A Pharmacokinetic (PK)-Pharmacodynamic (PD) Relationship Exists for Efficacy of Iloperidone, a Novel Investigational Atypical Antipsychotic Agent

#507

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ABSTRACT

Introduction: Iloperidone is an investigational mixed D_2/5-HT_2 antagonist antipsychotic with affinity for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_6 receptors. This profile predicts clinical efficacy for schizophrenia with reduced extrapyramidal side-effects. We investigated the exposure-response relationship for iloperidone through PK-PD modeling analysis.

Methods: Iloperidone plasma levels were obtained at steady state after dose administration during two phase 3 trials. Only patients who reached target dose and were maintained at that dose level ≥5 days (reaching steady state) were included in PK-PD analysis. Trial data were combined with those of a previous PK study, which found that the PK of iloperidone was dose linear from 2 to 12 mg bid, to build a population PK model. C_{avg} = 0 was assigned to placebo-treated patients as baseline for comparison. After modeling, predicted or simulated values of C_{avg} at last steady state dose for patients from the two phase 3 studies were made and correlated with last available efficacy measurements using multiple regression analysis.

Results: Schizophrenia symptom improvement was associated with higher iloperidone C_{avg} after baseline adjustment (study drug ranges, 12-24 mg/d). Statistically significant greater proportions of responders (≥20% improvement from baseline) in iloperidone-treated patients had C_{avg} ≥5 ng/mL (n = 43) compared with those with C_{avg} <5 ng/mL (n = 224) for 4 out of 5 efficacy scales ($P < .05$) (Positive and Negative Syndrome Scale [PANSS] total, PANSS positive, PANSS general psychopathology, and Brief Psychiatric Rating Scale [BPRS]).

Conclusions: Iloperidone showed an exposure-response relationship, suggesting that the minimal effective exposure level for iloperidone is 5 ng/mL. Therefore, full therapeutic iloperidone benefit should be assessed once steady state is achieved. Therapy with iloperidone has the potential to be patient individualized through consideration of this PK-PD relationship and tolerability/adverse effects.

INTRODUCTION

- Iloperidone, an investigational mixed D_2/5-HT_2 antagonist antipsychotic with high affinity for 5-HT_{2A}, D_2, and D_3 receptors; moderate affinity for D_4, 5-HT_6, 5-HT_7, and $NE_{\alpha 1}$ receptors; and low affinity for 5-HT_{1A}, D_1, and H_1 receptors, is expected to have clinical efficacy for a broad range of schizophrenia symptoms and a reduced potential for extrapyramidal side effects.[1-4]
- The objective of this study was to evaluate the relationship between iloperidone plasma levels and efficacy measures using pharmacokinetic (PK) and pharmacodynamic (PD) modeling.

METHODS

Study Population and Design

- Male and nonpregnant female patients with schizophrenia or schizoaffective disorder
- Two double-blind, placebo- and active-controlled, multicenter trials (ILP3000 and ILP3005) were included in the study.
- Patients were randomized to 6 weeks of treatment with
  - ILP3000: Iloperidone 2 mg two times daily (bid), 4 mg bid, or 6 mg bid; haloperidol 7.5 mg bid; or placebo
  - ILP3005: Iloperidone 6 to 8 mg bid, 10 to 12 mg bid; risperidone 3 to 4 mg bid; or placebo
- Patients who received the same bid dosage for ≥5 days were designated as reaching steady state.
- Plasma samples were collected from patients who achieved steady state doses at days 14, 28, and 42, or at the time of premature discontinuation.
- Primary response was calculated as the absolute change between baseline and the last available measurement for efficacy and safety variables.

Assessments

Efficacy

- Positive and Negative Syndrome Scale (PANSS) total score (PANSS-T)
- PANSS positive score (PANSS-P)
- PANSS negative score (PANSS-N)
- PANSS general psychopathology score (PANSS-GP)
- PANSS-derived Brief Psychiatric Rating Scale (BPRS)

Population PK Modeling

- Concentration data from the PK study CILO0112 were independently combined with data from the ILP3000 and ILP3005 trials to build population PK models.
- The superposition principle was assumed because the analysis results of CILO0112 demonstrated that the PK profile of iloperidone was dose linear from 2 to 12 mg bid.
- Patients from all 3 trials were assumed to have similar PK characteristics.
- A model showing the predicted mean daily concentration (C_{avg}) per dose of iloperidone was generated using the NONMEM (nonlinear mixed effect modeling) software, version V.[5]

PK-PD Evaluations

- For each patient, C_{avg} was obtained through PK modeling.
- C_{avg} was correlated with efficacy or safety measurements using multiple or logistic regression models, adjusting for baseline measurements.
- Patients who were randomized to placebo were assigned a C_{avg} of 0 mg as a baseline for comparison.

