2.0 SYNOPSIS

Name of Sponsor:

Astex Pharmaceuticals, Inc., 4420 Rosewood Drive, Suite 200, Pleasanton, CA 94588

Name of Finished Product: SGI-110 for injection, 100 mg; SGI-110 diluent for reconstitution, 3 mL

Name of Active Ingredient: Guadecitabine (SGI-110)

Study Number and Title of Study: Study SGI-110-04*;* A Phase 3, Multicenter, Open-label, Randomized Study of SGI-110 versus Treatment Choice (TC) in Adults with Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy

Trial Registry Number: NCT02348489; EudraCT Number: 2014-001233-89; Health Canada CN 180672

Investigators and Study Centers: 144 principal investigators at 144 study centers in 24 countries enrolled subjects in this study (*North America*: 22 study centers in the United States (US), 6 in Canada; *European Union (EU)*: 13 in Italy, 12 in France, 10 in Spain, 6 in Germany, 6 in Poland, 3 in Belgium, 3 in Czech Republic, 3 in Denmark, 3 in Hungary, 2 in Austria, 2 in Bulgaria, 2 in Finland, 2 in Romania, 2 in Sweden, 2 in United Kingdom (UK), 1 in Netherlands; *Other European*: 3 in Russia, 1 in Serbia; *Asia-Pacific*: 22 in Japan, 10 in South Korea, 4 in Australia, 4 in Taiwan.

Publications Based on the Results of this Study (at the time of this report): No peer-reviewed publications.

Study Period (Years):	**Phase of Development:** 3
19 March 2015 (first subject signed informed consent) 25 November 2016 (last subject signed informed consent) 31 May 2018 (data cut-off date)	

Trial Interruption: None.

Scientific Background and Explanation of Rationale:

Guadecitabine is a next-generation hypomethylating agent (HMA), which acts through DNA methyltransferase (DNMT) inhibition. First-generation epigenetically targeted HMAs include azacitidine and decitabine, which are both approved in the US and the EU. Decitabine is the active metabolite of guadecitabine and is approved in more than 60 countries for AML or MDS.

HMAs are incorporated into replicating DNA during the synthesis phase (S-phase) of the cell cycle and thereby inhibit DNMT to induce hypomethylation. Because the currently available HMAs have short half-lives (about 30 min) the exposure of dividing leukemia cells to these agents is short. Guadecitabine is not metabolized by cytidine deaminase, the enzyme that degrades decitabine. Guadecitabine is a dinucleotide of decitabine and deoxyguanosine, which are linked by a 3'→5' phosphodiester bond. Gradual cleavage of this bond by phosphodiesterase Type 1 and other enzymes results in continuous formation of decitabine from guadecitabine, prolonging its exposure window, which may result in more efficient incorporation into DNA of leukemia cells during S-phase of the cell cycle. The prolonged exposure window and reduced peak plasma concentrations of decitabine formed after dosing with subcutaneous (SC) guadecitabine may result in better access to target tissues over time and is the proposed basis for potential increased efficacy compared with much shorter exposure following IV decitabine. In addition, guadecitabine is administered as a small volume (~1 mL) SC injection as opposed to 1-hour IV infusion or large volume SC administration requiring multiple injection sites for each injection as for decitabine and azacitidine.

Objectives:

Primary Objective:

- To assess and compare efficacy (complete response [CR] rate and overall survival [OS]) between guadecitabine and TC in adults with previously untreated AML who were not considered candidates for intensive remission induction chemotherapy.

Secondary Objectives:

- To assess and compare effects of guadecitabine and TC in adults with previously untreated AML who were not considered candidates for intensive remission induction chemotherapy with respect to the following variables:
  - CRc (CR+ CR with incomplete blood count recovery [CRi] + CR with incomplete platelet recovery [CRp]) rate.

- Number of days alive and out of the hospital (NDAOH).
- Progression-free survival (PFS).
- Transfusion needs.
- Health-related quality of life (QOL).
- Duration of CR.
- Safety.

Exploratory Objectives:

- To assess the influence of demographic and disease characteristics on treatment outcomes of CR and OS.
- To evaluate PK exposure-response relationships with efficacy and safety parameters.

Study Design and Methods:

This was a Phase 3, multicenter, randomized, open-label, active-controlled study to compare the efficacy and safety of guadecitabine versus TC in adult subjects with previously untreated AML (treatment naïve AML; TN AML) who were not candidates for intensive remission induction chemotherapy. Randomization was 1:1 and was stratified by age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), study center region, and secondary AML or poor-risk cytogenetics. Selection of one of the TC options was made by the investigator prior to randomization. Subjects were to receive study treatment as soon as possible after randomization.

