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Title: INTERIM ANALYSIS OF A RANDOMIZED PHASE 1 TRIAL IN HEALTHY VOLUNTEERS INVESTIGATING THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF A NOVEL FLT3/IRAK4 INHIBITOR, LOMONITINIB (ZE46-0134)

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Clinical

Background:

Lomonitinib is a highly potent and selective pan-FLT3/ IRAK4 inhibitor that targets clinically relevant FLT3 mutations (ITD, TKD) including the gatekeeper mutation as well as IRAK4, a putative escape pathway for FLT3-driven AML. In vitro studies with FLT3-specific cell lines demonstrate potent inhibition and differential decrease of FLT3 protein expression as compared to gilteritinib. Multiple *in vivo* studies with both xenograft and syngeneic immune competent murine models demonstrated that lomonitinib has superior efficacy to gilteritinib in ITD and gatekeeper mutation-dependent disease and demonstrates synergistic efficacy when administered in combination with Bcl-2 or menin inhibitors. Unlike gilteritinib, lomonitinib had minimal toxicity observed in pre-clinical rodent toxicology studies at exposures well in excess of the anticipated therapeutic exposure.

Aims:

We sought to do first-in-human clinical trial of lomonitinib in healthy volunteers.

Methods:

We conducted a Phase 1, single-center, prospective, randomized, double-blind placebo-controlled study of 4 SAD cohorts of lomonitinib administered orally to healthy adult participants. In addition, the study will include a total of 3 MAD cohorts. The primary objective was pharmacokinetics (PK), secondary objective was safety, and exploratory objective was pharmacodynamics (FLT3 target engagement). This interim analysis focuses on the 4 SAD cohorts (2, 10, and 50 mg; and 10 mg with food) and the first MAD cohort.

Results:

A total of 40 healthy subjects were treated on trial, 24 were treated with a single dose of lomonitinib (6 subjects dosed with 2 mg, 6 subjects with 10 mg, 6 subjects with 50 mg, and 6 subjects with 10 mg with a high fat meal), 6 subjects were dosed for 7 days with 50 mg on Day 1 and 10 mg on Days 2-7 (MAD cohort 1), and 10 subjects were dosed with placebo (8 in the SAD and 2 in the MAD). Lomonitinib was well tolerated with no treatment-related safety signals reported in any SAD or MAD cohort. The PK of lomonitinib was linear with mean plasma exposure values that increased proportionally with increases in dose from 2 to 50 mg and with a modest positive food effect at 10 mg when dosed after a high fat meal. There was a slow absorption with a Tmax (6 to 24 hours) and an extended half-life of approximately 92 hours. Because of the extended half-life and safety of lomonintib, we utilized a loading strategy (50 mg day 1) to reach rapid steady state concentration (Css) followed by a maintenance dose of 10 mg QD on Days 2-7. Pharmacokinetic data from the MAD cohort 1 confirmed that the loading dose of 50 mg on Day 1 permitted achievement of steady state exposures for 10 mg QD by day 4. Consistent with studies in human cells in vitro, oral administration of lomonitinib in healthy human subjects demonstrated target engagement of FLT3-ITD in an ex vivo plasma inhibition assay toward FLT3-ITD cell line at doses of ≥ 10 mg, which is anticipated to be in the therapeutic dose range based on preclinical data.

Summary/Conclusion:

Lomonitinib demonstrates favorable PK and safety profiles when administered orally as single dose, with dose-

proportional increases in systemic exposure, target engagement, and no treatment-related adverse events. In addition, lomonitinib was well tolerated with no treatment-related safety signals in the first MAD cohort thereby enabling a rapid FLT3 engagement strategy by using a loading dose that is not possible with other FLT3 inhibitors. A phase 1B study in R/R AML with mutated FLT3 has been initiated.

Keywords: KMT2A, Acute myeloid leukemia, Experimental therapeutics