PII-050

Clinical Pharmacology of Imetelstat, A First-in-Class Oligonucleotide Telomerase Inhibitor

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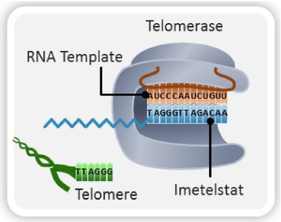
INTRODUCTION

- Imetelstat is a first-in-class telomerase inhibitor in development for the treatment of myeloid malignancies, including treatment of transfusion-dependent anemia in lower-risk myelodysplastic syndromes (LR-MDS).
- Imetelstat is a 13-mer N3'→P5' thio-phosphoramidate oligonucleotide with a lipid tail to enhance cellular uptake[1-2]. 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 active site enzyme inhibitor.
- 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[3-11].
- 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* in xenograft mouse models and indicated that higher imetelstat doses were associated with greater plasma exposure and target engagement[12-13].
- The IMerge Phase 3 study (NCT02598661) established the benefit/risk of imetelstat 7.5 mg/kg q4w in LR-MDS, demonstrating a statistically significant and clinically meaningful improvement in red blood cell transfusion independence over placebo and a manageable safety profile[14].
- The clinical benefit of imetelstat in myelofibrosis (MF) was demonstrated in the IMbark Phase 2 randomized dose-finding study (NCT02426086)[15]. The confirmatory IMpactMF Phase 3 study (NCT04576156) is ongoing to evaluate a potential improvement in overall survival for imetelstat compared to best available therapy in patients with MF[16].

Figure 1. Imetelstat Mechanism of Action



OBJECTIVE

Evaluate the clinical pharmacology properties of imetelstat to support its optimal use to treat transfusion-dependent anemia in patients with LR-MDS at the proposed clinical dose of 7.5 mg/kg* every-4 weeks (q4w) administered over 2 h IV infusion.

METHODS

- The imetelstat clinical pharmacology program consists of clinical trials in patients with solid tumor or hematologic malignancies across a wide range of doses (0.4 to 11.7 mg/kg) and schedules (qw to q4w interval) and supportive nonclinical studies in human biomaterials and animals.
- Evaluations included characterization of single and multiple-dose PK, ADME properties, effect of intrinsic factors on imetelstat PK, drug-drug interaction (DDI) liability, proarrhythmic potential, and immunogenicity.
- Imetelstat PK properties and sources of PK variability were evaluated with noncompartmental and population PK (popPK) analysis from 7 pooled studies **(González Sales ASCPT 2024, PII-128)**.

RESULTS

ADME Properties

- AUC increases in a more than dose proportional manner over the 0.4-11.7 mg/kg range.
- Little to no accumulation is observed following repeat doses **(Figure 2)**.
- Imetelstat has moderate variability, with geometric mean (CV%) C_{max} of 89.2 µg/mL (27.2%) and $AUC_{0\text{-}28d}$ of 554 h·µg/mL (43.4%) in MDS following a 7.5 mg/kg dose.

Absorption

- Imetelstat is administered via IV infusion, and T_{max} is observed at the end of infusion **(Figure 2)**.

Distribution

- Human plasma protein binding is 94% *in vitro*.
- Nonclinical ADME studies demonstrate rapid distribution of imetelstat from plasma to tissue, with highest concentrations in bone marrow (site of action for myeloid diseases), and liver, kidney, and spleen.

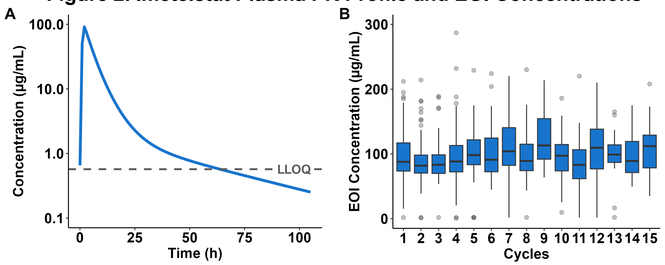
Metabolism

- Like other oligonucleotides, imetelstat is likely metabolized into smaller fragments by nucleases in tissues and the component fragments are excreted in urine[17-21].
- Hepatic cytochrome p450 (CYP) enzymes are not expected to metabolize imetelstat, as reported for other oligonucleotides[19, 22].

