(PF853) PRECLINICAL CHARACTERIZATION OF CGT1145, A NOVEL, WILD-TYPE-SPARING, JAK2 V617F MUTANT-SELECTIVE INHIBITOR

Topic: 15. Myeloproliferative neoplasms - Biology & translational research

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Background

JAK2 V617F is the most common mutation in BCR-ABL-negative myeloproliferative neoplasms (MPNs), present in ~95% of patients with polycythemia vera and ~50% of patients with essential thrombocythemia or primary myelofibrosis. This acquired point mutation in the JAK2 pseudokinase (JH2) domain results in the constitutive activation of JAK2 kinase (JH1) signaling leading to cytokine-independent growth of hematopoietic cells. Approved JAK2 inhibitors, such as ruxolitinib, are kinase domain binders that can alleviate symptoms and improve outcomes in patients with MPNs. However, even with long-term treatment, this therapy rarely leads to reductions in variant allele frequency or molecular remission due to dose-limiting toxicities from wild type (WT) JAK family target engagement. A JAK2 V617F mutant-selective inhibitor has the potential to selectively target mutant clones and alter pathological biology, while avoiding hematologic tolerability issues. Herein, we report the preclinical characterization of CGT1145, a JAK2 V617F JH2 mutant-selective inhibitor, which shows potential best-in-class potency and selectivity against JAK2 WT.

Results

A custom HTRF competition binding assay, using purified JH1 and JH2 domains and custom fluorescent tracers, demonstrated preferential binding to the JH2 domain (6300 nM JH1 / 0.3 nM JH2, 21,000-fold selective). Cellular activity was measured via HTRF phospho-STAT5 in GM-CSF stimulated TF-1 (JAK2 WT) and HEL 92.1.7 (JAK2 V617F homozygous) cells. CGT1145 has an IC_{50} of 91 nM in the mechanistic JAK2 V617F cellular assay and is 89-fold selective over JAK2 WT in this assay. Additional assays have been performed and support superior selectivity in inhibition of pSTAT5. This compound shows high kinome selectivity with advanceable oral bioavailability across species. Target engagement in vivo was studied using athymic nude mice subcutaneously implanted with HEL 92.1.7 cells. At 4-hours post-dose, CGT1145 showed dose dependent inhibition of tumor pSTAT5, reaching >95% inhibition at 50 mg/kg (AlphaLISA). In a mouse model of splenomegaly which mimics human MPN, athymic nude mice were implanted intravenously with Ba/F3-EPOR-JAK2V617F cells. Treatment with CGT1145 led to dose dependent inhibition of splenomegaly, with normalized spleen weights (equivalent to naïve controls and ruxolitinib treatment) at 50 mg/kg BID and 100 mg/kg QD. The efficacy of CGT1145 was further evaluated in a heterozygous JAK2 V617F transgenic mouse model, which recapitulates a classic MPN-like phenotype. CGT1145 treatment normalized spleen weights and hematologic parameters, and decreased erythroid precursor accumulation in the spleen. These findings indicate restoration of bone marrow function and attenuation of extramedullary hematopoiesis, supporting the potential of CGT1145 as a disease modifying therapy. Additionally, CGT1145 was well tolerated over the course of all in vivo efficacy studies.

Summary/Conclusion

CGT1145 is a potential best-in-class, JAK2 WT sparing, JAK2 V617F JH2 mutant-selective inhibitor that has the potential to provide significantly higher target engagement compared to approved JAK inhibitors. By selectively inhibiting JAK2 V617F signaling while preserving JAK2 WT signaling, CGT1145 has the potential to more effectively eradicate JAK2 V617F MPN-propagating cells, induce molecular remission, and minimize toxicities associated with non-selective JAK inhibition.