**INTRODUCTION**

- Imetelstat is a first-in-class telomerase inhibitor in development for the treatment of myeloid malignancies, including treatment of transfusion-dependent anemia in patients with lower-risk myelodysplastic syndromes (LR-MDS).
- Imetelstat is a 13-mer N3P triphosphoramidate oligonucleotide with a rigid tail to enhance cellular uptake and stability. It has a sequence complementary to and specifically binds with high affinity to the template region of the RNA component of human telomerase (Figure 1).
- Imetelstat and other oligonucleotide classes have structural similarities; however, the mechanism of action for imetelstat is not antisense based, as it does not target mRNA of any gene. Instead, it acts as a classical RNaseH-dependent elimination from the central compartment.
- Telomerase inhibition by imetelstat leads to loss of a malignant cell’s ability to maintain telomere length, resulting in inhibition of cell proliferation and death of malignant cells.
- Nonclinical proof-of-concept studies for imetelstat correlated pharmacokinetic (PK) exposure, pharmacodynamic effect (target engagement by inhibition of telomerase activity) and tumor growth inhibition in vivo on xenograft mouse models and indicated that higher imetelstat doses were associated with greater plasma exposure and target engagement.

**OBJECTIVES**

- Investigate the population pharmacokinetics (popPK) of imetelstat across its clinical development program.
- Characterize imetelstat PK properties, identify and quantify sources of PK variability, and investigate the potential need for individualized dosing recommendations.

**METHODS**

- The imetelstat popPK model was developed based on data collected from 7 clinical studies (Table 1), including PK (serial and sparse), dosing, demographic, disease status, laboratory, and anti-drug antibody (ADA) status data.
- Plasma concentrations were analyzed using a hybrid ELISA assay; lower limit of quantitation ranged from 0.367 µg/mL to 0.588 µg/mL.

**RESULTS**

- The final dataset included 424 patients and 4375 imetelstat plasma concentration measurements (Table 1).
- 58.3% (2474/424) of included patients were male.
- Median (range) baseline body weight was 75.0 kg (44.0-117.0 kg).
- Final covariates effects were generally modest (Figure 4).
- No clinically relevant effects that would require dose adjustment were seen for age, sex, race, eGFR, renal impairment, or hepatic impairment.
- Significant difference in exposure between MF and MDS, which may be due to splenomegaly in MF and increased tissue uptake of imetelstat.
- Allometrically scaled BW effect improved fit, with limited exposure variation at extreme body weights.

**CONCLUSIONS**

- Imetelstat popPK was best characterized with a 2-compartment nonlinear disposition model with saturable binding/distribution to the peripheral compartment and dose- and time-dependent elimination from the central compartment (Figure 2).
- Inter-individual variation (IV) was included on CL, Vc, Kmax, and residual variability.
- Residual variability was modeled by an additive error model.
- All parameters were estimated with adequate precision (Table 2).

**REFERENCES**

1. Asai A et al. 2003 63(14), 3931-3939.
2. Herbert B et al. 2005 24(33), 5262-5268.
17. Leukemia. 2022 140 (Supplement 1):6826-6829.