Clinical Evaluation of ARRY-614, a Dual p38/Tie2 Inhibitor for Patients with Myelodysplastic Syndromes, Identifies Unique Disease-Related and Drug-Related Biomarkers

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Rationale and Study Design

- Stressors such as overproduction of myelosuppressive cytokines, aberrant angiogenic signaling and the presence of an abnormal clone in the bone marrow of patients with MDS are common findings
- These stressors cause apoptosis of progenitors & support cells resulting in anemia, neutropenia and thrombocytopenia
- p38 & Tie2 are over-activated in MDS bone marrow and support to contribute to disease-induced myelosuppression
- Inhibition of p38 or Tie2 may enable bone marrow repopulation: – Blocking stress signaling – Blocking inappropriate apoptosis and senescence
- ARRY-614 is a potent, small molecule, dual p38/Tie2 inhibitor for potential treatment of MDS that is being studied in Phases 1/2 trials
- Encouraging preliminary clinical activity and target inhibition have been observed

Patient Characteristics and Clinical Results

- ARRY-614 Safety
  - Well tolerated at QD dosages up to 1200 mg (maximally administered dose)
- Safety profile at 1200 mg QD (n = 16)
  - Adverse events mainly Grade 1-2; incidences < 40%
  - Grade 3 treatment-related AEs: rash (n = 2) and diarrhea (n = 3)
  - Only one dose-limiting toxicity (Cycle 1; Grade 3 macular skin rash
  - Only one patient off study due to a treatment-related AE (diarrhea)
  - Rash and diarrhea manageable with treatment and/or dose reductions

- ARRY-614 Hematologic Improvement
  - Overall, durable HI observed in 14 of 44 evaluable patients (32%) (p=0.0961 vs. control)
  - HI rate 38% at maximally administered dose (1200 mg QD)
  - 5 b-line responses
  - Median duration: 21 weeks, range 8 - 97
  - Median by lineage (n, weeks): Hb-e (n=8, 26, 10 - 97), Hb-p (n=6, 14, 8 - 68), Hb-N (n=5, 21 - 16, 24 - 100)
  - Responders baseline characteristics (n = 14)
    - 13 ≥ prior HMA, 13 IPSS int-1, 12 with 2-3 cytopenias, 7 with abnormal cytogenetics
  - Median time to HI: 14 weeks (range 7-28)

- ARRY-614 Inhibits phospho-p38 both Mechanistically and Functionally
  - Phospho-p38 and Tie2 in plasma and whole blood samples were inhibited in a dose-dependent manner.
  - Evidence for inhibition of phosphorylated p38 in plasma was consistent with the clinical activity observed in these patients.

Potential Disease-Related Changes in Plasma Markers were Identified

- Changes in plasma markers were observed in patients who received ARRY-614 and were consistent with the inhibition of p38 and Tie2.
- These changes were correlated with clinical responses and provided evidence of the mechanism of action of the drug.

Additional Findings

- Additional disease-related markers included MIP-1β, VACM-1, CCL20 and the Tie2 ligand, ANG2.

Inhibition of Plasma EPO Consistent with Hematologic Improvement

- EPO was highly elevated at baseline in patients and decreased in response to ARRY-614 treatment.
- Long-term hematologic improvement was observed in all lines, including in lineages with low plasma response.
- An optimized formulation of ARRY-614 is currently under investigation in clinical trials for patients with lower-risk MDS.

Study Objectives

- Primary: Safety, tolerability and MTD
- Secondary: Response per IWG 2006 PD profile and best post-dose samples of bone marrow biopsies for markers of target
- Plasma samples for possible markers of disease and drug response

Example of Durable HI (Erythroid and Platelet)

- Day 15 geometric Mean (±) is plotted for plasma concentration-time profiles
- Patient variability in plasma concentrations, exposure profile, and PK parameters were observed
- ARRY-614 exposure (AUC) may be dose-proportional despite variability

- Median T2, 3 hours; L1, 8 hours
- p38 IC50 (pSSP-induced TNFα in whole blood (human)) - 60 nM = 33 nM/L

Potential Disease-Related Changes in Plasma Markers with Phase 2 Data

- p38 inhibits the MAPK family of serine/threonine kinases that are involved in the regulation of cellular growth, differentiation, and survival.
- EPO is a potent, dual inhibitor of p38 MAPK and Tie2 that has demonstrated encouraging clinical activity and tolerability in a Phase 1 study in patients with heavily pretreated lower-risk MDS.
- Clinical trials are ongoing to further evaluate the safety and efficacy of ARRY-614 in patients with low-risk MDS.

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Summary

- ARRY-614 is a potent, dual inhibitor of p38 MAPK and Tie2 that has demonstrated encouraging clinical activity and tolerability in a Phase 1 study in patients with heavily pretreated lower-risk MDS.
- Long-term hematologic improvement was observed in all lines, including in lineages with low plasma response.
- 38% hematopoietic improvement was observed at the highest dose tested (1200 mg QD)
- Decreases in plasma chemokines and bone marrow p38 suppression improve primary target
- EPO remained suppressed for 120 days, and thus may be associated with disease modification

Additional Design Methods

- Genetic predisposition to disease
- A subset of markers was evaluated for change from baseline during ARRY-614 treatment (MSD, chemokine cytokine human antibody panel).
- Of interest were antibodies using IL-1/tumor necrosis factor (IL-1) cytokine panel.
- ARRY-614 was selected based on IL-1 receptor antagonist which is known to have a beneficial effect on cytokine activity.

- Post treatment decreases in MP-10 and others (i.e. IL-8, IP-10) appeared related to acute drug exposure and consistent with functional inhibition of phospho-p38.
- Over the course of 28 days, inhibition of this chemokine is attenuated, similar to findings reported with other phospho-p38 inhibitors studied clinically.
- This is the first report of loss of chemokine/cytokine inhibition with evidence of persistent p38 inhibition suggesting this phenomenon is due to a compensatory pathway

- EPO inhibition was evaluated at baseline and reduced in response to ARRY-614 treatment long-term reductions in plasma EPO were observed in patients with HI and may be associated with disease modification

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