Statistical Analysis

- To analyze the PK-PD relationship, the C_{avg} at the last steady state dose was correlated with the last available efficacy assessment.
- When the last administered dose was at steady state but plasma samples were not collected, simulation was used to obtain the mean concentration for the last steady state dose received.
- The relationship between the 5 efficacy measurements and the individual modeled concentration values was assessed using multiple regression analysis.
- The relationship between ESRS and PK profile was analyzed using logistic regression and multiple regression models.

RESULTS

Patient Population

- For the ILP3000 trial, 269 patients treated with iloperidone were included in the PK modeling; 267 patients were included in the PK efficacy analysis.
- For the ILP3005 trial, 266 patients treated with iloperidone were included in the PK modeling; 298 patients receiving iloperidone and 152 receiving placebo were included in the PK efficacy analysis.

Efficacy of Iloperidone

- Schizophrenia symptom improvement was associated with higher iloperidone C_{avg} after adjusting for baseline for doses ranging from 12 to 24 mg/d.
- On a per trial basis, iloperidone treatment significantly improved 4 of 5 efficacy measures in the ILP3000 trial and all 5 efficacy measures in the ILP3005 trial.
- In a pooled analysis, iloperidone treatment demonstrated significant improvement for all 5 efficacy measurements (**Figures 1-5**).
- Maximal response was observed at 5-8 ng/mL and exceeded a clinically meaningful threshold for improvement (>20% reduction in baseline PANSS-T score) (**Figure 1**).
- Similar responses were observed for each of the PANSS subscores and for the BPRS (**Figures 2-5**).

Figure 1. Relationship Between Mean Iloperidone C_{avg} and Change in PANSS-T.

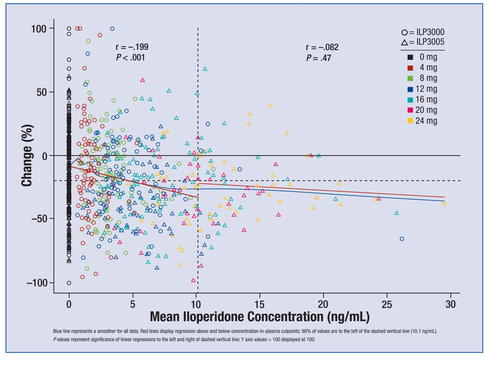


Figure 2. Relationship Between Mean Iloperidone C_{avg} and Change in PANSS-P.

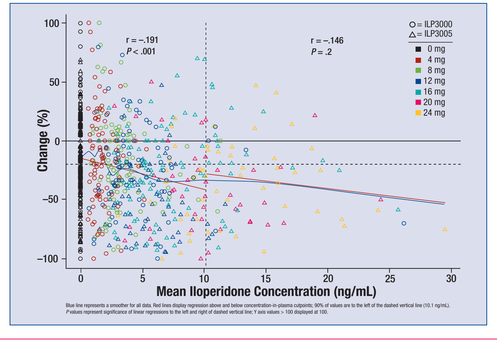
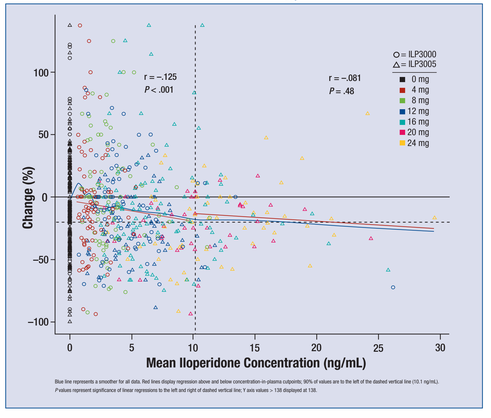


Figure 3. Relationship Between Mean Iloperidone C_{avg} and Change in PANSS-N.