The sponsor, investigator, and study subjects were not blinded in this study. To minimize potential observer bias of unblinded response assessment, disease response was assessed by a blinded independent central pathologist. In addition, an independent data monitoring committee (DMC) was established to provide independent analysis of accumulating safety and efficacy data, and to make recommendations to the sponsor and Study Steering Committee (SSC), as needed, to modify or discontinue the trial. The sponsor did not review the randomized data summaries by treatment arm provided to the DMC by an independent statistician.

Response was assessed through evaluation of peripheral blood (PB) and/or bone marrow (BM) using IWG 2003 AML Response Criteria. Response was assessed on Day 1 of each cycle starting with Day 1 of Cycle 3. BM samples were collected at screening then at the end of Cycles 2, 4, and 6 (Day 1 of Cycles 3, 5, and 7) unless PB showed persistence of leukemic blasts that excluded the possibility of a marrow response. After Cycle 6 (ie, starting with Day 1 of Cycle 7), BM aspirate/biopsy was repeated every 3 months for the first year on study and then every 6 months thereafter until PB or BM assessment showed disease progression or relapse. Blood samples (CBC with differential used for assessment of response in PB) were collected on Day 1 of each cycle; and also on Days 8, 15, and 22 of Cycles 1 and 2; on Day 15 of Cycles ≥3, and at the investigator's discretion for subject management.

Number of Subjects:

	Total	Guadecitabine	TC
Planned	800	400	400
Screened (signed informed consent form [ICF])	949	--	--
Randomized	815	408	407
Treated	793	401	392

Diagnosis and Main Eligibility Criteria:

Eligible subjects were adults with previously untreated AML who were not considered candidates for intensive remission induction chemotherapy based on either age (≥75 years) or <75 years and having at least one of the following: poor performance status (ECOG PS of 2-3), clinically significant heart or lung comorbidities, liver transaminases over 3 times the upper limit of normal, other contraindications to anthracycline therapy, or other comorbidities incompatible with intensive remission induction chemotherapy. For eligibility, AML diagnosis was cytologically or histologically confirmed by the investigator according to the 2008 World Health Organization (WHO) classification (with BM or PB blast counts ≥20%). Creatinine clearance (as estimated by the Cockroft-Gault or other medically acceptable formulas) must have been ≥30 mL/min.

Subjects who were candidates for intensive remission induction chemotherapy were excluded, as were subjects who were not candidates for any active therapy with TC comparators. Subjects were also excluded if they had extramedullary central nervous system AML; second malignancy requiring active therapy; prior treatment with decitabine or azacitidine; significantly compromised liver function; refractory congestive heart failure

unresponsive to medical treatment, active infection resistant to all antibiotics, or advanced pulmonary disease requiring >2 L/min oxygen.

Test Product, Dose and Mode of Administration, Lot Number(s):

Guadecitabine was supplied in 2 vials; one each of SGI-110 for injection, 100 mg (lyophilized active drug substance, dry powder) and SGI-110 diluent for reconstitution, 3 mL (liquid diluent).

- SGI-110 for injection (100 mg), Lot No. 16E11, 14D10, 14J02, 15B03-27716, 15D14, 15H26, 16C07, 16I28, 17B15, 17F09.
- SGI-110 diluent for reconstitution (3 mL), Lot No. 14C18, 14H13, 15B03-27717, 15D13, 15H21, 15K18.

The powder was reconstituted with the diluent at the study center at a target concentration of 100 mg/mL, resulting in a "ready to use" solution of guadecitabine drug product (DP).

Test Product Dose: guadecitabine 60 mg/m^2 SC daily on Days 1-5 of a 28-day cycle.

Control Product, Dose and Mode of Administration, Lot Number(s):

Study centers in the US and Japan obtained TC products from commercially available supply. The sponsor provided TC products to study centers in other regions.

