Document Description: Provisional Cover Sheet (SB16)

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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country i
Jeffrey	B	Etter	Boulder	CO	US

All Inventors Must Be Listed -- Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Title of Invention	ORAL AZACITIDINE AND EFFICACIOUS ESCALATED DOSAGE FORMS
Attorney Docket Number (if applicable)	298068-00042

Correspondence Address

Direct all correspondence to (select one):

(•) The address corresponding to Customer Number	( ) Firm or Individual Name
Customer Number	03705

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

(•) No.

( ) Yes, the name of the U.S. Government agency and the Government contract number are:

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Entity Status
Applicant claims small entity status under 37 CFR 1.27

○ Yes, applicant qualifies for small entity status under 37 CFR 1.27

◉ No

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Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature				Date (YYYY-MM-DD)	May 15, 2008
First Name	Patrick	Last Name	Higgins	Registration Number (If appropriate)	39709

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

A Phase 1, Open-label, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Oral Azacitidine in Subjects with Melodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML)

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ORAL AZACITIDINE AND EFFICACIOUS ESCALATED DOSAGE FORMS

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The present invention is drawn toward azacitidine compositions and dosage forms thereof for oral administration which, for example, yield continuous low-dose drug release profiles upon oral administration and thereby result in improved efficacy, safety, pharmacokinetics, and pharmacodynamics. Oral dosages described herein are administered, for example, for the treatment of myelodysplastic syndromes (MDS) or acute myelogenous leukemia (AML) conditions. Etter, J.B., U.S. Application Ser. No.11/849,958 in incorporated in its entirety by reference. See, for example, the primary examples, and formulation #1 described therein.

Oral azacitidine dosages (and methods of administration thereof and/or methods of treatment of at least one condition, including but not limited to MDS and AML) of the present invention may range, for example, between about 50 mg/m^2/day and about 2,000mg/m^2/day, between about 100 mg/m^2/day and about 1,000mg/m^2/day, between about 100 mg/m^2/day and about 500mg/m^2/day, between about 120 mg/m^2/day and about 250mg/m^2/day. Particular dosages, for example, are about 120 mg/m^2/day, about 140 mg/m^2/day, about 150 mg/m^2/day, about 180 mg/m^2/day, about 200 mg/m^2/day, about 220 mg/m^2/day, about 240 mg/m^2/day, about 250 mg/m^2/day, about 260 mg/m^2/day, about 280 mg/m^2/day, about 300 mg/m^2/day, about 320 mg/m^2/day, about 350 mg/m^2/day, about 380 mg/m^2/day, about 400 mg/m^2/day, about 450 mg/m^2/day, and about 500 mg/m^2/day.

A phase 1, open-label, dose-escalation study to evaluate the safety, pharmacokinetics, and pharmacodynamics of oral azacitidine in subjects with myelodysplastic syndromes (MDS) or acute myelogenous leukemia (AML) is described herein. Azacitidine, a cytidine analog, through its effects on DNA metabolism, gene expression, and cell differentiation, has proven beneficial in treatment of MDS and AML. Most notably, prolonged azacitidine therapy recently has been shown to approximately double 2-year survival in higher-risk MDS subjects compared to conventional care. Azacitidine is currently approved for intermittent subcutaneous (SC) and intravenous administration. Development of an oral formulation would provide more convenient dosing, eliminate injection-site reactions, and

allow evaluation of novel, continuous low-dose regimens that may sustain demethylation and improve efficacy. A proprietary formulation of oral azacitidine was shown to be absorbed in a pilot, single-dose study (ASCO 2007). *See*, e.g., U.S. Application Ser. No.11,849,958.

Multicenter, open-label, Phase 1, sequential design, dose-escalation study of oral azacitidine. The study is designed to evaluate the maximum tolerated dose (MTD), dose limiting toxicities (DLTs), safety, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of increasing doses of orally administered azacitidine in subjects with MDS or AML. Azacitidine was administered SC (75 mg/m2/day x 7 days) during cycle 1, then orally starting at 120 mg x 7 days/28 day cycle. Drug levels were measured in plasma and urine, and PD effects including global LINE methylation and gene-specific methylation were assayed.

Results

Currently, no toxicities have been observed in subjects who have completed both the SC and oral phases of the study at 120 mg The study continues at the 180 mg dose level. Preliminary PK analysis indicates detectable plasma levels at the 120 mg oral dose. A comparison of plasma PK profiles and PD effects of azacitidine administered at increasing oral doses compared to those of azacitidine administered SC at the approved dose of 75 mg/m2/day for all subjects evaluated to date.

Conclusions

Results of oral 5-azacitidine indicate that this formulation is orally bioavailable and safe in subjects with MDS, for example.

* * *

EXHIBIT I

Attached hereto, is an Example (image Poster), entitled **A Phase 1, Open-label, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Oral Azacitidine in Subjects with Melodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML)**, intended for presentation at ASCO 2008, on or about May 16, 2008.

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