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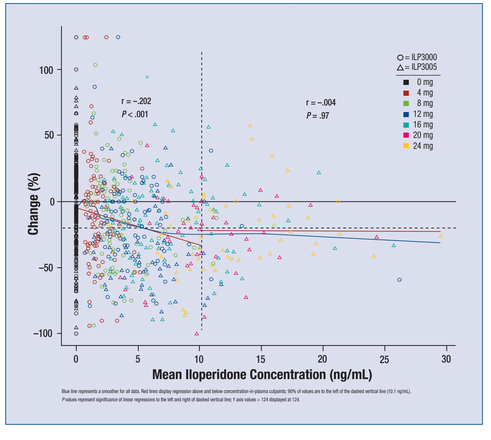
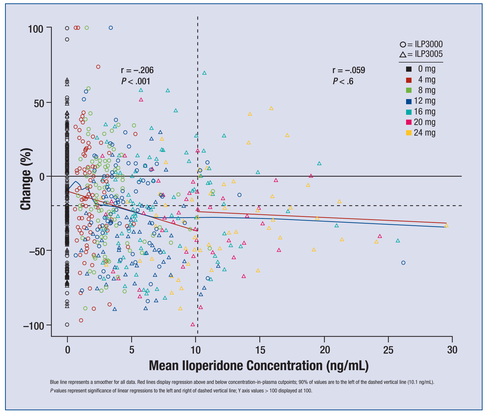


Figure 5. Relationship Between Mean Iloperidone C_{avg} and Change in BPRS.



CONCLUSIONS

- Treatment with iloperidone demonstrated an exposure-response relationship for all 5 efficacy measures.
- An effective exposure level for iloperidone appeared to be 5 ng/mL.
- Therapy with iloperidone has the potential for individualizing patient therapy based on this PK-PD relationship and tolerability/adverse effects.
- These data show a possible plateau in the concentration-response curve, suggesting that increasing iloperidone concentrations yield little additional improvements.

ACKNOWLEDGMENTS

This study was performed by Novartis Pharmaceuticals. The following people are recognized as being involved in generating the data presented in this poster: Peiming Ma, Michael Merz, Greg Sedek, Mark Schmidt, and Rocco Zaninelli.

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1. Kalkman HO et al. *Life Sci.* 2003;3:1151-1159.
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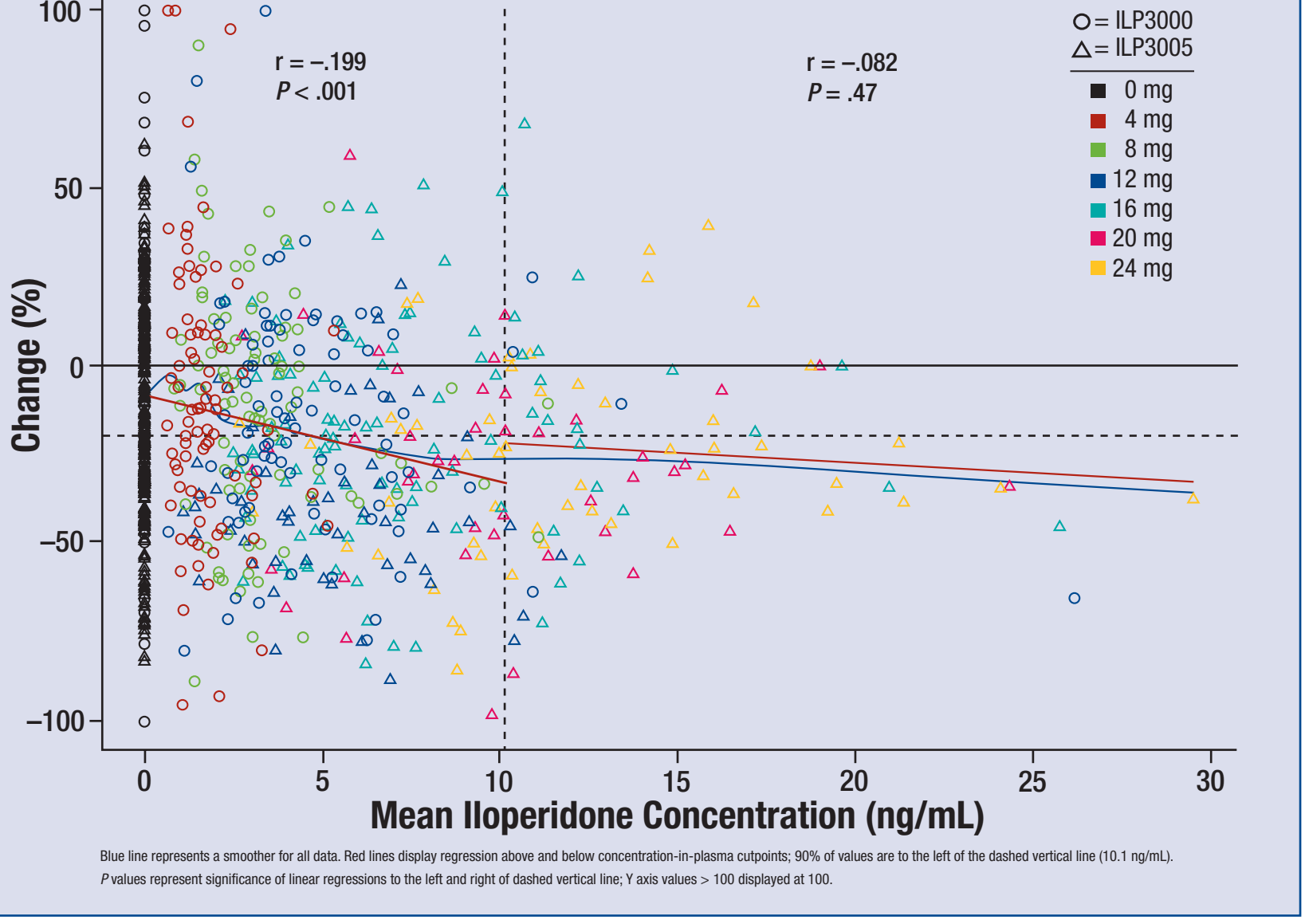

