



Development of an Oral Dosage Form of Azacitidine: Overcoming Challenges in Chemistry, Formulation, and Bioavailability.

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Blood 2006 108:4850;

Article

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Abstract

Azacitidine (Vidaza®), an epigenetic modifier which exerts its therapeutic effect through gene demethylation, is currently approved in a subcutaneous (sc) dosage form for the treatment of myelodysplastic syndromes (MDS). Low-dose, chronic demethylation may lead to improved antiproliferative activity while minimizing side effects. Such chronic demethylation would require a convenient, more frequent dosing schedule. It has, therefore, been an objective of Pharmion Corporation to develop an oral dosage form of azacitidine that could improve the safety and efficacy attributes of the parenterally administered formulation plus have desirable pharmacokinetic characteristics. Azacitidine presents several significant challenges with respect to oral administration including sub-optimal physiochemical characteristics, hydrolytic instability, and active enzymatic degradation – all non-conducive to high passive intestinal tract absorption. Moreover, the drug requires formulated tablet strengths accommodating widely flexible treatment regimens yet must be formulated to avoid the chemical and enzymatic degradation occurring presystemically. Additionally, nonclinical testing of azacitidine bioavailability is hampered by inappropriate animal models representing human gastrointestinal tracts conditions, low tolerability of the drug in several animal species, widely variable pharmacokinetic behavior, and lack of highly sensitive bioanalytical methods for measuring the drug. Data on orally administered azacitidine are sparse but hint at some degree of bioavailability in mice where multiple oral dosing with the drug resulted in lower LD50 values than multiple dosing by the intravenous route (data on file at Pharmion). A published report following long term oral dosing (0.2 mg/kg/day of azacitidine plus 200 mg tetrahydrouridine 3 days per week) in a patient with sickle cell disease resulted in significant increases in total and fetal hemoglobin suggesting absorption of the drug followed by systemic effects (Dover, 1985). A study recently conducted in dogs given azacitidine orally (6 mg/kg) compared to sc and iv (2 mg/kg) showed the drug was absorbed rapidly by the oral route (T_{max} , 15 min) with absolute bioavailability of 67% (compared to 71% following sc dosing). Additional *in vitro* and *ex vivo* characterization of azacitidine stability and permeability have been performed. Data from these studies have been utilized to develop a solid oral dosage form of azacitidine that will move forward into additional animal testing and clinical evaluation. Highly sensitive bioanalytical methods have also been developed for the quantitation of azacitidine in dog and human plasma. A single oral dose escalation study will be conducted in patients to assess the safety, tolerability, and pharmacokinetics of orally administered azacitidine. Data will be evaluated continuously during the dose escalation study. Information generated from these studies will be used to appropriately design a full oral azacitidine clinical development program.



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2006, The American Society of Hematology

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Guillermo Garcia-Manero et al., Blood, 2009

Extended Dosing of Oral Azacitidine (CC-486) for 14 and 21 Days Provides More Effective Methylation Reversal Than a 7-Day Schedule

Pharmacokinetics of DFN-15, a novel oral solution of celecoxib, versus celecoxib 400-mg capsules: A randomized crossover study
Pal A et al., MDLinx, 2017

ABT-538 is a potent inhibitor of human immunodeficiency virus (HIV) high oral bioavailability in humans.

D J Kempf et al., Proc Natl Acad Sci U S A, 1995

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Eric Laille et al., Blood, 2012

Phase I/II Study of MGCD0103, an Oral Isotype-Selective Histone Deacetylase (HDAC) Inhibitor, in Combination with 5-Azacitidine in Higher-Risk Myelodysplastic Syndrome (MDS) and Acute Myelogenous Leukemia (AML).
Guillermo Garcia-Manero et al., Blood, 2007

A Comparative Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of Azacitidine Following Subcutaneous (SC) and Oral Administration in Subjects with Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML), Results From a Phase 1 Study.
Kyle J MacBeth et al., Blood, 2009

Phase 1 Assessment of an Orally Bioavailable Formulation of Gallium Nitrate (G4544).
Thomas Julian et al., Blood, 2007

Quantitative Analysis of Tozadenant Using Liquid Chromatography-Mass Spectrometric Method in Rat Plasma and Its Human Pharmacokinetics Prediction Using Physiologically Based Pharmacokinetic Modeling
Lee et al., Molecules, 2019

Identification and Pharmacokinetic Studies on Complanatuside and Its Major Metabolites in Rats by UHPLC-Q-TOF-MS/MS and LC-MS/MS
Yao, Yu-Feng et al., Molecules, 2018

Development and Characterization of an Amorphous Solid Dispersion of Furosemide in the Form of a Sublingual Bioadhesive Film to Enhance Bioavailability

De Caro et al., Pharmaceutics, 2017

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