- Cytarabine, 100 mg/5 mL. Lot No. C021979AA, CY11401A, CY11504A, CY11603A, FN6352
- Decitabine, 50 mg. Lot No. DKBS500, EBBS600, EKBS100, EKBS300, EKBS301, EJZU400, EKZT100, FAZTH00, GDZTR00, GKZT000, GEZTI00, HCTZ400, HJZSU00
- Azacitidine, 100 mg. Lot No. GE50041, GE50429, GE60002, H6071, H6168, PV4109, H7051

Suggested treatment regimens for TC products were as follows:

- 20 mg cytarabine given SC twice daily (BID) on Days 1-10 every 28 days.
- 20 mg/m^2 decitabine given as a 1-hour IV infusion daily on Days 1-5 every 28 days.
- 75 mg/m^2 azacitidine given IV or SC daily on Days 1-7 every 28 days.

Other TC treatment parameters such as dose adjustment guidelines followed locally approved prescribing information and institutional standard practice.

Duration of Treatment:

Guadecitabine treatment was given for at least 6 cycles in the absence of unacceptable toxicity or disease progression requiring alternative therapy. Beyond 6 cycles, treatment continued as long as the subject continued to benefit based on investigator judgment.

Duration of treatment for TC followed locally approved prescribing information and institutional standard practice.

Study Endpoints:

Co-Primary Endpoints:

- CR rate based on modified IWG 2003 AML Response Criteria.
- OS, defined as the number of days from randomization to death.

Secondary Endpoints:

- CRc (CR+CRi+CRp) rate.
- NDAOH.
- PFS, defined as the number of days from date of randomization to date of disease progression, initiation of an alternative anti-leukemia therapy, or death, whichever occurred first.
- Number of red blood cell (RBC) or platelet transfusions (units) over the duration of the study treatment.
- Health-related QOL by EQ-5D (consisting of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale [EQ VAS]).
- Duration of CR, defined as the time from first CR to time of relapse.
- Incidence and severity of AEs.
- 30- and 60-day all-cause mortality.

Statistical Methods:

All subjects analysis set = all screened subjects; efficacy analysis set = all randomized subjects (according to randomization); safety analysis set = all treated subjects (according to treatment received); PK analysis set = all subjects who had PK samples collected and successfully analyzed.

Assuming a CR rate of approximately 0.20 (Kantarjian et al 2012; Fenaux et al 2010; Burnett et al 2007) for subjects treated in the TC group (all TC therapies combined) and assuming an increase in CR rate to 0.30 or higher could be achieved by treating subjects with guadecitabine, 800 subjects (400 per treatment group) provided approximately 89% power to detect the overall difference of 0.10 when using a 2-sided Cochran Mantel-Haenszel test having 2-sided alpha level of 0.04. For survival, the primary analysis performed after 670 death events provided 90% power to detect a hazard ratio (HR) of approximately 0.78 (a difference in median survival of 7 months in the TC group versus 9 months in the guadecitabine group), when using a 2-sided stratified log-rank test at an 0.05 alpha level.

Test Sequence: By trial design, the overall (2-sided) alpha level of 0.05 was split between the co-primary endpoints of CR (0.04) and OS (0.01). CR rate was tested first in the sequence at an alpha level of 0.04. A positive CR analysis ($P \leq 0.04$) served as the gatekeeper to subsequent analyses. If the test for CR was positive, then hierarchical analyses were to be conducted at the 0.05 alpha level for OS, and subsequently for CRc rate, NDAOH, and PFS (in that order) if the preceding test was positive. If the test for CR was not significant, then hierarchical analyses were to be conducted at the 0.01 level for OS, CRc, NDAOH, and PFS.

Co-Primary Endpoints: CR rate was compared between guadecitabine and TC groups using Cochran Mantel-Haenszel test at an alpha of 0.04, stratified by the stratification factors used at randomization. OS curves were estimated using Kaplan-Meier (K-M) method and formally compared between guadecitabine and TC groups using a 2-sided stratified log-rank test, stratified by the same stratification factors used at randomization. Sensitivity analyses were conducted for CR rate and OS to evaluate the robustness of the treatment effect.

Secondary Endpoints: CRc rate was compared between treatment groups using a Cochran Mantel-Haenszel test with the same stratification variable as for CR and OS. NDAOH was compared between treatment groups using an analysis of variance model (ANOVA) with stratification variables used as fixed factors. PFS was compared between treatment groups using a stratified log-rank test.

The number of RBC and platelet transfusions up to Day 180 was summarized descriptively, 95% CI of the mean was also provided. The EQ-5D-5L index values and EQ VAS up to Day 180 were analyzed descriptively and using a mixed model approach for repeated measures. Duration of CR was estimated using a K-M method for subjects who achieved a CR during the study, and a separate K-M analysis including all subjects was conducted (using a 0-day event duration for subjects who did not achieve CR).

