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Novel Nonlinear Population Pharmacokinetic Model of Imetelstat, a First-in-Class Oligonucleotide Telomerase Inhibitor

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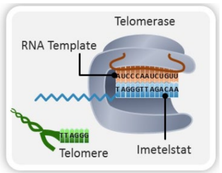
INTRODUCTION

- Imetelstat is a first-in-class telomerase inhibitor in development for the treatment of myeloid malignancies, including treatment of transfusion-dependent anemia in patients with 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



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 patients receiving imetelstat in 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 hybridization ELISA assay; lower limit of quantitation ranged from 0.367 µg/mL - 0.588 µg/mL.

Table 1. Clinical Studies Included in popPK Analysis

Study Number (NCT) Phase/Design	Population (N)	Imetelstat Dose (2 h IV infusion)
CP14A004 (NCT00594126) Phase 1; open-label, dose-escalation	Multiple myeloma (N=19)	QW: 3.2 to 7.2 mg/kg Days 1 and 8 Q3W: 6.0 mg/kg
CP04-151 (NCT00124189) Phase 2; open-label, dose-escalation	Chronic lymphoproliferative disease (N=72)	QW: 20 to 240 mg/m^2 (*6 h infusion) QW: 160 or 200 mg/m^2 Days 1 and 8 Q3W: 200 mg/m^2
CP05-101 (NCT00310895) Phase 1; open-label, dose-escalation	Solid tumor malignancies (N=22)	QW: 0.4 to 4.8 mg/kg Days 1 and 8 Q3W: 4.8 to 11.7 mg/kg Q4W: 9.4 or 11.7 mg/kg
CP14B013 (NCT01242930) Phase 2; open-label, alone or in combination with lenalidomide	Multiple myeloma (N=13)	Days 1 and 8 Q4W: 7.5 or 9.4 mg/kg
CP14B015 (NCT01243073) Phase 2; open-label	Essential thrombocythemia or polycythemia vera (N=20)	QW: 7.5 or 9.4 mg/kg
MYF2001/IMbark (NCT02426086)[15] Phase 2; randomized, dose-finding	Myelofibrosis (N=107)	Q3W: 4.7 or 9.4 mg/kg
MDS3001/IMerge (NCT02598661)[14] Phase 2; open-label, single-arm Phase 3; double-blind, randomized, placebo-controlled	Lower-risk myelodysplastic syndromes (N=171)	Q4W: 7.5 mg/kg

- Preliminary modeling considered 1- and 2-compartment models following 0-order input from IV infusion.
- Inspection of PK profiles showed greater than dose proportional exposures, therefore nonlinear models were investigated.
- Based on physiological considerations and oligonucleotide properties, body weight (BW) was incorporated on imetelstat PK properties using allometric scaling coefficients[17,18].
- Covariates were investigated for influence on imetelstat PK with stepwise forward addition (decrease in objective function value (OFV) of ≥6.635 ($p \leq 0.01$)) to develop the full covariate model, followed by backwards elimination (increase in OFV of ≥10.83 ($p \leq 0.001$, with 1 degree of freedom)) to derive the final model.
- Model evaluation was assessed through goodness-of-fit plots and visual predictive checks (VPCs).
- Forest plots were developed to visualize the effects of significant covariates on imetelstat exposure.
- Software included R v4.1.3 for dataset assembly, and NONMEM® v7.4 (ICON, Ellicott City, MD) and Pirana v2.9.8 (Certara, Princeton, NJ) for popPK analysis.

RESULTS

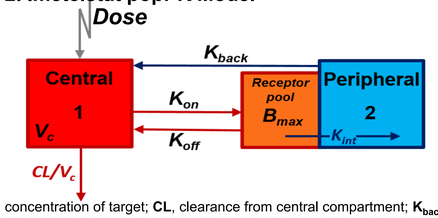
Patient Characteristics

- The final dataset included 424 patients and 4375 imetelstat plasma concentrations **(Table 1)**.
- 58.3% (247/424) of included patients were male.
- Median (range) baseline body weight was 75.0 kg (44.0–161 kg).
- Baseline spleen volume data were only available for Study MYF2001.
- ADA data were available for MYF2001 and MDS3001.

Imetelstat popPK Model

- Imetelstat PK 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)**.

