This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2 SYNOPSIS

Title of Study:	A Pivotal Randomized Study of Lonafarnib (SCH 66336) Versus Placebo in the Treatment of Subjects With Myelodysplastic Syndrome (MDS) or Chronic Myelomonocytic Leukemia (CMML) Who Are Platelet Transfusion Dependent With or Without Anemia (Protocol No. P02978)	
Investigator(s):	18 US, 5 Germany, 3 Ecuador, 4 Colombia, 3 Italy, 2 Austria, 2 Puerto Rico, 2 Greece, Peru, El Salvador, 2 Singapore, Spain, 3 Canada, 2 Czech Republic	
Study Center(s):	Multicenter global at 50 study centers.	
Publication(s):	Not applicable.	
Studied Period:	06 MAY 2005 to 26 SEP 2008	**Clinical Phase:** 3

Objectives

Primary Objective: To assess the clinical benefit of lonafarnib compared to placebo, where benefit is measured by the proportion of subjects who achieved platelet transfusion independence for any 8-consecutive-week period after randomization without worsening of red blood cell (RBC) transfusion requirements or hemoglobin (untransfused) during the same 8-consecutive-week period of platelet transfusion independence.

Secondary Objective(s): To compare hematologic response rate (complete remission [CR], partial remission [PR], hematologic improvement [HI]), 4-weekly RBC transfusion events (number of RBC transfusion events during a 4-week period), active bleeding events (number and severity), infections (number of Common Terminology Criteria for Adverse Events [CTCAE] Grades 3 and 4 infections and days of acute antibiotic, antifungal and/or antiviral intervention), and safety between the two groups.

Additionally, subjects will be followed for survival. Pharmacokinetics (PK), pharmacodynamics (PD), and pharmacogenomics (PG) was also to be assessed at participating sites in subjects who consented to these additional tests.

Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study of best supportive care plus lonafarnib versus best supportive care plus placebo in the treatment of subjects with MDS or CMML who were platelet transfusion dependent conducted in compliance with Good Clinical Practices. Best supportive care for MDS/CMML subjects consisted of platelet and red blood cell transfusions and antibiotics. Due to their general lack of efficacy and the fact that concomitant administration with study treatment may have confounded interpretation of the results, the use of hematopoietic growth factors during study treatment was limited to:

a) stable dose of erythropoietin/darbopoietin for severe anemia (for at least 12 weeks prior to randomization and continued throughout the study) and

b) use of granulocyte colony stimulating factor (G-CSF) during the double-blind phase of the study in subjects with absolute neutrophil count (ANC) <500/μL and fever ≥38.0°C (measured orally) or suspected sepsis or documented infection.

The study consisted of an 8-week retrospective and a 4-week Prospective Screening Period, with the main purpose of assessing Baseline platelet and RBC transfusion requirements of subjects. Subjects who met the selection criteria at the end of the 12-week Screening Period were stratified (based on number of platelet transfusions received and International Prognostic Scoring System [IPSS] score [redacted] and randomized into a Treatment Period of 3 cycles (1 cycle = 28 days). Any subjects who developed unacceptable toxicity, subjects with refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), or CMML who transformed to acute myelogenous leukemia (AML; defined as ≥30% bone marrow myeloblasts), or subjects with Refractory anemia with excess blasts in transformation (RAEB-T) who had disease progression (defined as a ≥50% increase in bone marrow myeloblasts) were discontinued from the study at any time.

Subjects who failed to achieve an initial platelet response (ie, 4 consecutive weeks of platelet transfusion-free interval without worsening of RBC transfusions or hemoglobin) by the end of Cycle 3 (of double-blind phase) were discontinued from the study and treatment may have been unblinded. Nonresponders assigned to the placebo arm were eligible to receive open-label treatment at the discretion of the investigator. Nonresponders assigned to the lonafarnib arm who received substantial clinical benefit in one or more of the secondary endpoints, but discontinued the double-blind part due to nonresponse (in primary endpoint) at the end of Cycle 3, were enrolled into the open-label part of the study upon sponsor approval. The subjects who were responders at the end of Cycle 3 (achieved at least 4 consecutive weeks of platelet transfusion independence by the end of Cycle 3) continued on double-blind study treatment.

The final efficacy analysis was to be performed when all randomized subjects had either discontinued the study

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or completed at least 4 cycles of double-blind treatment.

An independent review committee was to review the primary efficacy data on an ongoing basis and determine if the subjects were platelet transfusion dependent at the time of randomization and if they achieved platelet transfusion independence without worsening of RBC transfusion requirements or hemoglobin values

(untransfused).

Number of Subjects: 47 subjects were enrolled into the study.