The incidence and severity of adverse events (AEs) and 30- and 60-day all-cause mortality were summarized with descriptive statistics. No formal statistical testing between the treatment groups was planned for safety assessments.

Exploratory Endpoints: Subgroup analyses were performed to explore the influence of baseline variables and the individual TC therapy administered on the efficacy outcomes of CR rate and OS.

A previously developed Population PK model was applied to calculate model-derived estimates for total cycle exposures (C_{max} and AUC) from sparse PK samples collected in Cycle 1 for guadecitabine and decitabine for use in exposure-response analysis for efficacy and safety. The analyses of exposure-efficacy and exposure-safety relationships were performed separately for patients who received guadecitabine and patients who received decitabine IV. The following analyses were performed to assess relationships of CR with exposure for each exposure measure: frequencies of CR were tabulated and compared between tertiles of exposure; distributions of exposure were compared for patients with and without CR using box plots; and probability of CR was explored using logistic regression models.

RESULTS:

Subject Disposition: There were 815 subjects randomized in the study (408 guadecitabine, 407 TC) and 793 subjects treated (401 guadecitabine, 392 TC). Preselected TC prior to randomization was decitabine, 351 subjects (43%); azacitidine, 340 subjects (42%); and cytarabine, 124 subjects (15%). Overall, the median follow-up time was 766 days (IQR 671-896 days). Reasons for treatment discontinuation and study withdrawal were similar in the guadecitabine and TC groups. Overall, the most common reasons for treatment discontinuation were progressive disease (34.8%), death (29.0%), subject decision (10.7%), and adverse event (9.7%). The most common reason subjects withdrew from the study was death (81.2%). As of the data cut-off date, 51 subjects (6.3%) were continuing to receive study treatment, more on guadecitabine (34 subjects, 8.3%) than TC (17 subjects, 4.2%).

There were no protocol deviations that had a significant impact on the study results.

Demographics and Baseline Characteristics: The overall mean age of subjects was 75.9 years (range: 56 to 94 years). Most subjects were white (73.9%) and 58.0% were male. Most subjects (62.2%) were ≥75 years old and approximately half of subjects had ECOG PS 2 or 3 (50.4%), including 9.8% with ECOG PS 3 (10.8% on guadecitabine, 8.8% on TC). In addition, 34.5% had poor risk cytogenetics and 36.6% of subjects had secondary AML. The median percent blasts as determined by central pathologist was 15.0% in peripheral blood and 56.0% in bone marrow. There were 14.7% of subjects with a white blood cell (WBC) count of ≥20,000/μL and 69.7% of subjects had >30% BM blasts. Baseline demographics, disease characteristics, and hematologic parameters were well balanced between guadecitabine and TC groups.

EFFICACY RESULTS:

In the hierarchical testing order, CR was tested first. The test for CR rate was not significant at the 0.04 level; therefore, the test for OS was conducted at an alpha level of 0.01. The test for OS was not significant and per the pre-defined hierarchical testing plan, no further testing was performed.

	Guadecitabine (N=408)	TC (N=407)	Treatment Difference
Primary Endpoints			
Complete Response (CR) Rate	79 (19.4%)	71 (17.4%)	1.92
96% Confidence Interval (CI)			(-3.67, 7.50)
P value [a]			0.4820
Overall Survival			
Death Events	336 (82.4%)	340 (83.5%)	
K-M Estimate, days (95% CI)			
25th percentile	71.0 (59.0, 96.0)	92.0 (73.0, 112.0)	
Median	213.0 (187.0, 255.0)	254.0 (223.0, 282.0)	
75th percentile	584.0 (498.0, 643.0)	503.0 (426.0, 587.0)	
12-month survival rate (95% CI)	0.37 (0.32, 0.42)	0.36 (0.31, 0.40)	
24-month survival rate (95% CI)	0.18 (0.14, 0.22)	0.14 (0.11, 0.18)	
Primary Stratified Log-Rank Test [b]			0.7328
Cox Regression HR (95% CI) [c]			0.97 (0.83, 1.14)
Secondary Endpoints			
CRc (CR+CRi+CRp) Rate	93 (22.8%)	91 (22.4%)	0.39
95% CI			(-5.34, 6.13)
NDAOH in First 6 Months			
Mean (SD)	98.1 (63.60)	105.7 (63.58)	
LS Mean	98.9	106.7	-7.8
(95% CI)	(92.4, 105.4)	(100.2, 113.2)	(-16.2, 0.7)
Progression Free Survival (PFS)			
Events	385 (94.4%)	378 (92.9%)	
K-M Estimate, days (95% CI)			
Median	159 (136.0, 178.0)	166 (148.0, 179.0)	

[a] Cochran Mantel-Haenszel (CMH) method adjusting for stratification factors used at randomization.
[b] Log-rank test, stratified by stratification factors used at randomization.
[c] Cox proportional-hazard model (with treatment group as the independent variable, stratified by the stratification factors used for randomization).

