Abstract: PB2627

Title: TRIAL IN PROGRESS: PHASE II STUDY OF THE NLRP3 INFLAMMASOME & MYDDOSOME INHIBITOR HT-6184 IN PATIENTS WITH LOW OR INTERMEDIATE-RISK MYELODYSPLASTIC SYNDROME (MDS)

Abstract Type: Publication Only

Topic: Myelodysplastic syndromes - Clinical

Background:

HT-6184 is a first-in-class, allosteric inhibitor of the inflammasome scaffold protein NEK7. By inducing conformational changes that prevent NEK7-NLRP3 interaction necessary for NLRP3 inflammasome assembly and IRAK1/4 activation, HT-6184 inhibits both Toll-like receptor (TLR)-priming as well as NLRP3 inflammasome complex assembly. Unlike NLRP3 ATPase-targeted inhibitors, HT-6184 effectively extinguishes NLRP3 activation and induces the disassembly of activated inflammasome complexes and circulating ASC specks. This results in potent inhibition of IL-1-family cytokine generation (IL-1β release IC50 = 22 nM in THP-1 differentiated macrophages) and the abrogation of pyroptosis. The NLRP3 inflammasome is a key biological driver of ineffective hematopoiesis in MDS that is reinforced by non-canonical IRAK1/4 signaling propagating leukemic stem cell self-renewal.

A first-in-human phase I study performed in normal volunteers showed that oral administration of HT-6184 was readily absorbed, had a prolonged elimination half-life, and effectively blocked NLRP3 inflammasome activation at low doses.

Aims:

The current Phase IIa study evaluates the efficacy, safety, and pharmacodynamics of HT-6184 administered to up to 40 adult patients with a diagnosis of very low, low, or intermediate-risk myelodysplastic syndrome (MDS) and symptomatic anemia, as defined by the Revised International Prognostic Scoring System (IPSS-R).

Methods:

All subjects will have signed Informed Consent, have symptomatic anemia, be refractory, intolerant of or ineligible for treatment with an erythroid stimulating agent (ESA), and have discontinued prior ESA at least 2 weeks prior to study treatment. The study will measure the rate of hematological improvement (according to IWG 2018 criteria), including transfusion dependence and changes in hemoglobin level as primary study endpoints. Secondary endpoints will further assess safety and tolerability, the effect of HT-6184 on biomarkers of inflammasome activation, and changes in clone size as measured by somatic gene mutation variant allele frequency. HT-6184 is administered orally on a weekly 5 days on and 2 days off schedule on a 28-day cycle. From cycle 5 to cycle 8, dosing with epoetin alfa subcutaneously (SC) weekly or darbepoetin alpha SC every 2 weeks is permitted in subjects not responding to HT-6184 monotherapy at week 16.

Results:

This is a trial in progress. Results are currently ongoing. Available patient data will be presented.

Summary/Conclusion:

This multi-center, Phase IIa clinical trial started enrollment and first patient treatment on 9 December 2023, with the study now active in 8 centers. Preliminary safety, efficacy, and biomarker outcomes data from HT-6184 treatment will be presented

Keywords: Myelodysplastic syndrome, Phase II, Clinical trial, Inflammation