Test Product, Dose, Mode of Administration, Batch No(s): Lonafarnib 200 mcg po; Batch Nos: [redacted]

Diagnosis and Criteria for Inclusion: Subjects with a diagnosis of MDS according to the French-American-British Cooperative Leukemia Group (FAB) classification, defined as RA, RARS, RAEB, and RAEB-T, or CMML were enrolled based on the following criteria:

1. Subject had pathologically documented MDS confirmed by bone marrow aspirate (BMA) conducted prior to randomization.

Type	Bone Marrow (BM) Blasts	Peripheral Blood (PB) Blasts	Other
RA	<5%	≤1%	
RARS	<5%	≤1%	>15% ringed sideroblasts
RAEB	5 to <20%	<5%	
RAEB-T	20 to < 30%	≥5%	presence of Auer rods
CMML	<20%	<5%	>1 x 10^3/μL monocytes in PB, no Auer rods

2. Subjects with chemotherapy-/radiotherapy-associated MDS (ie, secondary MDS) were **not** eligible.
3. At Screening (Day -28):

   Subject had platelet and RBC transfusion data, and hemoglobin and platelet values available for the immediately preceding 8-week period (ie, the retrospective Screening Period) prior to study enrollment. In addition, the following requirements must have been satisfied:

   - Subject must have had received 1 to 8 platelet transfusion events during the first 4-week interval (Day -84 to Day -57) and 1 to 8 platelet transfusion events during the second 4-week interval (Day -56 to Day -29) of the 8-week retrospective Screening Period.
   - The number of platelet transfusion events during the first 4 weeks of the retrospective Screening Period (Day -84 to Day -57) and the second 4 weeks of the retrospective Screening Period (Day -56 to Day -29) must have not differed by greater than 4.
   - If the subject is RBC transfusion dependent, the number of RBC transfusion events during the first 4 weeks of the retrospective Screening Period (Days -84 to -57) and the second 4 weeks of the retrospective Screening Period (Day -56 to Day -29) must not have differed by greater than 4.

   Note: For the purposes of this protocol, a transfusion event was defined as a transfusion of a blood product (eg, RBCs or platelets) given for the same indication on the same day. If a transfusion was initiated before midnight but continued into the next day, it was deemed one transfusion event. If multiple units of a blood product were transfused at different times on the same day for the same indication this was also considered one transfusion event.
4. At Randomization:

   The platelet and RBC transfusion data, and hemoglobin and platelet values obtained during the 4-week Prospective Screening (Day -28 to Day -1) confirmed the results of the retrospective Screening Period. In addition, subject must have met the following requirements to be randomized.

   - Subjects must have received 1 to 8 platelet transfusion events during each of the 4-week periods (Day -84 to Day -57, Day -56 to Day -29, and Day -28 to Day -1) prior to randomization.
   - The number of platelet transfusion events during each of the three 4-week periods prior to randomization (Day -84 to Day -57, Day -56 to Day -29, and Day -28 to Day -1) were to have been within ±2 of the average number of transfusion events per 4-week period during the entire 12-week

period (Day -84 to Day -1) prior to randomization.

- For RBC transfusion independent subjects, the average hemoglobin value during the first 4 weeks of the retrospective Screening Period (Day -84 to Day -57) and the second 4 weeks of the Retrospective Screening Period (Day -56 to Day -29) must not have differed by greater than 2 g/dL from the average hemoglobin values obtained during the Prospective Screening Period (Day -28 to Day -1).
- For RBC transfusion dependent subjects, the number of RBC transfusion events during each of the three 4-week periods prior to randomization (Day -84 to Day -57, Day -56 to Day -29, and Day -28 to Day -1) must have been within ±2 of the average number of transfusion events per 4-week period during the entire 12-week period (Day -84 to Day -1) prior to randomization.
- There should have been no change in the reasons for transfusions given during the retrospective versus the Prospective Screening Period (ie, fixed transfusion criteria selected on Day -28 should still have applied for all transfusions given during the Prospective Screening [Day -28 to Day -1]).

5. Subject was ≥18 years old at the start of study drug administration.
6. Subject had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2 on Day -1.
7. Subject had the following laboratory values within 72 hours prior to start of study medication:

   Serum creatinine ≤1.5 x upper limit of normal (ULN).

   Total bilirubin ≤2 mg/dL with the exception of documented Gilbert's Syndrome.

   Serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) ≤2.5 x ULN or alkaline phosphatase ≤4 x ULN.
8. Greater than 12 weeks (prior to randomization) from any investigational drug use (of any type).
9. Greater than 12 weeks (prior to randomization) from any chemotherapy, radiotherapy, or immunotherapy.
10. Greater than 12 weeks (prior to randomization) from any treatment for MDS/CMML (eg, azacitidine) other than best supportive care.
11. No history of acute myelogenous leukemia (AML; bone marrow myeloblasts ≥30%) or bone marrow or peripheral blood stem cell transplantation or treatment with donor lymphocyte infusion.
12. Greater than 12 weeks (prior to randomization) from any initial or changed doses of treatment with Oprelvekin (Neumega) and treatment with erythropoietin/darbopoietin. Subjects who required hematopoietic growth factors, such as erythropoietin/darbopoietin (unstable doses), or oprelvekin (Neumega) were not eligible. Subjects who were on a stable dose of erythropoietin (EPO) or darbopoietin (DARBO) for the duration of the 8-week retrospective and 4-week Prospective Screening Period were not allowed to continue EPO/DARBO throughout the study.
13. No Grade ≥2 nausea or Grade ≥1 vomiting (despite adequate antiemetic medication) or any condition that could interfere with taking oral medication.
14. No current or prior treatment with farnesyl transferase inhibitors.
15. No known history of immune thrombocytopenic purpura (ITP).
16. No use of ketoconazole within 72 hours prior to start of study medication or throughout the study.
17. No subjects at poor medical risk because of active/uncontrolled nonmalignant systemic disease or active uncontrolled infection.
18. No subjects with known human immunodeficiency virus (HIV) positivity or Acquired immunodeficiency syndrome (AIDS)-related illness.
19. No subjects with evidence of other malignancy within 5 years prior to start of study medication, except for in situ neoplasms or adequately treated basal cell or squamous cell carcinoma of the skin.
20. No subjects with active psychiatric or mental illness making informed consent or careful clinical follow-up unlikely.
21. No pregnant or breast-feeding women.
22. Subjects of childbearing potential must have been using an effective method of contraception, which needed to be continued throughout the study treatment and for 6 months following the last dose of study drug.
23 Subject provided written informed consent for treatment and follow-up (must be obtained and documented

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prior to any study-specific procedures).

24. No marked Baseline prolongation of the QTc interval, CTCAE Grade ≥1.

Duration of Treatment: 52 weeks.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Placebo, twice a day (BID), oral, Batch nos: [redacted]

Criteria for Evaluation

Primary Efficacy Endpoint: The achievement of platelet transfusion independence for any 8-consecutive-week period, with no worsening of RBC transfusion requirements or hemoglobin (untransfused) during the same 8-consecutive-week period.

Worsening of RBC transfusion requirements or hemoglobin during the same 8-consecutive-week period is defined as follows:

1. For RBC transfusion independent subjects at Baseline (ie, subjects who had less than one RBC transfusion event every 4 weeks as clinically indicated during the 12 weeks prior to randomization)
   - development of RBC transfusion dependence (defined as requiring at least one RBC transfusion event every 4 weeks as clinically indicated during the duration of platelet transfusion independence) or
   - hemoglobin below 11 g/dL and a decrease in average 4-weekly hemoglobin of ≥2 g/dL during the duration of platelet transfusion independence compared to baseline (average of Day -21, Day -14, Day -7, and Day -1) or
2. For subjects who required RBC transfusions at baseline (ie, subjects who required one or more RBC transfusion events every 4 weeks as clinically indicated during the 12 weeks prior to randomization)
   - more than 50% increase from Baseline in the average number of RBC transfusion events per 4-week period during the duration of platelet transfusion independence.

Fixed Individual Criteria for Platelet and RBC Transfusions: To ensure that the same criteria for platelet and RBC transfusions are used within an individual subject for the 12-week Screening Period (8-week retrospective and 4-week prospective prior to randomization) and at least for the first 4 cycles of double-blind study treatment, the following steps will be taken:

On the first day of Prospective Screening (Day -28), the transfusion criteria was determined for each individual subject based on the 8-week retrospective transfusion data.

These criteria for transfusion were documented on the Fixed Transfusion Criteria page of the electronic case report form (eCRF) and should be adhered to in the 4-week prospective screening as well as during the double-blind study treatment. Each platelet and RBC transfusion event and the primary reason for the transfusion were documented on the appropriate Therapeutic Procedures - Platelet and RBC pages of the eCRF.

Any of the following reasons were selected as fixed transfusion criteria:

a) clinically significant symptoms (eg, hemorrhage, bleeding for platelet transfusions or poor tissue oxygenation/constitutional anemia for RBC transfusions);

b) actual laboratory value being below a specific platelet or hemoglobin value;

c) combination of both a) and b) - either clinically significant symptoms or laboratory value below a certain value.