Primary:

The CR rate was 19.4% for guadecitabine and 17.4% for TC, the difference was 1.92% higher for guadecitabine (96% CI: -3.67-7.5); and was not statistically significant (*P* =0.4820; stratified CMH test). Overall, the results of the planned sensitivity analyses for CR rate were consistent with the results of the primary analysis. The CR rates were numerically higher for guadecitabine than TC for each of the sensitivity analyses conducted (ie, unistratified Chi-square, all treated subjects, excluding not evaluable (NE) subjects, and excluding unconfirmed AML); and the odds ratio (OR) of the guadecitabine vs TC logistic regression was >1 (OR 1.14; 95% CI 0.80-1.63).

Median OS was 213 days (7.1 months) for guadecitabine and 254 days (8.5 months) for TC. The stratified log-rank test did not reach statistical significance (*P*= 0.7328). The HR was 0.97 (95% CI 0.83-1.14). Survival was

shorter for guadecitabine than TC in the 25th and 50th percentiles. The K-M survival curves intersect at approximately 300 days (10 months) and survival was longer for guadecitabine than TC for the 75th percentile (19.5 vs 16.8 months). The 12-month survival rates were similar between guadecitabine and TC (37% and 36%); and the 24-month survival rate was numerically higher for guadecitabine than TC (18% vs 14%). Overall, the results of the planned sensitivity analyses for OS (ie, as treated safety analysis set, additional censoring for antileukemia treatment, and excluding subjects with unconfirmed AML) were consistent with the results of the primary analysis. In a post hoc exploratory survival analysis for subjects who achieved any CR (CR, CRp, or CRi) the point estimate of the HR favored guadecitabine compared to TC (HR: 0.72, 95% CI 0.50-1.05).

Secondary:

- CRc rates were similar between the guadecitabine and TC groups (22.8% and 22.4%, respectively).
- The mean NDAOH over 6 months (3.3 and 3.5 months) and per patient-year rates (297 and 299 days) were similar between the guadecitabine and TC groups.
- PFS K-M survival curves were similar between the guadecitabine and TC groups (HR: 0.99, 95% CI 0.86-1.15). Median PFS was 5.3 months and 5.5 months for guadecitabine and TC, respectively.
- Transfusions were similar between guadecitabine and TC during the first 6 months (means: 16.2 and 15.6 units for RBC; 12.5 and 14.4 units for platelets for guadecitabine and TC, respectively).
- Over the first 6 months, index EQ-5D-5L scores were similar between guadecitabine and TC groups (LS mean difference of -0.019, 95% CI -0.058-0.020). Descriptive EQ-5D-5L scores favored TC in the first 6 months.
- Over the first 6 months, VAS scores slightly improved (increased) from baseline for both groups with an LS mean change from baseline of 0.87 for guadecitabine and 1.13 for TC.
- The median duration of CR among complete responders was similar between guadecitabine and TC (7.2 and 7.7 months, respectively).

Exploratory:

Across the subgroups examined (demographic and disease characteristics, individual TC, and genetic mutations), the treatment effect of guadecitabine versus TC for CR rate and OS were generally consistent with the results of the primary analyses of CR and OS. While most of the point estimates of the odds ratios for CR were >1 (ie, favored guadecitabine) and the point estimate of most of the hazard ratios for OS were <1 (ie, favored guadecitabine); all the CIs included 1, indicating no difference between the treatment groups (or the sample size was too small for meaningful interpretation). The only notable exception was the subgroup analysis of OS by *TP53* status, where the HR for mutant *TP53* patients (n=94) was 1.8 (95% CI 1.17-2.78) and the CI excluded 1; while the HR for wild type (WT) *TP53* patients (n=696) was 0.86 (95% CI 0.73-1.01).

Pharmacokinetics and Exposure Response:

The mean plasma guadecitabine concentration was highest at the first collection time point of 1.5 hours after injection and declined afterward. Decitabine formed metabolically from guadecitabine SC administration stayed longer in blood circulation than decitabine following decitabine IV administration confirming longer exposure to the active metabolite decitabine following guadecitabine administration.

