Ambit and Astellas Announce Presentation of Results from Phase 2 ACE Study of Quizartinib in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) at the 54th Annual Meeting of the American Society of Hematology

Highest level of single agent activity observed to date for FLT3-targeted therapy in relapsed/refractory AML

Additional Phase 1 and Phase 2 studies evaluating monotherapy quizartinib and combination with other agents in AML are ongoing

Atlanta, Dec. 10, 2012 – Astellas Pharma Inc. (Tokyo: 4503, Astellas) and Ambit Biosciences Corporation announced today that the results from a completed Phase 2 study with the investigational FLT3 inhibitor, quizartinib (AC220), as an oral monotherapy treatment regimen in patients with relapsed or refractory acute myeloid leukemia (AML) were presented at the 54th Annual Meeting of the American Society of Hematology (ASH).

The Phase 2 ACE study recruited patients into two separate cohorts of patients with relapsed/refractory AML, and the results from each cohort of were presented in individual oral sessions. Highlights of the combined key findings in FLT3-ITD positive patients were as follows:

- Approximately 50 percent of FLT3-ITD positive patients achieved a CRc, or composite complete response (CRc: complete remission (CR) + complete remission with incomplete platelet recovery (CRp) + complete remission with incomplete hematologic recovery (CRi)),
- Approximately 50 percent of FLT3-ITD positive patients who were refractory (i.e. had no response to their prior AML therapy) achieved a CRc,
- Approximately one-in-three FLT3-ITD positive patients who had relapsed or were refractory after two prior lines of treatment or after a prior hematopoietic stem cell transplant (HSCT) received a potentially curative HSCT following treatment with quizartinib,
- As of Sept. 28, 2012, 35 (18 percent) FLT3-ITD positive patients had survival of greater than 12 months

"AML is amongst the most challenging hematological malignancies to treat, and patients with activating FLT3 mutations have a particularly poor prognosis and often relapse or are refractory to current treatment options," said Jorge Cortes, M.D., Internist and Professor, Deputy Chair, Department of Leukemia, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas. "The findings from the Phase 2 ACE study with quizartinib in patients with relapsed and refractory AML are especially encouraging. In the patients with the FLT3-ITD mutation, quizartinib represents the most active single-agent we have observed with any class of investigational drugs in this challenging patient population. We look forward to further investigation of quizartinib in the expanding clinical program which includes multiple treatment strategies and subpopulations of AML patients".

In addition to the clinical benefit observed in FLT3-ITD positive patients, there was substantial evidence of activity in FLT3-ITD negative patients, with approximately one-in-three of these patients achieving a CRc and a comparable percentage receiving HSCT as in the FLT3-ITD positive group.

Safety findings in the study were primarily gastrointestinal, myelosuppression and QT prolongation, and these were generally mitigated with dose modifications. Twenty-two percent of patients experienced an

adverse event (AE) that resulted in treatment discontinuation, with progressive disease being the most common AE.

"The results of this large Phase 2 ACE trial demonstrate the clinical benefit achieved with quizartinib in heavily pretreated AML patients with limited therapeutic options," said Athena Countouriotis, M.D., Chief Medical Officer of Ambit. "A substantial portion of patients who relapsed or were refractory to two prior lines of treatment, or a prior HSCT, were successfully bridged to HSCT, which is considered the only potentially curative procedure for patients diagnosed with AML. For those patients who are not eligible for HSCT, prolonged quizartinib use may positively impact quality of life as an outpatient treatment. Further, these results showed a safety and tolerability profile comparable with what was observed in an early study, but with a lower rate of asymptomatic Grade 3 QT prolongation."

Summary of the Phase 2 ACE Study Design
This open-label Phase 2 trial included a total of 333 patients with relapsed or refractory AML. Data from 271 patients were reported here from the "confirmatory" phase of the study. Data from 62 patients from an "exploratory" phase had been reported earlier. In the "confirmatory" phase, quizartinib was investigated in two separate cohorts, and each of these cohorts was presented in separate oral sessions this week:

- Cohort 1: Patients who are 60 years of age or older who are relapsed after one first-line chemotherapy regimen (with or without consolidation) and after first remission of less than 12 months duration or are primary refractory to first-line chemotherapy
- Cohort 2: Patients who are 18 years of age or older, including patients 60 years of age or older, who are relapsed or refractory after one second-line (salvage) regimen or are relapsed or refractory after HSCT

Quizartinib was administered orally, once-a-day, at a starting dose of 90 mg/day (females) or 135 mg/day (males), in 28-day treatment cycles until disease progression, elective HSCT or unacceptable toxicity that could not be mitigated with dose adjustments. The co-primary endpoints were CRc (CR + CRp + CRi) and CR. Additionally, partial response (PR), overall survival (OS), HSCT rates, molecular pharmacodynamic (PD) biomarkers and standard safety assessments were evaluated.

Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients ≥ 60 Years of Age with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia (Abstract #43)
Jorge Cortes, M.D., Internist and Professor, Deputy Chair, Department of Leukemia, Division of Cancer Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Data through Sept. 28, 2012 (representing at least 10 months of follow-up for overall survival), were presented from a cohort comprised of patients aged 60 years or older with AML relapsed in less than one year or refractory to 1st-line chemotherapy. A total of 133 patients - 90 (68 percent) FLT3-ITD positive, 42 (32 percent) FLT3-ITD negative and one patient whose FLT3 genotype status was unknown -- were included in this cohort and constitute the basis for this analysis.

- For FLT3-ITD positive patients
    - The CRc rate was 53 percent (3 percent CR+CRp and 50 percent CRi),
    - The median duration of CRc was 10.4 weeks,
    - An additional 21 percent of patients achieved a PR,
    - Of those refractory to their prior AML therapy, 70 percent achieved at least a PR with quizartinib,
    - The rate of HSCT after quizartinib use was 9 percent, which was likely impacted by patient age and other comorbid factors in this patient population,
    - The median overall survival was 25.3 weeks,

    - Those who were able to be bridged to a HSCT had an OS of 32.2 weeks vs. 24.9 weeks for those who did not receive a HSCT,
    - Twelve patients (13 percent) are considered "long-term survivors" given they remained alive for more than 12 months

- For FLT3-ITD negative patients:
    - The CRc rate was 36 percent (5 percent CR+CRp and 31 percent CRi),
    - The median duration of CRc was 9.3 weeks,
    - An additional 10 percent of patients achieved a PR,
    - Of those refractory to their last prior AML therapy, 55 percent achieved at least a PR with quizartinib
    - The rate of HSCT after quizartinib use was 2 percent, which was likely impacted by patient age and other comorbid factors in this patient population,
    - The median overall survival was 19.0 weeks,
    - Five patients (12 percent) are considered "long-term survivors" given they remained alive for more than 12 months

- The most common treatment-emergent AEs were nausea (53 percent), diarrhea (42 percent), fatigue (39 percent), febrile neutropenia (38 percent), vomiting (37 percent), anemia (31 percent) and QT interval prolongation (27 percent). There was one occurrence of Grade 4 QT prolongation with torsade de pointes, which resolved after stopping quizartinib. QT interval prolongations were asymptomatic, transient, and none were fatal. A total of 35 patients (27 percent) experienced an AE resulting in discontinuation of quizartinib, with the most common AE leading to discontinuation being progressive disease.

- Overall, responses (CRc) were achieved in over 50 percent of elderly patients with the FLT3-ITD mutation. These responses are clinically meaningful given they allowed some patients to be bridged to a stem cell transplant, and others remained alive for more than 12 months (all but one patient did not receive a HSCT). Additionally, nearly one-in-three patients without the FLT3-ITD mutation responded to quizartinib and may also benefit from its future use. Quizartinib is well tolerated, with gastrointestinal toxicities being the most common as well as reversible QT prolongation which was infrequently grade 3, with one case of Grade 4 QT prolongation, at the doses used in this trial. These data suggest that quizartinib may be an option for achieving leukemic control for elderly AML patients that no longer respond, or are refractory, following front-line chemotherapy. For a percentage of elderly AML patients who can tolerate a HSCT, quizartinib may be able to provide a bridge to potentially curative HSCT. For those who are not HSCT candidates, prolonged quizartinib use may positively impact quality of life given its outpatient delivery.

Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia After Second-Line Chemotherapy or Hematopoietic Stem Cell Transplantation (Abstract #673)

Mark Levis, M.D., Ph.D., Associate Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland

Data through Sept. 28, 2012 (representing at least 10 months of follow-up for overall survival), were presented from a cohort comprised of patients aged 18 years or older with AML relapsed or refractory to second-line, salvage chemotherapy or relapsed after HSCT. A total of 138 patients – 100 (72 percent) FLT3-ITD positive and 38 (28 percent) FLT3-ITD negative – were included in this cohort and constitute the basis for this analysis.

- For FLT3-ITD positive patients:
    - The CRc rate was 46 percent (6 percent CR+CRp and 40 percent CRi),

    - The median duration of CRc was 12.1 weeks, which was likely impacted by a high percentage (37 percent) of patients who were bridged to HSCT,
    - An additional 27 percent of patients achieved a PR,
    - Of those refractory to last prior AML therapy, 75 percent achieved at least a PR with quizartinib,
    - The rate of HSCT after quizartinib use was 37 percent, which represents clinical benefit in this heavily pretreated patient population,
    - The median overall survival was 22.9 weeks, with the impact of bridge to HSCT shown by a median overall survival of 33.3 weeks in those who received a subsequent HSCT after quizartinib compared to median overall survival of 17.7 weeks in those patients who did not undergo a subsequent HSCT,
    - Twenty-three patients (23 percent) are considered "long-term survivors" given they remained alive for more than 12 months

- For FLT3-ITD negative patients:
    - The CRc rate was 32 percent (6 percent CR+ CRp and 26 percent CRi),
    - The median duration of CRc was 7.0,weeks, which was likely impacted by a high percentage (37 percent) of patients who were bridged to a HSCT,
    - An additional 16 percent of patients achieved a PR,
    - Of those refractory to their last AML therapy, 48 percent achieved at least a PR with quizartinib,
    - The rate of HSCT after quizartinib use was 37 percent, which represents clinical benefit in this heavily pretreated patient population,
    - The median overall survival was 25.6 weeks,
    - Ten patients (26 percent) are considered "long-term survivors" given they remained alive for more than 12 months

- The most common treatment-emergent AEs were nausea (53 percent), vomiting (41 percent), febrile neutropenia (38 percent), diarrhea (37 percent), anemia (34 percent), QT interval prolongation (27 percent) and fatigue (24 percent). QT interval prolongations were asymptomatic, transient, and there were no Grade 4 events or deaths associated with QT prolongation. A total of 25 patients (18 percent) experienced an AE resulting in discontinuation of quizartinib, with the most common AE leading to discontinuation being progressive disease.