Secondary Efficacy Endpoints:

a. Hematological Response Rate (per International Working Group [IWG]): Complete Remission (CR), Partial Remission (PR), and Hematologic Improvement (HI)

b. Average 4-weekly RBC transfusion requirements (number of transfusion events/4-week period)

c. Active bleeding (number and severity of events): defined as acute, overt bleeding events that persist despite use of conventional local interventions (eg, pressure bandage, etc)

d. CTCAE Grade 3 or 4 Infections: Number of events and days of acute antibiotic, antifungal and/or antiviral intervention for infections or clinical conditions (eg, febrile neutropenia)

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Safety Endpoints: Frequency and severity of adverse events.

Pharmacokinetics (PK), pharmacogenomics (PG), and pharmacodynamics (PD)[Human analog of DNAJ a surrogate marker to quantify inhibition of farnesylation (HDJ-2)] and farnesyltransferase [FTase]) was also assessed at participating sites in subjects who consented to these additional tests. Subjects were also followed for survival.

Independent Review of Primary Efficacy Parameter: An independent review by 3 outside non-Schering experts was to serve to verify that all subjects were platelet transfusion dependent at baseline and achieved platelet transfusion independence for at least 8 consecutive weeks without worsening of RBC transfusion requirements or hemoglobin value (untransfused) [redacted] An independent central review of the bone marrow slides and the cytogenetic reports was to be performed to confirm diagnosis and hematological response.

Statistical Methods: The primary efficacy analysis was the comparison of the two treatment groups with respect to the proportion of subjects who achieved platelet transfusion independence for any 8-week consecutive period after randomization without worsening of RBC transfusions or hemoglobin (untransfused) during the same period (see Response Criteria above) in the intent-to-treat population using the Cochran-Mantel-Haenszel test adjusted for stratification factors. Subjects who were randomized and discontinued treatment without achieving a response regardless of their duration of treatment were to be classified as a nonresponder. Additionally the 95% confidence interval (CI) for the odds ratio was to be provided. If the primary objective of the study was achieved, then the secondary endpoints were to be evaluated. The treatment groups would also be compared for the following secondary endpoints: hematological response rate (CR, PR, HI), average 4-weekly RBC transfusion requirements, number of active bleeding events (CTCAE Grade 3 and 4), and number of Grade 3/4 infections. The Hochberg procedure was to be used to maintain a type one error of 0.05 for the secondary endpoints.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Analysis: The following PK parameters were to be summarized: Minimum (predose) plasma concentrations (Cmin [predose]) at time of PK sampling. The PD data (HDJ-2 shifts and FTase) were to be summarized. For PG data, expression differences between pre and post treatment data and significantly different genes which appear to be influenced by the study treatment were to be summarized. [redacted]

Efficacy: This study was terminated early due to insufficient evidence of efficacy. A blinded review of the data showed that there were an insufficient number of subjects who had achieved the primary measure of benefit and therefore the probability of demonstrating a clinical benefit with lonafarnib was small, and did not justify continuing to expose subjects to toxicities of the treatment program in the experimental arm. As a result, no final statistical analyses were performed for the primary and secondary endpoints, and the results of this study are being presented in an abbreviated study report.

Safety: Treatment-emergent AEs were reported in 100% of subjects in both the lonafarnib and placebo groups. The primary toxicity in the lonafarnib group was gastrointestinal. The most common AEs (occurring in ≥30% of subjects) included diarrhea (lonafarnib, 87%; placebo, 54%), nausea (lonafarnib, 39%; placebo, 33%), and vomiting (lonafarnib, 35%; placebo, 29%). Treatment-related AEs were reported in 91% of lonafarnib subjects and 67% of placebo subjects.

The most common severe and life-threatening AEs were diarrhea. Serious AEs were reported in 48% of lonafarnib subjects and 63% of placebo subjects, respectively. The most common SAEs were diarrhea (17%), febrile neutropenia (13%), and pyrexia (13%) in the lonafarnib group, and diarrhea (13%) in the placebo group. Ten subjects (43%) in the lonafarnib group and 7 (29%) subjects in the placebo group discontinued treatment due to AEs. The AEs most frequently leading to study discontinuation was diarrhea, 13% in the lonafarnib group, and 13% in the placebo group.

The hematologic parameters that most frequently demonstrated a shift from Grade 0 to 2 values at Baseline to Grade 3 to 4 values during treatment were hemoglobin and white blood cell count (WBC).

Ten (22%) of subjects died within 30 days of end of treatment. Disease progression was the most common cause of death in both treatment groups.

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CONCLUSIONS:

- Lonafarnib subjects reported a greater number of treatment-related adverse events compared to the placebo group.
- The most frequently reported treatment-emergent and treatment-related adverse event was diarrhea.
- Upon review of the data, of the 46 evaluable subjects, there were no responses according to the protocol-specified criteria. Therefore, due to the lack of observed efficacy, the study was terminated.

Date of the Report: 17 JUL 2009