**Initial Findings from the PACE Trial: A Pivotal Phase 2 Study of Ponatinib in Patients with CML and Ph+ ALL Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I Mutation**

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On behalf of the PACE Study Group

**Background:** Despite progress in chronic myeloid leukemia (CML) therapy with tyrosine kinase inhibitors (TKIs), patients (pts) who fail dasatinib or nilotinib or pts with T315I mutation have no treatment options. Ponatinib is a potent, oral, pan-BCR-ABL inhibitor active against the native enzyme and all tested resistant mutants, including the uniformly resistant T315I mutation.

**Methods:** The PACE trial (Ponatinib Ph+ALL and CML Evaluation) was initiated in September 2010. The objective of this international, single-arm, open-label, phase 2 trial is to establish the efficacy and safety of ponatinib. Pts with refractory CML in chronic, accelerated or blast phase (CP, AP or BP), or Ph+ acute lymphoblastic leukemia (ALL), resistant or intolerant (R/I) to dasatinib or nilotinib or with the resistant T315I mutation received 45 mg ponatinib orally once daily in one of 6 cohorts: CP R/I; CP T315I; AP R/I; AP T315I; BP/ALL R/I; BP/ALL T315I. The primary endpoints are major cytogenetic response (MCyR) for CP and major hematologic response (MaHR) for AP, BP or ALL. The trial is ongoing; projected enrollment is approximately 450. Data as of 18 July 2011 are reported.
Results: At analysis, 403 pts were enrolled; 397 were treated and eligible. The median age was 59 (range, 18-94) years, 52% were male. Diagnoses were: CP R/I, n=188; CP T315I, 48; AP R/I, 52; AP T315I, 15; BP/ALL R/I, 51; BP/ALL T315I, 43. Median time from initial diagnosis to start of ponatinib was 6.2 years. Prior TKIs included imatinib (93%), dasatinib (85%), nilotinib (66%), and bosutinib (8%); 94% failed ≥2 prior TKIs, and 57% failed ≥3 prior TKIs. Overall, 88% had a history of resistance to dasatinib or nilotinib, and 12% were purely intolerant.

Mutation status was determined centrally by MolecularMD. Overall, 106 pts had the T315I mutation. Of 291 R/I pts, 110 (38%) had non-T315I BCR-ABL mutations, most frequently F317L (10%), F359V (5%), E255K (4%), and G250E (4%).

To date, 343 (85%) pts remain on therapy, 60 (15%) have discontinued (42 BP/ALL): 24 (6%) progressive disease (20 BP/ALL); 11 (3%) AE (3 pain, 3 thrombocytopenia, 1 each haemorrhage, loss of consciousness, enterocolitis, cytokine release syndrome, hepatotoxicity/pleuro-pericardial effusion after overdose); 8 (2%) died (3 related; 7 BP/ALL); 17 (4%) other. The most common drug-related AEs (≥10% any grade) were thrombocytopenia (19%; 15% grade 3/4), rash (18%), dry skin (13%), myalgia (12%), abdominal pain (11%; 3% grade 3/4), headache (11%), arthralgia (11%). Overall, 67 (17%) pts experienced at least 1 related SAE. The most common related SAEs (≥5 cases) were pancreatitis 15 cases (3.7%), 5 cases each (1.2%) diarrhea, anemia, febrile neutropenia, and pyrexia.

At the time of reporting, 159/397 eligible pts were evaluable for the primary endpoints. Median follow-up was 57 days. Of CP pts, 83 had an assessment at 3 months (10 at 6 months) or discontinued. In CP R/I, 25/60 (42%) attained MCyR (15 CCyR). In CP T315I, 13/23 (57%) had MCyR (11 CCyR). The overall CP MCyR rate was 38/83 (46%) (26 CCyR). Of AP, BP/ALL pts, 76 had an assessment at 1 month or later or discontinued. In AP, 17/23 (74%) R/I and 1/1 T315I pts achieved MaHR. In BP/ALL, 11/30 (37%) R/I and 6/22 (27%) T315I pts had MaHR.

Conclusion: In this first analysis of the pivotal PACE trial, ponatinib has a favorable early safety profile, similar to that observed in phase 1, but with a lower incidence of pancreatitis. Initial response data after short follow-up indicate ponatinib has substantial anti-leukemic activity in this heavily pretreated population, and in pts with refractory T315I. These early efficacy signals replicate initial response results reported in the phase 1 setting. Updated data will be presented at the annual meeting.
ponatinib: PACE trial interim results published in ASH abstract 2011

- 159 of 397 (40%) eligible patients evaluable for primary endpoints
- Median follow-up of 57 days

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<th>CP (MCyR)</th>
<th>AP (MHR)</th>
<th>BP/ALL (MHR)</th>
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<tr>
<td>R/I</td>
<td>42%</td>
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<td></td>
<td>25/60</td>
<td>17/23</td>
<td>11/30</td>
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<tr>
<td>T315I</td>
<td>57%</td>
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<td></td>
<td>13/23</td>
<td>1/1</td>
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<td>Total</td>
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- Primary endpoint for CP patients is major cytogenetic response (MCyR)
- Primary endpoint for AP/BP/ALL patients is major hematologic response (MHR)
- Most common related SAEs were pancreatitis (3.7%), diarrhea, anemia, febrile neutropenia, pyrexia (1.2% each)

Data as of 18 July 2011