Exploring Capecitabine: A Key Drug in Cancer Therapy

Assessing Capecitabine's Pharmocokinetic Variability in Breast Cancer and Colorectal Cancer Patients

Type of Study

An open-label, multicenter, randomized, two-treatment, two-sequence, four-period, single-dose, full-replicate crossover bioequivalence study. It compares the sponsor’s Capecitabine 500 mg oral suspension (50 mg/mL) with the reference product, XELODA® 500 mg tablets, in adult cancer patients (colorectal and breast) under fed conditions (standardized light meal).

Objective

To evaluate the bioequivalence of the sponsor’s Capecitabine 500 mg oral suspension (50 mg/mL) in comparison to XELODA® 500 mg tablets in adult cancer patients (colorectal and breast) under fed conditions.

To monitor the safety and tolerability profile of the study formulations.

Situational Analysis

A Chinese Pharmaceutical company wanted submit the bioequivalence data generated from this study to the relevant regulatory authorities as part of an ANDA application. The approval of this application would permit the marketing of the Capecitabine 500 mg oral suspension as a generic equivalent to XELODA®.

Molecule Overview

Capecitabine is an oral prodrug of 5-fluorouracil (5-FU), a widely used chemotherapeutic agent for treating breast and colorectal cancers. It is converted into 5-FU primarily within tumor tissues, enhancing its targeted effect. Capecitabine’s oral administration provides a convenient treatment option, and understanding its pharmacokinetics is vital for optimizing dosing strategies and reducing potential side effects.

Veeda supported the client in following services for the successful execution of the study

- Study Design & Execution
- Patient Recruitment & Retention
- Investigational Product Management (IMP)
- Investigational Product Administration
- Local Regulatory Applications
- Ethics Committee Dossiers Submissions
- PK and PD Blood Sample Management
- Recruitment and Retention
- Biostatistics & Data Management
- Medical & Protocol writing

Highlights of Results Delivered

To get **32** evaluable subjects **39** were enrolled in the study

A total of **21** blood samples were collected in each period

Study Submitted to **EU**

- Optimized recruitment strategy to fast-track progress within the initial **3-4 months.**
- Consistent patient follow-up resulted in a significantly reduced dropout rate of **4-5% versus the expected 10%.**

Safety Assessment parameters assessed throughout the study as below

- Subjects were monitored throughout the study to ensure safety and minimize the risk of adverse events (AEs)
- Safety assessments included Medical History, Vital Signs, Clinical Examinations, Clinical Laboratory Tests, Chest X-Ray, and 12-lead ECG
- Hematology: Monitoring of blood counts, including hemoglobin, white blood cells (WBC), and platelets, to detect potential myelosuppression or other blood-related issues
- Chemistry Panels: Assessment of liver function tests (e.g., AST, ALT, bilirubin) and renal function tests (e.g., creatinine, BUN) to evaluate potential hepatic or renal toxicity
- Electrolytes: Monitoring of electrolytes such as potassium, sodium, and calcium to identify any imbalances that could be related to Capecitabine treatment.