Figure 2. Imetelstat popPK Model



B_{max}, total concentration of target; **CL**, clearance from central compartment; K_{back}, transfer rate from peripheral to central compartment; K_{int}, internalization rate constant; K_{off}, dissociation rate constant; K_{on}, binding rate constant; V_c, central volume of distribution

- Inter-individual variation (IIV) was included on CL, V_c, B_{max}, and residual variability.
- Residual variability was modeled by an additive error model.
- All parameters were estimated with adequate precision **(Table 2)**.

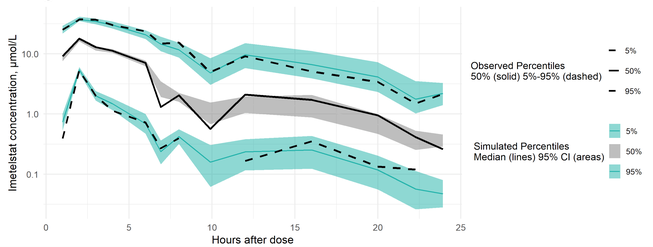
Table 2. Parameter Estimates from Final popPK Model

Parameter (units)	Value	RSE (%)	Shrinkage (%)
CL (L/h/70k kg)	0.969	3.38	—
V_c (L/70 kg)	3.91	2.54	—
K_{back} (1/h/70 kg)	0.0305	8.13	—
B_{max} (µmol/L)	15.5	6.80	—
K_{int} (L/h/70 kg)	0.0864	10.6	—
K_{on} (L^2/(µmol/L · h)	0.157	8.58	—
K_{off} (L/h)	0.608	10.8	—
Effect of spleen volume on B_{max}	0.672	29.6	—
Effect of myelofibrosis on B_{max}	1.35	7.18	—
Effect of multiple myeloma on V_c	−0.239	27.4	—
Effect of dose on CL	−0.390	9.79	—
Effect of myelofibrosis on CL	0.650	8.45	—
Effect of sex on CL	−0.313	16.1	—
Effect of time on CL	6190	6.11	—
Effect of sex on V_c	−0.121	27.0	—
IIV on CL (CV%)	43.6	4.26	10.4
Correlation of ETA on CL and V_c (*r*)	55.6	10.4	—
IIV on V_c (CV%)	25.4	6.01	19.6
IIV on B_{max} (CV%)	43.5	9.27	44.1
IIV residual variability (CV%)	55.5	4.04	16.7
Residual variability (CV%)	22.2	3.88	13.2

Model Evaluation and Simulations

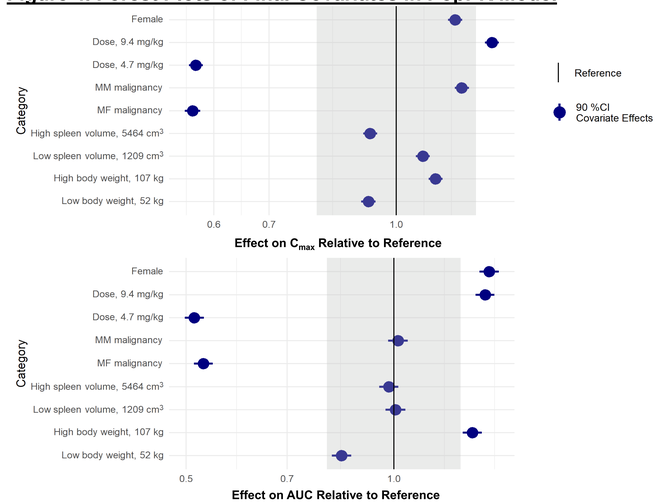
- The VPC confirms final model appropriateness **(Figure 3)**.

Figure 3. VPC for Final Imetelstat PopPK Model



- Final covariates effects were generally modest **(Figure 4)**.
- No clinically relevant effects that would require dose adjustment were seen for age, sex, race, mild to moderate 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.

Figure 4. Forest Plots of Final Covariates in PopPK Model



Reference patient: male of 70 kg with MDS receiving 7.5 mg/kg imetelstat. Reference spleen volume (MF only): 3010 cm^3. Gray shading: 80-125% change relative to reference. Exposures simulated after single dose for N=100 virtual patients simulated per category.

CONCLUSIONS

- Imetelstat PK was described by a 2-compartment model with saturable binding/distribution to the peripheral compartment and dose- and time dependent elimination from the central compartment.
- The analysis supports the BW-based dosing approach, established the lack of need for dose individualizations in various subpopulations, and supports dose differences based on malignancy type (e.g., LR-MDS vs MF).
- The final popPK model can be used to reliably derive individual exposure metrics for exposure–response analyses.

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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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