Blue line represents a smoother for all data. Red lines display regression above and below concentration-in-plasma cutpoints; 90% of values are to the left of the dashed vertical line (10.1 ng/mL).
P values represent significance of linear regressions to the left and right of dashed vertical line; Y axis values > 100 displayed at 100.

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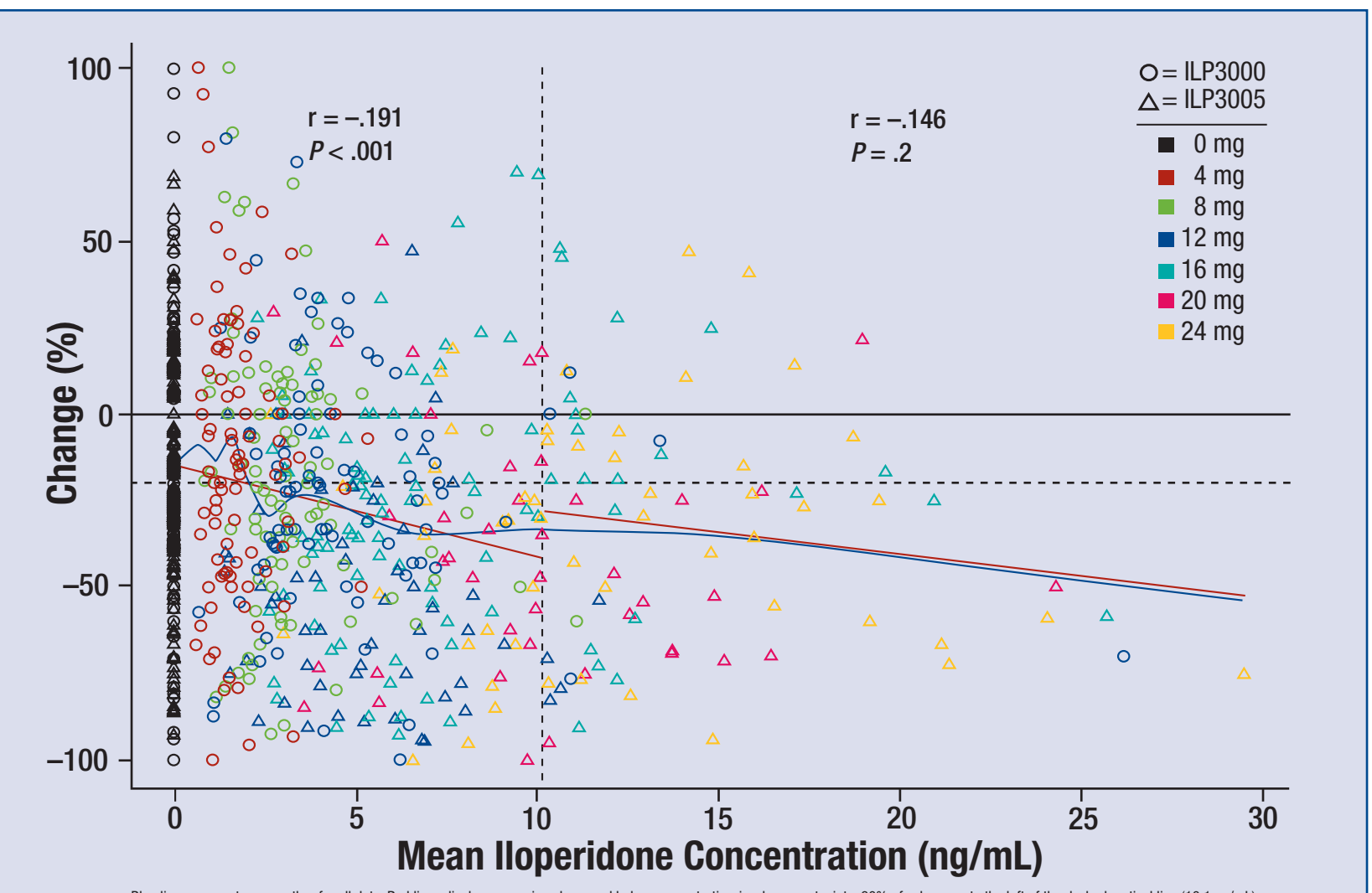

