CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	ZARNESTRA®	
Name of Active Ingredient(s)	tipifarnib (R115777)	

Protocol No.: R115777-AML-301

Title of Study: A Randomized Study of Tipifarnib Versus Best Supportive Care (Including Hydroxyurea) in the Treatment of Newly Diagnosed Acute Myeloid Leukemia (AML) in Subjects 70 Years or Older

Principal Investigator: Jean-Luc Harousseau, M.D., [redacted], [redacted] France

Publication (Reference): None

Study Period: 26 October 2004 to clinical cutoff date of 21 May 2007

Phase of Development: 3

Objectives: The primary objective was to compare overall survival of subjects treated with tipifarnib and subjects treated with best supportive care, which may have included hydroxyurea and will thereafter be referred to as BSC.

The primary comparison was performed for all randomized subjects, and, if indicated as per protocol prespecified criteria, a secondary comparison was performed for the subgroup of subjects with "acute myeloid leukemia (AML) with myelodysplasia," which included subjects with AML classified as per the World Health Organization (WHO) classifications "AML with multilineage dysplasia," and "AML and myelodysplastic syndromes, treatment-related."

Secondary objectives included a comparison of the following endpoints: progression-free survival; 1-year survival estimate; complete remission rate; rate of morphologic leukemia-free state; and health resource utilization (number and duration of hospitalizations, incidence of hospitalizations for infections, and a summary of blood product transfusions). Secondary objectives also included an assessment of the safety profile of tipifarnib and to identify potential genetic markers that may be predictive of response to tipifarnib. The pharmacogenomic results will be reported separately.

Methodology: This was a Phase 3, randomized, multicenter, multinational, and open-label study comparing tipifarnib with BSC, in the treatment of elderly subjects (70 years of age and older) with newly diagnosed AML. Eligible subjects were not fit for standard induction chemotherapy, as determined by physician assessment, or did not wish to receive such therapy.

One protocol amendment (29 September 2005) was implemented. The major changes in the protocol included an additional analysis of the subgroup of subjects with AML with myelodysplasia as defined in the Objectives, an increase in the sample size and number of events required for clinical cutoff, an increase to 3 weeks for the time between diagnosis and randomization, changes in the criteria for exclusion due to renal impairment, changes in the definition of progressive disease, and a reduction of subject exposure to bone marrow biopsies for the BSC group.

Subjects who met all inclusion and none of the exclusion criteria were randomly assigned in a 1:1 ratio to either the BSC or tipifarnib group using a central interactive voice response system. Subjects were stratified at randomization based on Eastern Cooperative Oncology Group (ECOG) performance status (performance score: 0-1 versus 2) and age group (<75 years versus ≥75 years). Randomization was to occur no later than 3 weeks after diagnosis and within 1 day of Cycle 1, Day 1 of the Treatment Phase.

The Treatment Phase consisted of 28-day cycles with 21 days of consecutive treatment (tipifarnib) followed by a mandatory 7-day rest period. Adverse events, concomitant medications, and clinical laboratory analytes were recorded weekly. Specific dose modifications were allowed as defined in the protocol. The Treatment Phase continued until disease progression, intolerable toxicity, death, loss to follow-up, investigator decision, or withdrawal of consent to further treatment. After discontinuation of study treatment (Posttreatment Phase), subjects may have received other supportive care as considered appropriate by the investigator, and were to be followed for subsequent AML therapy and assessment of survival status every 30 days until study completion. Subjects who achieved complete remission and had received up to 3 subsequent cycles of treatment were to have discontinued study treatment but should have remained on study. If the subject subsequently relapsed, the subject may have been retreated with tipifarnib. The clinical cutoff date for the analysis of efficacy was the time at which the Johnson & Johnson Pharmaceutical Research and Development clinical team knew 394 deaths had occurred.

Number of Subjects (planned and analyzed): There were 450 subjects planned, and 457 subjects were randomized into the study. Efficacy analyses were performed on the following analysis sets: All Randomized Subjects, the subgroup AML With Myelodysplasia Subjects, and the Per Protocol Subjects.