Among investigated exposure measures, safety (Grade ≥3 AEs) and efficacy outcomes (CR and OS) were most correlated with AUC of active metabolite decitabine exposure after SC guadecitabine administration.

SAFETY RESULTS:

Extent of Exposure: The overall extent of exposure was similar for guadecitabine and TC, with both groups receiving a median of 5.0 cycles (range 1-38 cycles for guadecitabine, 1-34 cycles for TC). Exposure was also similar within the preselected decitabine and azacitidine groups, but for the preselected cytarabine group exposure was longer for guadecitabine subjects (median 5.0 cycles) than cytarabine subjects (median 2.0 cycles).

In general, the differences in AE incidence between guadecitabine and TC regardless of causality were small, but the incidence was numerically higher in the guadecitabine group than the TC group for most AE categories except for deaths due to AEs.

Overview of AEs:

	Number (%) of Subjects			
	Guadecitabine (N=401)		TC (N=392)	
Subjects with any AE	393	(98.0%)	387	(98.7%)
Subjects with any Grade ≥3 AE	367	(91.5%)	343	(87.5%)
Subjects with an AE Leading to Discontinuation of Study Treatment	41	(10.2%)	26	(6.6%)
Subjects with any Serious AE (SAE)	325	(81.0%)	296	(75.5%)
Deaths (due to an AE)	115	(28.7%)	117	(29.8%)
Other Subjects with an SAE	210	(52.4%)	179	(45.7%)
Subjects with any Related AE	263	(65.6%)	245	(62.5%)
Subjects with any Related Grade ≥3 AE	201	(50.1%)	169	(43.1%)
Subjects with a Related AE Leading to Discontinuation of Study Treatment	15	(3.7%)	7	(1.8%)
Subjects with any Related SAE	123	(30.7%)	85	(21.7%)
Deaths (due to a Related AE)	17	(4.2%)	14	(3.6%)
Other Subjects with a Related SAE	106	(26.4%)	71	(18.1%)

The AEs that occurred with highest incidence in guadecitabine subjects were pneumonia, febrile neutropenia, thrombocytopenia, constipation, diarrhea, and neutropenia. In TC subjects, the highest incidence AEs were pyrexia, constipation, nausea, febrile neutropenia, and thrombocytopenia. AEs that occurred at a higher rate in guadecitabine subjects included febrile neutropenia, diarrhea, injection site events, and pneumonia. AEs that occurred at a higher rate in TC subjects included pyrexia, nausea, and vomiting.

Incidence of AEs (All Grades) in ≥15% of Subjects in Any Group by Decreasing Incidence

	Number (%) of Subjects			
MedDRA Preferred Term	Guadecitabine (N=401)		TC (N=392)	
Pneumonia	144	(35.9%)	92	(23.5%)
Febrile Neutropenia	141	(35.2%)	107	(27.3%)
Thrombocytopenia	127	(31.7%)	105	(26.8%)
Constipation	124	(30.9%)	114	(29.1%)
Diarrhoea	124	(30.9%)	88	(22.4%)
Neutropenia	115	(28.7%)	89	(22.7%)
Anaemia	98	(24.4%)	87	(22.2%)
Injection Site Events[a]	80	(20.0%)	49	(12.5%)
Hypokalemia	95	(23.7%)	79	(20.2%)
Pyrexia	95	(23.7%)	117	(29.8%)
Oedema Peripheral	93	(23.2%)	78	(19.9%)
Decreased Appetite	91	(22.7%)	62	(15.8%)
Nausea	91	(22.7%)	108	(27.6%)
Cough	79	(19.7%)	66	(16.8%)
Dyspnoea	65	(16.2%)	53	(13.5%)
Asthenia	64	(16.0%)	58	(14.8%)
Fatigue	64	(16.0%)	50	(12.8%)
Sepsis	62	(15.5%)	48	(12.2%)
Vomiting	57	(14.2%)	67	(17.1%)

[a] Injection Site Events is a group term with events determined by medical assessment.

Grade ≥3 AEs that occurred with the highest incidence in guadecitabine subjects were febrile neutropenia, pneumonia, thrombocytopenia, neutropenia, anemia, and sepsis. In subjects who received TC, the highest incidence Grade ≥3 AEs were febrile neutropenia, thrombocytopenia, neutropenia, pneumonia, anemia, and sepsis. There was a higher incidence of Grade ≥3 febrile neutropenia and pneumonia in guadecitabine subjects than TC subjects. Guadecitabine subjects also had a higher incidence of Grade ≥3 blood and lymphatic system disorders (67.8% guadecitabine, 56.6% TC) and infections and infestations (56.1% guadecitabine, 46.7% TC).