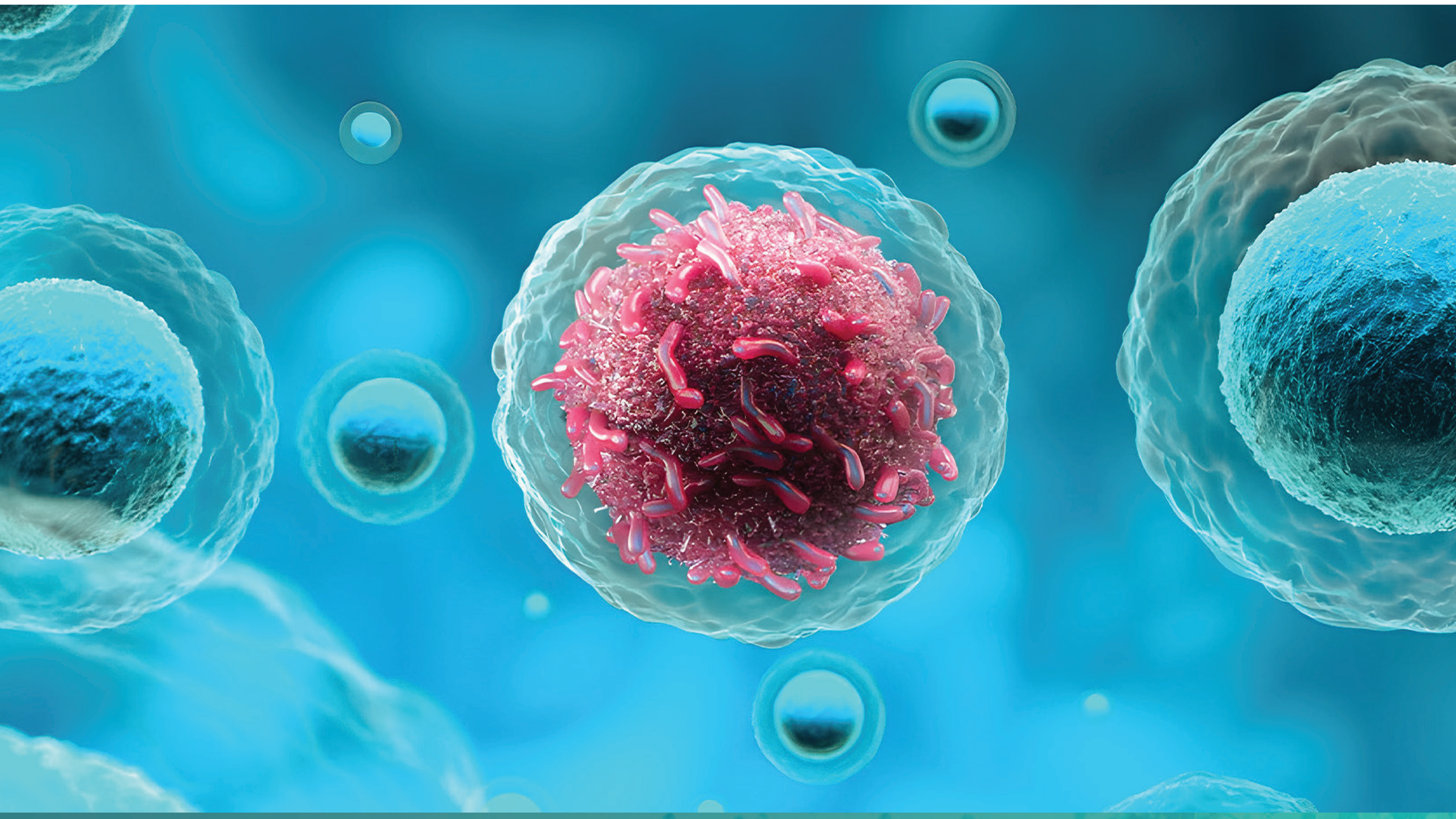
Major Study Challenges & Actions

Challenges	Action Plan
Inter-Patient Variability: Variability in pharmacokinetic parameters (e.g., Cmax, AUC) due to genetic factors, concurrent medications, or physiological differences affects drug efficacy & safety	• **Personalized Dosing Strategies**: Develop and implement individualized dosing based on pharmacokinetic profiles to optimize outcomes • **Comprehensive Data Collection**: Gather detailed patient history, medication use, and genetic information to better understand and mitigate variability
Adverse Effects Management: High plasma concentrations of Capecitabine can lead to adverse effects, such as gastrointestinal toxicity and hand-foot syndrome	• **Increased Monitoring**: Enhance monitoring frequency for gastrointestinal and dermatological symptoms and implement early intervention strategies • **Patient Education**: Educate patients on potential side effects and provide management strategies, including dietary modifications and skincare recommendations
Lack of Correlation with Clinical Outcomes: significant correlation found between pharmacokinetic parameters and tumor response rates, complicating links between pharmacokinetics and clinical efficacy	• **Investigate Other Biomarkers**: Explore additional biomarkers or clinical indicators for treatment response, such as tumor genetic profiles or circulating tumor DNA • **Comprehensive Data Collection**: Collect extensive clinical data, including imaging studies and patient-reported outcomes, for a complete picture of treatment efficacy
Data Quality and Management: Ensuring accurate data collection and management is challenging due to the complexity of pharmacokinetic studies	• **Standardized Procedures**: Develop & enforce standardized procedures for data collection, entry, and verification to ensure accuracy • **Training for Staff**: Provide thorough training on data collection and management procedures to minimize errors
Long-Term Follow-Up: Tracking long-term outcomes and delayed adverse effects post-study is challenging	• **Extended Follow-Up Plans**: Develop plans to monitor long-term outcomes and delayed adverse effects • **Regular Patient Contact**: Maintain contact with patients after the study to gather data on long-term health and late-emerging side effects

Conclusion

Capecitabine demonstrates a variable pharmacokinetic profile among patients with breast cancer & colorectal cancer. This variability necessitates personalized treatment approaches and careful monitoring to enhance efficacy and reduce toxicity. Future studies should focus on exploring genetic and physiological factors contributing to this variability and evaluating the potential benefits of dose adjustments based on pharmacokinetic data.

Our dedicated efforts in optimizing recruitment strategies and maintaining consistent patient follow-up proved instrumental in the success of this study. Our targeted efforts enhanced the study's robustness and it was successfully submitted to the USFDA.



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