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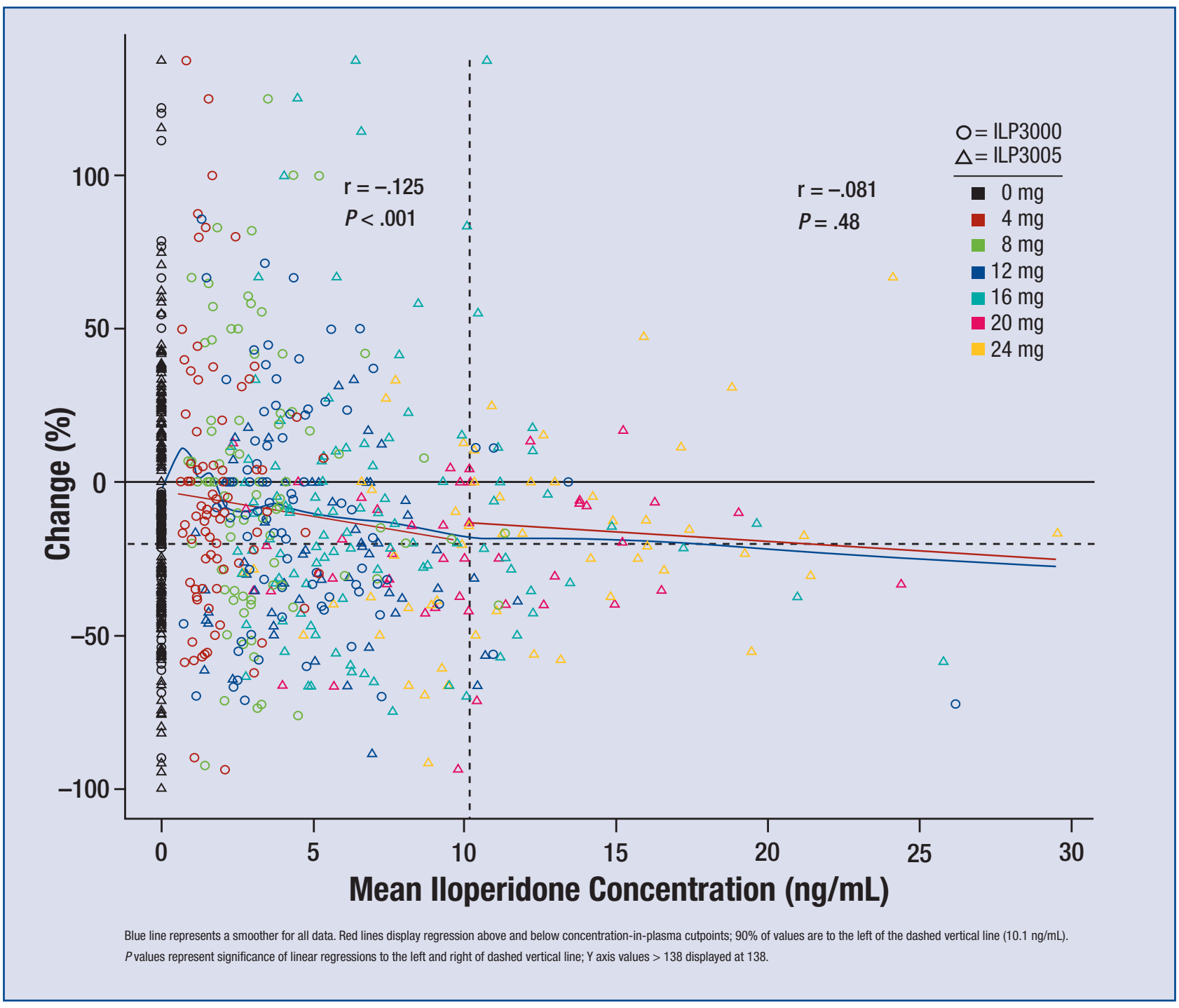