Elimination

- The apparent t½ of imetelstat in plasma following a 7.5 mg/kg dose in LR-MDS is 4.9 h, which likely reflects a distributional t½.
- In nonclinical ADME studies, urine is the primary route of elimination of radioactive imetelstat, with ~62 to 82% recovery in urine and ~12 to 21% recovery in feces after 168 h. Unchanged imetelstat is not detected in urine.

Figure 2. Imetelstat Plasma PK Profile and EOI Concentrations

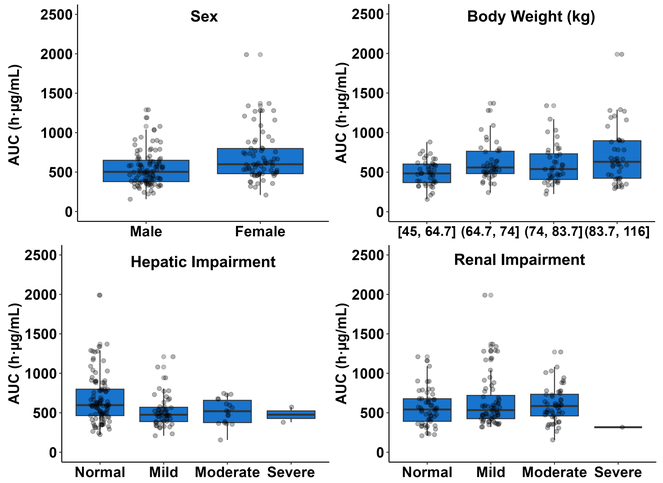


A) Model-predicted Cycle 1 concentration-time profile (N=170) and **B)** observed end of infusion concentrations (N=171) across cycles for patients with LR-MDS following 7.5 mg/kg q4w dosing.

Intrinsic Factors Influencing PK

- **Sex**: Females have lower clearance; given the limited impact on exposure (<30% increase) that is within the observed variation, dose adjustments are not warranted **(Figure 3)**.
- **Body Weight:** Theory-based allometric exponents for body weight were included on disposition parameters in popPK, supporting use of the body-weight based dosing regimen **(Figure 3).**
- **Organ Impairment:** No effect of mild to moderate hepatic or renal impairment, and limited data available on severe impairment **(Figure 3)**.
- **Age and Race:** No effect of age or race.

Figure 3. Box Plots of AUC by Intrinsic Factors in MDS



Model-predicted Cycle 1 AUC for patients with LR-MDS following a 7.5 mg/kg dose (N=170).

Drug-Drug Interactions

Effect of Other Drugs on Imetelstat: Like other oligonucleotides[19,22], imetelstat is unlikely to be the victim of DDIs mediated by CYP enzymes or drug transporters.

Effect of Imetelstat on Other Drugs:

- *In vitro* studies suggest that imetelstat is an inhibitor of OATP1B1, OATP1B3, OAT1, and UGT1A1.
- Considering imetelstat's short plasma t½, lack of accumulation, and q4w dosing, clinically relevant drug interactions with substrates of these transporters and enzyme are unlikely.

Proarrhythmic Potential

- Imetelstat does not inhibit the hERG channel at concentrations up to 140x unbound C_{max} *in vitro*.
- No treatment-related clinical signs or effects on CNS and cardiac parameters were found in monkeys at >2.6x human C_{max}.
- No indication of cardiac toxicity in imetelstat-treated patients.
- Concentration-QT analysis is ongoing with data from clinical QT substudy in LR-MDS patients.

Immunogenicity

- Anti-drug antibodies (ADA) developed at a low frequency in patients with LR-MDS (17%) in the IMerge study and MF (21%) in the IMbark study.
- No effect of ADA was found on imetelstat PK, safety, or efficacy in LR-MDS.

CONCLUSIONS

- Imetelstat disposition properties were well characterized in support of the 7.5 mg/kg q4w dosing regimen in LR-MDS.
- No dose adjustments are warranted for sex, mild to moderate renal or hepatic impairment, age, or race.
- Body-weight based dosing is supported by the popPK analysis.
- There are no clinically relevant drug-drug interactions for imetelstat.
- Based on integrated nonclinical and clinical assessments, an imetelstat effect on QT prolongation is unlikely.
- ADA develop at low frequency and do not affect the benefit/risk profile in LR-MDS.

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*Imetelstat dose level expressed in terms of imetelstat sodium (7.5 mg/kg imetelstat sodium = 7.1 mg/kg imetelstat active moiety).

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