Addressing Degradation Challenges in BCS Class III Biowaiver Applications Through PBPK Modeling (Part II)

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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.

Learning Objectives

- Present a case study of Cladribine Tablets with acid instability challenges
- Understand OGD's BE evaluation based on the totality of evidence for the Cladribine Tablets case study
- Understand the role of PBPK modeling in regulatory decision making for the approval of Cladribine Tablet

BE: bioequivalence; PBPK: physiologically-based pharmacokinetics

PBPK Supports 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
- Per Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021). Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m9-biopharmaceutics-classification-system-based-biowaivers
  - "In cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined"
  - "Significant degradation (>10%) of a drug precludes BCS high permeability classification"
  - So, it is challenging to determine whether this product is eligible for BCS-based biowaiver

PBPK Supports BCS Waiver for BCS Class III Drugs with Degradation

Question: How was the BCS-based waiver option included in revised PSG for cladribine tablets in August 2024?

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,[a] 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*[b] is submitted in the application. A decision regarding the acceptability of the waiver request can only be made upon assessment of the data submitted in the application.

II. **Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints**

Reference: Revised PSG for Cladribine Tablet. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022561.pdf

PBPK model was used to support that a BCS waiver is applicable for cladribine tablets despite degradation

Background Information Regarding Degradation

- **pH solubility data** showed significant degradation (>10%) of the drug substance in acid buffers.
- **Dissolution data**
  - Very rapid dissolution (i.e., >85% dissolved within the first 15 minutes) at pH 4.5 and pH 6.8.
  - However, at 0.1N HCl dissolved <85% of labeled amount within the first 15 minutes and decreasing amounts of the observed percent (%dissolved) were found at later time points in acidic medium (including 0.1N HCl at pH1.2 and FaSSGF medium at pH 1.6) for cladribine only (not total cladribine).

Risk Assessment Approach

- Literature evidence from in vivo studies assessing the impact of gastric pH change (i.e., PPI coadministration) on the rate and extent of absorption of cladribine.
- Comparison of cladribine degradation (extent and rate) between generic cladribine 10 mg tablet and Mavenclad 10 mg tablet across the physiologically relevant acidic pH range.
- Physiologically based pharmacokinetic modeling to assess the impact of drug degradation on in vivo performance of the drug product.