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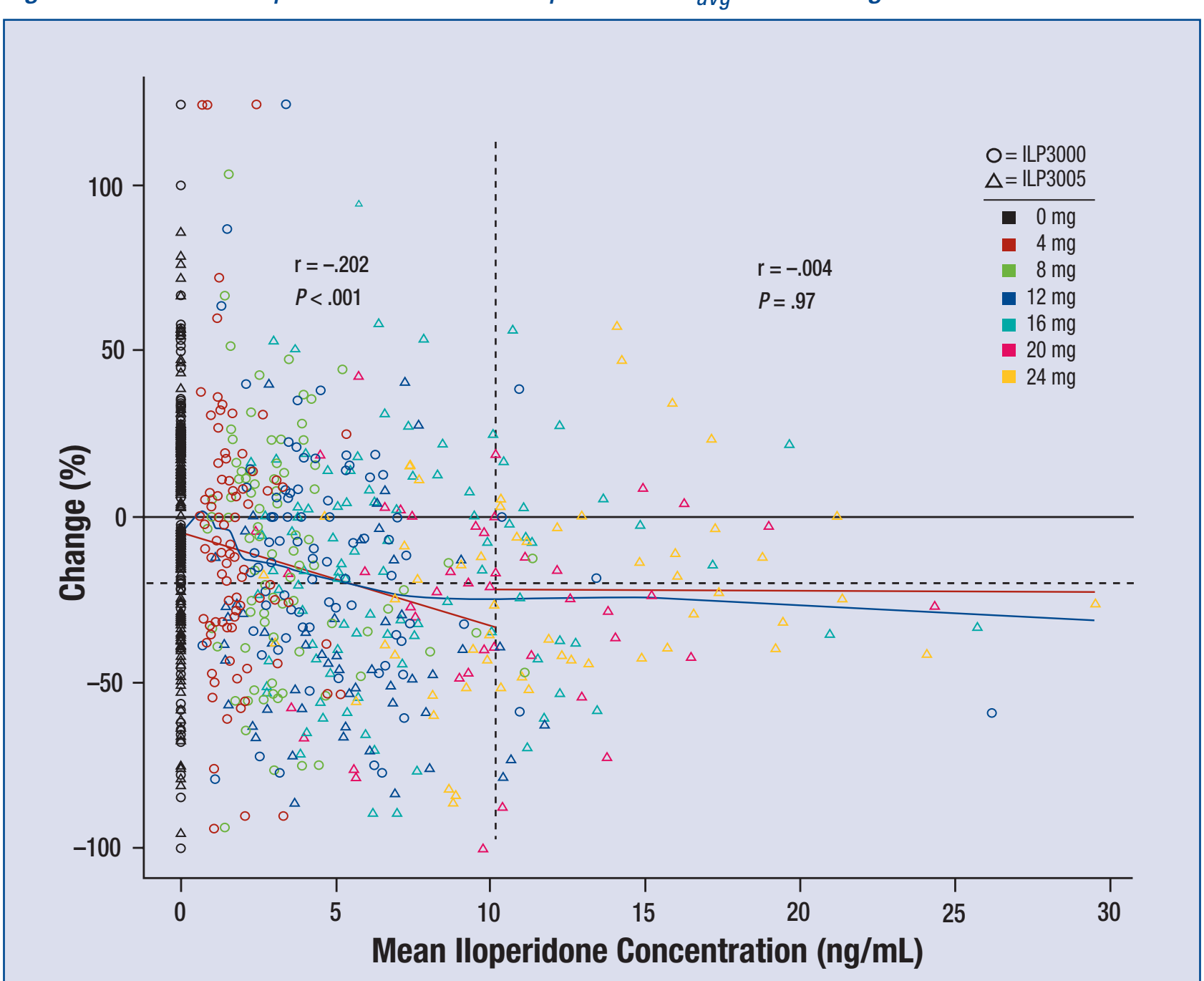