Incidence of Grade ≥3 AEs in ≥5% of Subjects in Any Group by Decreasing Incidence (Safety Population)

	Number (%) of Subjects			
MedDRA Preferred Term	**Guadecitabine (N=401)**		**TC (N=392)**	
Febrile Neutropenia	136	(33.9%)	104	(26.5%)
Pneumonia	118	(29.4%)	77	(19.6%)
Thrombocytopenia	114	(28.4%)	92	(23.5%)
Neutropenia	110	(27.4%)	81	(20.7%)
Anaemia	81	(20.2%)	70	(17.9%)
Sepsis	61	(15.2%)	47	(12.0%)
Hypokalaemia	33	(8.2%)	35	(8.9%)
Leukopenia	32	(8.0%)	28	(7.1%)

The most common related AEs and Grade ≥3 related AEs mirrored the AEs regardless of causality but with a lower incidence.

Deaths:

There were 676 deaths during the study and the primary causes of death were similar for guadecitabine and TC. Thirty-day all-cause mortality was similar in subjects who received guadecitabine (11.2%) and subjects who received TC (9.7%), while 60-day mortality was marginally higher for guadecitabine than TC (20.9% vs 17.1%).

The incidence of AEs with an outcome of death was similar for guadecitabine (28.7%) and TC (29.8%). AEs with an outcome of death with the highest incidence were sepsis (6.5%), pneumonia (5.0%), and septic shock (2.0%) in subjects who received guadecitabine, and pneumonia (5.6%), sepsis (5.1%), and cardiac arrest (2.0%) in subjects who received TC. TC subjects had a higher incidence of febrile neutropenia with an outcome of death (1.3%) than guadecitabine subjects (0.2%).

In subjects who received guadecitabine, related AEs with an outcome of death included pneumonia (4 subjects, 1.0%), sepsis (4 subjects, 1.0%), septic shock (3 subjects, 0.7%), and febrile neutropenia, hematophagic histiocytosis, small intestinal hemorrhage, general physical health deterioration, mucormycosis, and osteonecrosis (in 1 subject [0.2%] each). In subjects who received TC, related AEs with an outcome of death included sepsis (4 subjects, 1.0%), pneumonia (3 subjects, 0.8%), and febrile neutropenia, cardiac arrest, septic shock, device related infection, traumatic lung injury, acute respiratory failure and respiratory distress (in 1 subject [0.3%] each).

Serious AEs:

SAEs that occurred with highest incidence were pneumonia (28.4%), febrile neutropenia (25.2%), and sepsis (15.0%) in subjects who received guadecitabine, and febrile neutropenia (22.4%), pneumonia (19.6%), and sepsis (11.2%) in subjects who received TC. While the incidence of these SAEs was slightly higher with guadecitabine, there was no common SAE in the guadecitabine group with an incidence that was ≥1.5-fold higher than in the TC group.

Related SAEs mirrored the SAEs regardless of causality but with lower incidence. Related SAEs with highest incidence were febrile neutropenia (13.7%), pneumonia (8.5%), sepsis (4.0%), thrombocytopenia (1.7%), septic shock (1.2%), and anemia (1.0%) in subjects who received guadecitabine, and, febrile neutropenia (8.7%), pneumonia (4.8%), sepsis (2.3%), acute kidney injury (1.0%), diarrhea (1.0%), and septic shock (1.0%) in subjects who received TC.

Other Significant AEs

Fifteen guadecitabine subjects (3.7%) and 7 TC subjects (1.8%) discontinued treatment due to a related AE; just under half of these discontinuations (7 guadecitabine, 3 TC) occurred due to an infection event. The only related AEs leading to treatment discontinuation in more than 1 subject in either group were septic shock (2 guadecitabine subjects, 0.5%) and general physical health deterioration (2 guadecitabine subjects, 0.5%; 1 TC subject, 0.3%).

Treatment delays due to adverse events occurred in under half the subjects (48.1% guadecitabine, 41.8% TC). Dose reductions due to AEs were much less common (6.0% guadecitabine, 3.3% TC). Neutropenia was the most common AE leading to treatment delay and dose reduction.