Development of Cladribine PBPK Disposition Model

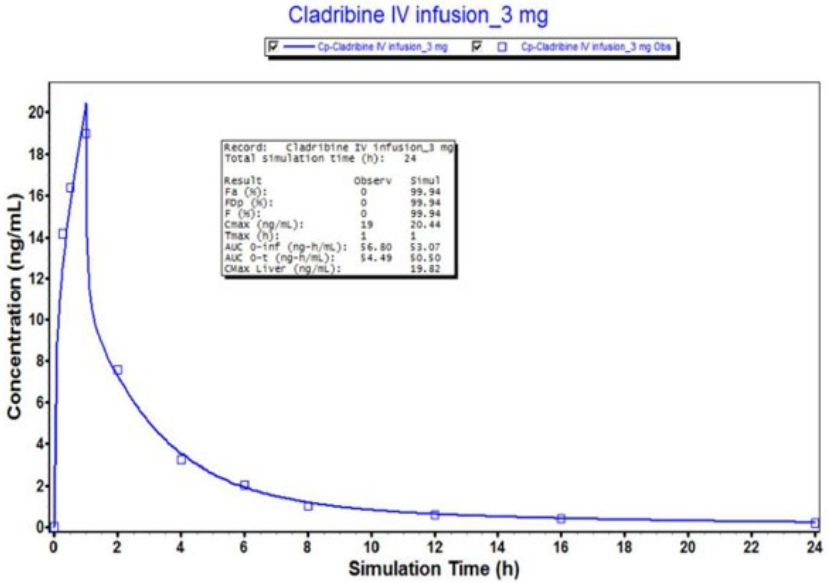
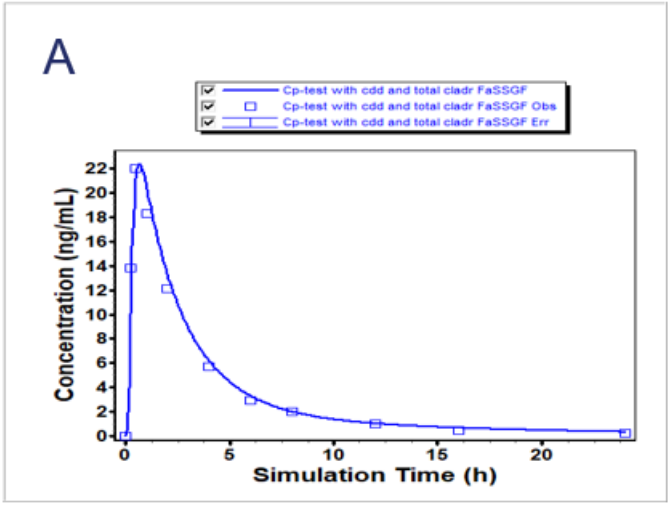
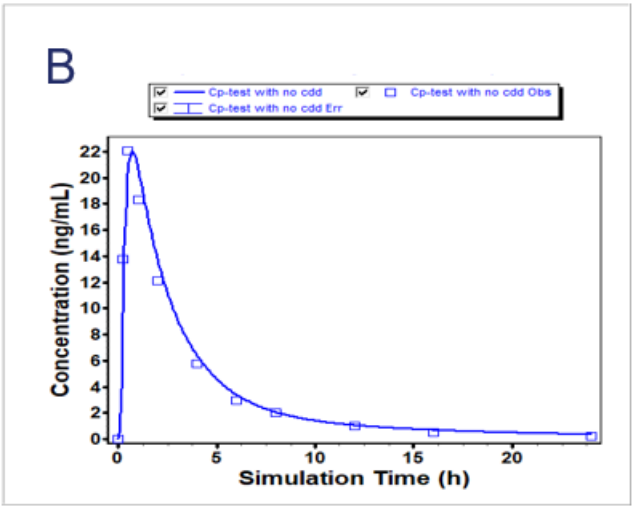


Figure. Observed vs predicted plasma concentration profile of cladribine after intravenous (IV) infusion (3 mg)

- IV data from literature (Hermann R et al. The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. Clinical Pharmacokinetics (2019) 58:283–297) was used to obtain disposition parameters.