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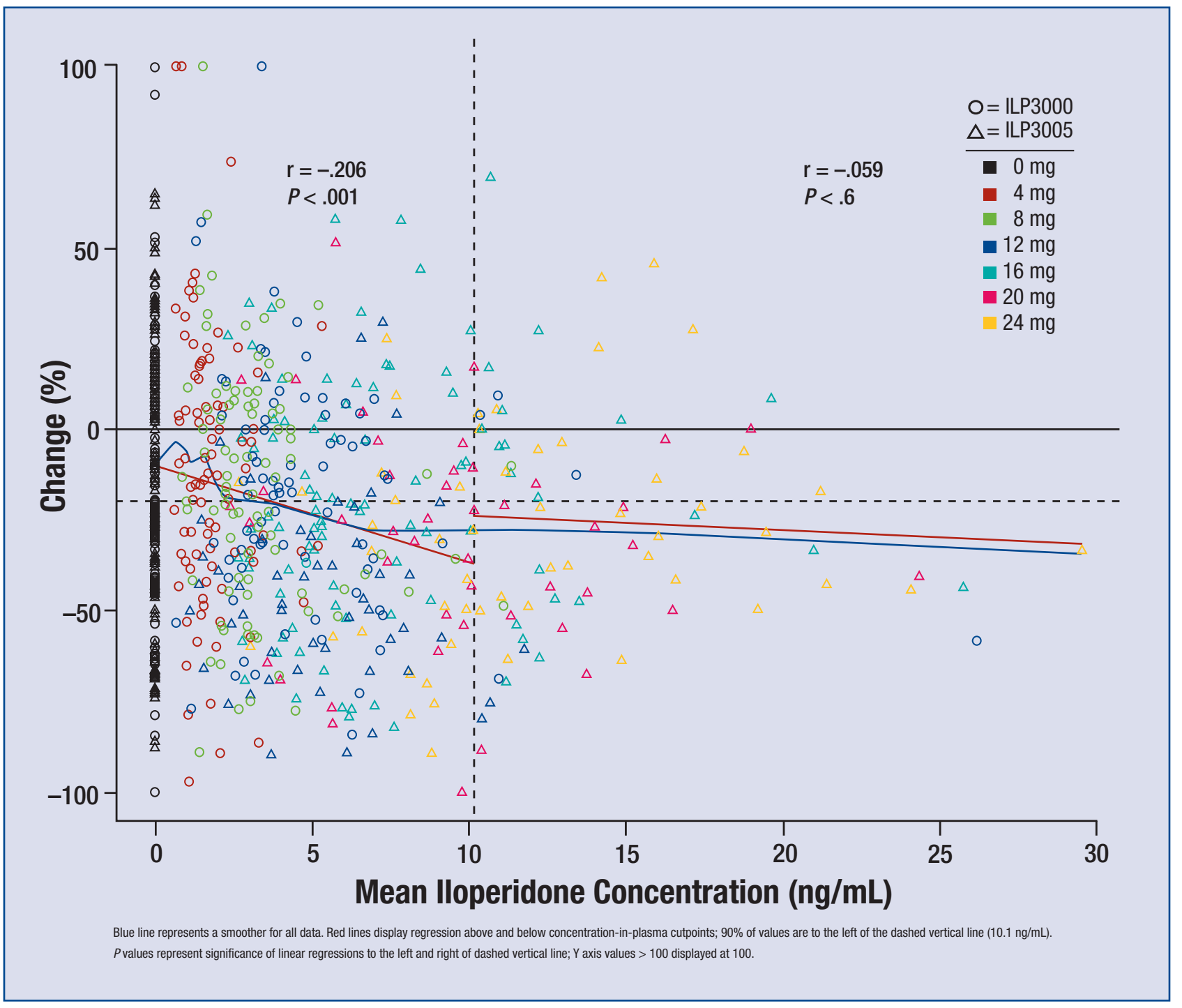

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