SYNOPSIS (CONTINUED)

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Number of Subjects (planned and analyzed) (Continued): In the All Randomized Subjects analysis set there were 457 subjects (n=229 for BSC and n=228 for tipifarnib); in the AML With Myelodysplasia Subjects analysis set there were 177 subjects (n=87 for BSC and n=90 for tipifarnib); and in the Per Protocol Subjects analysis set there were 375 subjects (n=195 for BSC and n=180 for tipifarnib). The safety analysis was performed on the All Treated Subjects analysis set, which included 454 subjects (n=229 for BSC and n=225 for tipifarnib).

Diagnosis and Main Criteria for Inclusion: The main criteria for inclusion included: pathologic confirmation of AML (≥20% bone marrow leukemic blasts); age of 70 years or older; newly diagnosed, de novo, or secondary AML; subject not medically fit or did not wish to be treated with induction chemotherapy; ECOG performance scores of 0, 1, or 2; and a signed informed consent form.

Test Product, Dose and Mode of Administration, Batch No.: Tipifarnib was administered orally at a dose 600 mg twice daily. Batch numbers for tipifarnib were: 3NG1539-X, 4DG2568-X, 5BG5127-X, 5DG5487-X, and 5GG5976-X.

Reference Therapy, Dose and Mode of Administration, Batch No: For the purposes of this study, the reference therapy, BSC, included blood product transfusions, prophylaxis or treatment of infection, and other therapy appropriate for the symptomatic treatment of AML and its complications. BSC did not include antileukemic agents other than commercially available hydroxyurea, which was administered according to standard practice and supplied by the sites.

Duration of Treatment: For tipifarnib treatment, the duration of a cycle was 21 days followed by a mandatory minimum 7-day rest period and may have been extended up to 8 weeks to permit recovery from adverse events. In the event of a grade 3 or 4 adverse nonhematologic event, tipifarnib treatment was to be temporarily withheld until toxicity improved to grade 1 or above. Dose adjustments as specified in the protocol were made following adverse events considered by the investigator to be drug related. Tipifarnib treatment was to be permanently discontinued in cases of progressive disease, inability to tolerate tipifarnib treatment even following dose reductions, or when there was no recovery from toxicity by Week 8 of the cycle. The investigator could decide to permanently discontinue treatment based on evaluation of the subject's condition. Treatment could also be discontinued due to serious adverse events or major protocol violations.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was overall survival. Secondary efficacy evaluations included progression-free survival; 1-year overall survival; complete remission rate; duration of complete remission and overall survival of responders; and rate of morphologic leukemia-free state. The secondary efficacy evaluations also compared health resource utilization and included: time to first hospitalization; duration of hospitalization; hospitalization due to infections; and a summary of transfusions. Complete remission required bone marrow aspiration showing less than 5% leukemic blasts and an absence of Auer rods; peripheral blood counts showing absolute neutrophil count (ANC) of at least 1,000/mm^3 (1 giga/L); platelet count of at least 100,000/mm^3 (100 giga/L); no peripheral leukemic blasts; blood-product transfusion independence; and an absence of extramedullary leukemia. Morphologic leukemia-free state required bone marrow aspiration showing less than 5% leukemic blasts; Auer rods not detected; and absence of extramedullary leukemia.

Safety: Safety evaluations included an assessment of the incidence, severity, seriousness, and causation of adverse events and clinical laboratory tests (hematology and serum chemistry) collected during the study. Clinical laboratory tests (serum chemistry and hematology) were performed during the Prerandomization Phase, within 48 hours of randomization, weekly thereafter during treatment and upon study termination.

Statistical Methods:

Sample size: A total of 450 subjects were to be randomized in a 1:1 ratio to provide the required 394 events (deaths) to detect a 33% improvement in median survival with tipifarnib (16 weeks) compared with BSC (12 weeks), with 80% power given a 2-sided significance level of 0.043.

Analyses: Hypothesis testing on overall survival involved a 2-step testing procedure (as outlined in the protocol and the statistical analysis plan), and if the prespecified significance level ($p < 0.043$) was not reached for the analysis of the All Randomized Subjects analysis set, further testing of the subgroup of subjects having AML With Myelodysplasia was not allowed.