Development of Cladribine PBPK Absorption Model



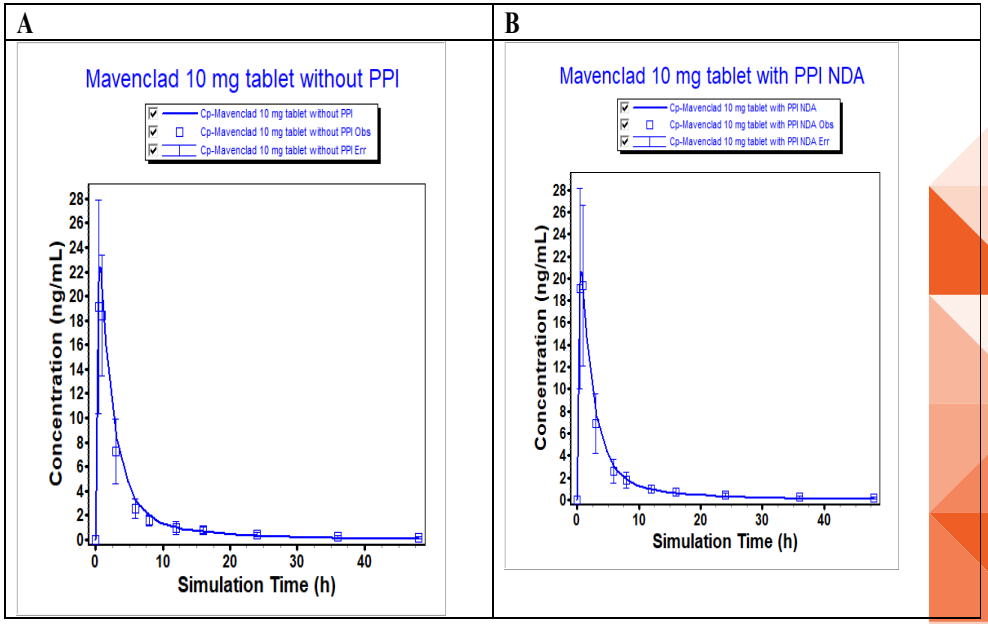


- A) Degradation data as model input to account for cladribine degradation in the model was needed when total cladribine In vitro dissolution (IVD) data in FaSSGF media were used as model inputs. B) Using cladribine only IVD data in FaSSGF media as input without degradation data also predicted well
- 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.

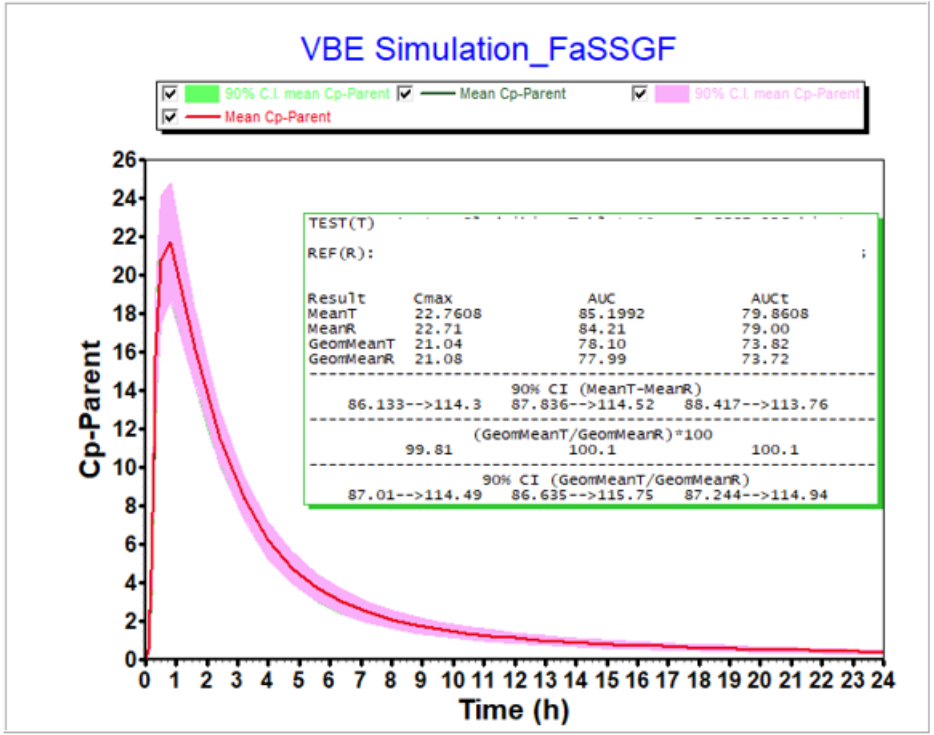


Observed PK data was obtained from reference: Hermann R et al. The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. Clinical Pharmacokinetics (2019) 58:283–297.

PPI: proton pump inhibitor

Model Application: VBE Using Dissolution in FaSSGF Medium

- VBE simulation was conducted comparing RLD and test cladribine 10 mg tablets under fasting conditions.
- The simulation 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 was updated to include a BCS Class III-based biowaiver option.

Revised PSG for Cladribine Tablet. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022561.pdf

Challenge Question

For cladribine case, what dissolution profiles could be incorporated into PBPK modeling to better predict the impact of cladribine degradation on BE:

A. Total cladribine in vitro dissolution data in FaSSGF media together with degradation data to account for cladribine degradation.

B. Using cladribine only in vitro dissolution data in FaSSGF media as input without degradation data

C. In vitro dissolution data using FaSSGF medium

D. All of the above

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Questions?

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