- Overall, responses (CRc) were achieved in 46 percent of heavily pretreated patients with the FLT3-ITD mutation. These responses are clinically meaningful given they allowed a high percentage (37 percent) of patients to be bridged to a stem cell transplant, and 23 percent of the FLT3-ITD positive patients remained alive for more than 12 months (of which 61 percent received a HSCT). The potential impact of bridge to HSCT was shown in the median overall survival for patients with the FLT3-ITD mutation which was 33.3 weeks for those who had a subsequent HSCT, compared to 17.7 weeks in those patients with the FLT3-ITD mutation who did not receive a subsequent HSCT. Nearly one-in-three patients without the FLT3-ITD mutation also responded to quizartinib and may benefit from its future use. Quizartinib is well tolerated, with gastrointestinal toxicities being the most common as well as reversible QT prolongation which was infrequently grade 3 (with no cases of grade 4 in this patient cohort) at the doses used in this trial. These data suggest that quizartinib may be an attractive option in this heavily pretreated patient population with limited therapeutic options. The benefit of bridge to HSCT had a clear impact in improving overall survival for these patients.

The Quizartinib Clinical Program

As of Dec. 1, 2012, approximately 450 patients have been enrolled into clinical trials evaluating quizartinib in AML, and in addition to the Phase 2 study presented this week, other ongoing trials with quizartinib include:

- ***"An Open Label Study to Evaluate the Safety and Efficacy of Two Doses of Quizartinib in Patients With Relapsed or Refractory Acute Myeloid Leukemia (NCT01565668)"*** The purpose of this Phase 2b study is to assess the safety and efficacy of additional dose strengths of quizartinib monotherapy in relapsed or refractory AML patients. In addition to evaluating clinical response and survival, assessment of PD biomarkers and pharmacokinetics (PK) will be performed. Patient enrollment started in May 2012, and the study is currently ongoing.

- ***"A Study to Assess AC220 Given in Combination With Induction and Consolidation Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) (NCT01390337)"*** The purpose of this Phase 1 study is to define the maximum tolerated dose of quizartinib when combined with induction and consolidation therapy, and as a maintenance therapy following induction and consolidation. Patient enrollment is ongoing.

- ***"A Study of AC220 Given After Transplant in Subjects With Acute Myeloid Leukemia (AML) (NCT01468467)"*** The purpose of this Phase 1 study is to define the maximum tolerated dose of quizartinib when given as maintenance therapy after treatment with an allogeneic HSCT. Patient enrollment is ongoing.

About Quizartinib
Quizartinib (AC220) is a novel, potent, highly selective, orally bioavailable FMS-like tyrosine kinase-3 (FLT3) inhibitor being developed in collaboration between Ambit Biosciences Corporation and Astellas Pharma Inc. Quizartinib is currently under evaluation in a Phase 2b clinical trial as monotherapy treatment for adult patients with relapsed or refractory AML, and in two Phase 1 studies in a combination treatment regimen with chemotherapy, and as a maintenance therapy following transplant, respectively.

About Ambit Biosciences
Ambit Biosciences is a privately held biopharmaceutical company engaged in the development of a robust pipeline of small molecule kinase inhibitors for the treatment of cancer, inflammatory disease and other indications. Ambit's lead compound, quizartinib (AC220), is a novel, potent, highly selective, orally bioavailable FMS-like tyrosine kinase-3 (FLT3) inhibitor, and is currently under clinical investigation in patients with relapsed or refractory AML and treatment-naïve AML. Ambit is developing quizartinib in collaboration with Astellas Pharma Inc. as part of a worldwide agreement to jointly develop and commercialize FLT3 kinase inhibitors in oncology and non-oncology indications. In addition to quizartinib, Ambit's clinical pipeline includes AC430, an oral JAK2 inhibitor, and CEP-32496, a BRAF inhibitor licensed to Teva. Ambit's preclinical portfolio includes a proprietary CSF1R inhibitor program. For more information, visit www.ambitbio.com.

About Astellas Pharma Inc.
Astellas Pharma Inc., located in Tokyo, Japan, is a pharmaceutical company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceuticals. Astellas has approximately 17,000 employees worldwide. The organization is committed to becoming a global category leader in Urology, Immunology (including Transplantation) and Infectious Diseases, Oncology, Neuroscience and DM Complications and Kidney Diseases. For more information on Astellas Pharma Inc., please visit the company website at www.astellas.com/en.

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