Other Safety Results:

No medically important or treatment-related trends were observed in clinical laboratory parameters or other observations related to safety that were not associated with myelosuppression and its complications. There were no effects on ECG parameters for guadecitabine or TC.

Analysis of ECG data collected on-drug during the time window to represent the approximate T_{max} of guadecitabine and active metabolite decitabine showed no effect on heart rate for guadecitabine. There was no signal of any effect on atrioventricular conduction or cardiac depolarization as measured by the PR and QRS interval durations for any of the treatment groups. There was no significant effect on cardiac repolarization as measured by the change from baseline to therapy on guadecitabine or the other treatment groups and the concentration effect modeling also did not show any effect on cardiac repolarization though the confidence intervals were quite wide. In conclusion, this trial did not demonstrate any effect of guadecitabine on ECG parameters; however, caution should be used in the interpretation of the ECG and PK-PD data since the analysis was done only at each site and the PK-PD model was limited to only one time point.

Consistent with the overall survival results based on *TP53* mutation status, results of an exploratory safety analysis based on *TP53* mutation status showed that for subjects with *TP53* mutation, early all-cause mortality, serious AEs, Grade ≥3 AEs, and AEs with an outcome of death were higher for guadecitabine than TC but mostly similar between guadecitabine and TC in subjects with WT *TP53*.

CONCLUSIONS:

This study was the largest prospective randomized study conducted to date in AML subjects who are not candidates for intensive induction chemotherapy using strict eligibility criteria that included very elderly subjects (≥75 years) and subjects with comorbidities or very poor performance status (ECOG PS 2-3). Subject demographic and disease characteristics were well balanced between the treatment groups. Most subjects (62.2%) were 75 years or older and half the subjects (50.4%) had poor performance status (ECOG PS 2 or 3).

The results of this study demonstrated the following:

- There was no statistically significant difference between guadecitabine and TC for the primary endpoints of CR rate or OS.
- There were no clinically meaningful differences between guadecitabine and TC for the secondary endpoints of CRc rate, NDAOH, or PFS; due to the pre-specified hierarchical testing plan these endpoints were not evaluated for statistical significance.
- Transfusion needs were similar between guadecitabine and TC during the first 6 months.
- Over the first 6 months, patient reported QOL assessments did not reveal clinically meaningful differences between the 2 treatment arms based on EQ-5D index scores and EQ-VAS.
- Duration of CR was similar between the treatment groups.
- Guadecitabine 60 mg/m^2 administered SC once daily on Days 1-5 of a 28-day cycle was tolerated in previously untreated adult subjects with AML who were not considered candidates for intensive chemotherapy. The safety profiles for guadecitabine and TC were similar; however, there was a slightly higher incidence of AEs of myelosuppression and infection in the guadecitabine group. Early 60- and 90-day all-cause mortality was slightly lower for the TC group but overall death due to AEs was similar for guadecitabine (28.7%) and TC (29.8%).
- There were no differences between treatment groups in CR or OS for any of the planned subgroup analyses. Most subgroups had an odds ratio for CR >1 (ie, favored guadecitabine) and a HR for OS <1 (ie, favored guadecitabine); however, most 95% CIs included 1. The only exception was survival in subjects with *TP53* mutation who appeared to do worse with guadecitabine (HR 1.80; 95% CI 1.17-2.78). Conversely, subjects with WT *TP53* appeared to do better with guadecitabine (HR 0.86; 95% CI 0.73-1.01). Exploratory analysis showed subjects who achieved any CR seemed to live longer on guadecitabine compared to TC (HR 0.72; 95% CI 0.50-1.05).
- Exploratory analysis showed that subjects with *TP53* mutation treated with guadecitabine had higher all-cause mortality rates and higher rates of Grade ≥3 AEs and SAEs than those treated with TC. In subjects with WT *TP53*, the incidence of AEs with an outcome of death was lower for subjects treated with guadecitabine than subjects treated with TC. The higher early toxicity and early mortality in subjects with *TP53* mutations explain the survival difference between guadecitabine and TC in those subjects as there were no other obvious differences in baseline characteristics between the treatment arms by *TP53* status. Excluding *TP53* mutant subjects improved both safety and overall survival results favoring guadecitabine compared to TC.

• Efficacy (CR and OS) and safety (Grade ≥3 AEs) outcomes were most correlated with AUC of active metabolite decitabine exposure after SC guadecitabine administration. • This trial did not demonstrate any effect of guadecitabine on ECG parameters.	
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