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Statistical Methods (Continued): Descriptive statistics, including frequency were provided for demographic, baseline, and safety data.

The Kaplan-Meier method was used to calculate all time-to-event efficacy variables (overall survival, duration of complete remission, progression-free survival, overall survival at 1 year, time to first hospitalization, duration of hospitalization, and time to first transfusion). Survival rates between the groups were compared using a stratified log-rank test adjusting for stratification factors (ECOG performance status and age group). Additional analyses included overall survival between the treatment groups by randomization strata, overall survival by prognostic factors (ECOG, age, karyotype, prior myelodysplastic syndrome [MDS], baseline lactate dehydrogenase [LDH], and baseline white blood cell [WBC] counts), and overall survival for responders. Cox regression analysis was used to test for the effects of treatment on survival, while adjusting for potential baseline adverse risk factors (age, ECOG, baseline bone marrow blast counts, AML with myelodysplasia, unfavorable karyotype, baseline LDH, and baseline WBC). Complete remission and morphologic leukemia-free state rates were compared between groups using the Mantel-Haenszel test, while adjusting for potential baseline adverse risk factors.

Adverse events were tabulated by the Medical Dictionary for Regulatory Activities (MedDRA, Version 9.0) system organ class and preferred term, according to frequency and toxicity grade per the National Cancer Institute Common Toxicity Criteria, (NCI CTC, Version 2.0), relationship to study medication, action taken, outcome, and type (hematologic vs. nonhematologic).

Laboratory data were summarized by grade according to NCI CTC, Version 2.0.

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

A total of 457 subjects were randomized into the study at 115 sites in 23 countries. There were slightly more males (54%) than females (46%). The median age was 76 years, and 24% of the subjects were 80 years or older. Nearly one-third of the subjects had unfavorable cytogenetics (karyotype analysis was not done or not available for 16% of the subjects), and 20% had prior MDS (defined as a history of at least 3 months of MDS evident on bone marrow examination). Overall, 24% of subjects had a baseline bone marrow blast count of 20%-30% (formerly classified as MDS RAEBt [refractory anemia with excess blasts in transformation] by the French-American-British classification [FAB]). The number of deaths at the time of clinical cutoff (21 May 2007) was 201 (88%) of 228 subjects in the tipifarnib group and 195 (85%) of 229 subjects in the BSC group.

Hypothesis testing on overall survival using the 2-step testing procedure gave an overall adjusted p-value of 0.527, which was not statistically significant. Therefore further testing on the subgroup of AML with myelodysplasia was not applicable. With a median follow-up of 574 days for tipifarnib and 539 days for BSC, the median overall survival was 107 days (95% confidence interval [CI] = 85, 129) for the tipifarnib group and 109 days (95% CI = 93, 136) for the BSC group. The hazard ratio (tipifarnib versus BSC) for overall survival was 1.02 (95% CI=0.84, 1.24). The p value from the stratified log-rank test on overall survival was 0.843, and the p value from the unstratified log-rank test was 0.847.

In the tipifarnib group, there were 18 (8%) subjects with a complete remission, the median duration of the complete remission was 239.5 days and the median overall survival was 666 days. There were no complete remissions in the BSC group. A morphologic leukemia-free state was achieved in 23 (10%) of the subjects in the tipifarnib group and 3 (1%) of the subjects in the BSC group. There was no difference in the 1-year overall survival rate (14.9% for tipifarnib versus 17.7% for BSC).

More subjects (72% versus 62%) were hospitalized on or after randomization in the tipifarnib group than in the BSC group. Adverse events related to underlying disease were the major reasons for hospitalization with both treatment groups (30% for tipifarnib versus 34% for BSC). In the tipifarnib group, 24% of the subjects were hospitalized for adverse events related to trial medication. The incidence of infections or febrile neutropenia leading to hospitalization was similar for the 2 groups. Nearly all subjects in the study had at least one blood product transfusion, and there were slightly more blood product transfusions with tipifarnib treatment compared with the BSC group (93% versus 86%). Most of the increased transfusion need was evident in within the first 30 days; from 31 days onward (up to 90 days), there were no differences in the number of transfusions for the 2 treatment groups. In both groups, more red blood cell transfusions were given compared with platelet transfusions.

