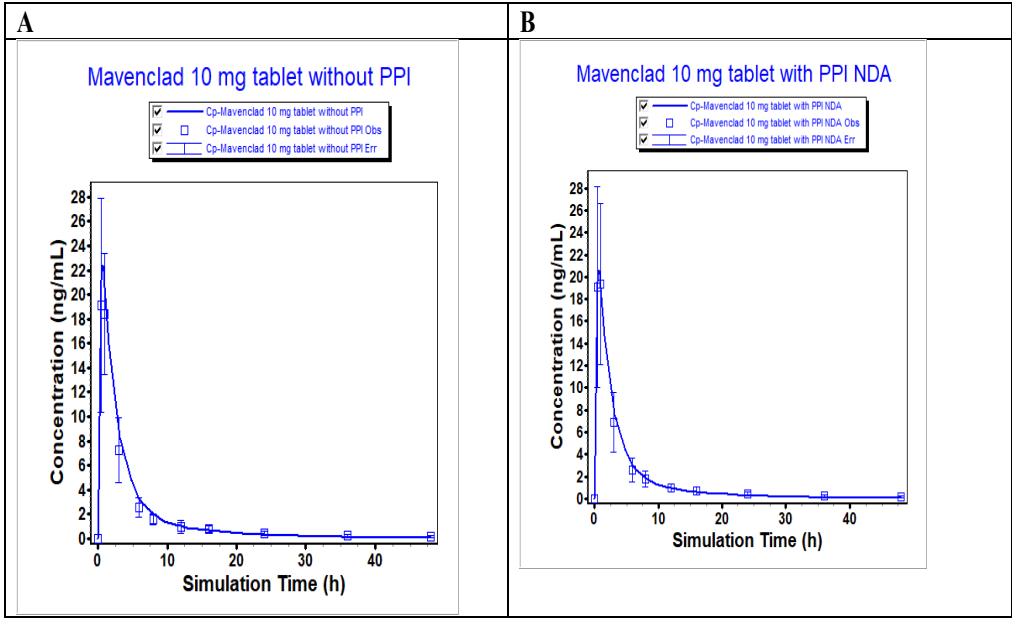


- A) Degradation data (.cdd file) as model input to account for cladribine degradation in the model was considered necessary when total cladribine In vitro dissolution (IVD) data in FaSSGF media. B) Using cladribine only IVD data in FaSSGF media as input without degradation data as .cdd file also predicted well
- IVD data using FaSSGF medium is biopredictive for fasted conditions

FaSSGF: Fasted State Simulated Gastric Fluid; Observed PK data was obtained from reference: Hermann R et al. The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. Clinical Pharmacokinetics (2019) 58:283–297.

Model Validation- with or without PPI

- The model replicated the results from in vivo findings that evaluated the differences between cladribine PK profile without and with PPI.
- Degradation at lower pH does not have significant impact on PK for both RLD and test products as evidenced by the similar PK in the absence and presence of PPI.

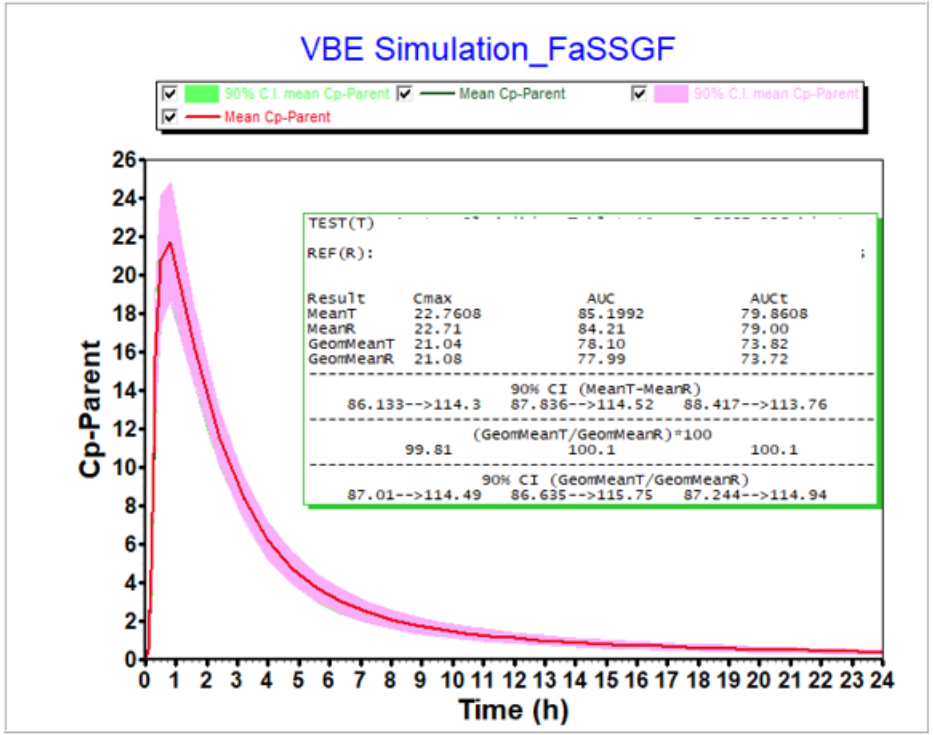


Observed PK data was obtained from reference: Hermann R et al. The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. Clinical Pharmacokinetics (2019) 58:283–297.

PPI: proton pump inhibitor

Model Application: VBE Using Dissolution in FaSSGF Medium

- Figure shows VBE simulation for cladribine 10 mg tablet comparing RLD and test cladribine 10 mg tablets under fasting conditions.
- The model demonstrated BE for RLD and test cladribine 10 mg tablets using degradation data (%degradation/hr at acidic condition) and biopredictive total cladribine dissolution data (in FaSSGF media). The impact of degradation is similar on RLD and test product.



Summary

- A PBPK model was developed to assess the impact of cladribine degradation under acidic conditions on BE by incorporating biopredictive dissolution data as direct model input.
- The model was able to predict the result from in vivo BA study that evaluated the impact of gastric pH changes on cladribine PK after the administration of PPI (i.e., pantoprazole).
- This model was then used to demonstrate that cladribine degradation in acidic conditions with similar rate between generic product and RLD does not impact BE of generic cladribine 10 mg tablet to RLD.
- PSG for cladribine oral tablets is updated to include a BCS Class III-based biowaiver option.

Challenges and Future Directions

Challenges:

- Appropriate in vitro testing and data input into PBPK model
  - Incorporating biopredictive dissolution data into PBPK model
- Availability of relevant PK data for model validation

Future directions:

- Internal and external collaborative effort to generate/obtain in vitro data, and biopredictive dissolution data for appropriate model input
- Extend currently validated approaches/ models for additional case scenarios and to establish a validated workflow for such cases

Conclusions

- Refer to the ICH M9 Guidance on BCS-based biowaiver to assess if the drug may be eligible for BCS class III biowaiver
- BCS class III biowaiver may be applicable with sufficient supportive data even though the current PSG does not include this option
- PBPK can support using BCS class III waiver as an alternative BE approach for IR products such as:
  - expanding biowaiver options for non Q1 / Q2 and non-rapidly dissolved BCS III drug products.
  - BCS class III drugs with degradation

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