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SUMMARY – CONCLUSIONS (Continued):

SAFETY RESULTS:

The adverse event profile is shown below:

Adverse Event Profile
(Study R115777-AML-301: All Treated Subjects Analysis Set)

	BSC (N= 229)		Tipifarnib (N= 225)	
	n	(%)	n	(%)
Adverse events	216	(94)	223	(99)
Grade 3 or 4 adverse events	172	(75)	202	(90)
Serious adverse events	112	(49)	150	(67)
Adverse events leading to treatment termination	4	(2)	25	(11)
Adverse events leading to death[a]	51	(22)	56	(25)

[a]Adverse events may or may not have been considered the main cause of death.

The most commonly reported adverse events were related to gastrointestinal disorders, myelosuppression or secondary to myelosuppression. Cytopenias and infections were the most common grade 3 or 4 adverse events; cytopenias were also the most common tipifarnib-related grade 3 or 4 adverse events. The rate of grade 3 or 4 infections was slightly higher in the tipifarnib group than in the BSC group (39% versus 33%, respectively), as was the incidence of febrile neutropenia (16% versus 10%, respectively). The incidence of grade 3 or 4 hypokalemia was higher with in the tipifarnib group compared with the BSC group (16% versus 6%), and was considered by the investigator to be related to tipifarnib treatment in 8% of the subjects. Grade 3 or 4 diarrhea was reported in 7% of subjects treated with tipifarnib, but there were no occurrences in the BSC group. One event of grade 3 renal failure was considered by the investigator to be related to tipifarnib treatment. The incidence of other grade 3 or 4 adverse events (fatigue, pyrexia, dyspnea, and cardiac failure) was similar in both groups.

Hematologic abnormalities were common at baseline (84% in the tipifarnib group versus 80% in the BSC group), and there were a slightly higher number of shifts from normal or grade 1 to grade 3 or 4 laboratory values for ANC and WBC in the tipifarnib group. During the course of treatment, 98% of subjects in the tipifarnib group and 92% of subjects in the BSC group had at least one grade 3 or 4 cytopenia. Although the overall percentages of combined grade 3 and 4 neutropenia, leukopenia, and thrombocytopenia as the worst grade during treatment were similar between the 2 groups, there was generally a higher percentage of grade 4 cytopenias with tipifarnib treatment. Grade 3 or 4 hemoglobin as the worst grade during treatment was similar for the 2 treatment groups (65% for tipifarnib versus 57% for BSC), indicating that disease progression was most likely the major cause of anemia during the study. The most common nonhematologic abnormality was hypokalemia, and the number of subjects with grade 3 or 4 hypokalemia as the worst grade during treatment was higher in the tipifarnib group compared with the BSC group (27% versus 16%, respectively).

The incidence of deaths on study was similar in the two groups (40% for tipifarnib versus 43% for BSC). There were slightly more early deaths (deaths recorded within 30 days from randomization) in the tipifarnib group than in the BSC group (21% versus 17%, respectively), which were accounted for by the slightly increased number of early deaths due to adverse events (11% versus 7%, respectively). The most common adverse events leading to early death and death on study were sepsis, cardiac failure, and pnuemonia. There were 4 (2%) deaths due to adverse events considered by the investigator to be related to tipifarnib treatment. The adverse events leading to these drug-related deaths were cerebral hemorrhage, febrile neutropenia, pneumonia, and sepsis.

CONCLUSIONS: In this multicenter, randomized study, treatment with tipifarnib did not result in an overall increase in survival in this elderly (mean age, 76 years) patient population (who were not suitable for induction chemotherapy) when compared with BSC. A small, but significant number of subjects had a complete remission or a morphologic leukemia-free state with tipifarnib treatment. There was a low incidence of drug-related deaths in the study, and tipifarnib treatment was generally well tolerated.

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