Phase 1/2 Study of the Activin Receptor-like Kinase-2 Inhibitor Zilurgisertib (INCB000928, LIMBER-104) as Monotherapy or With Ruxolitinib in Patients With Anemia due to Myelofibrosis

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Background

- Hepcidin is a key regulatory hormone for iron homeostasis, and elevated levels can cause functional iron-deficiency anemia[1]
- Hepcidin dysregulation contributes to anemia of chronic inflammation observed in several malignancies including myelofibrosis (MF)[2]
- MF-related anemia is associated with poor prognosis[3,4] and reductions in health-related quality of life[5]
- Activin receptor-like kinase-2 (ALK2; also known as ACVR1) contributes to MF-associated anemia via hepcidin upregulation[4,6]

Objective: To evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of zilurgisertib—a potent and selective oral ALK2 inhibitor—in patients with anemia due to MF

1. D'Angelo G. *Blood Res.* 2013;48(1):10-15; **2.** Chen Y, et al. *Blood*. 2020;136 (suppl 1):52-52; **3.** Passamonti F, et al. *Blood*. 2010;115(9):1703-1708; **4.** Naymagon L, Mascarenhas J. *Hemasphere*. 2017;1(1):e1; **5.** Tefferi A, et al. *Clin Ther.* 2014;36(4):560-566; **6.** Zhou A, et al. *Br J Haematol.* 2022;197(4):e49-e52.

Study Design

Ongoing open-label, multicenter, phase 1/2 dose-escalation and dose-expansion study (INCB 00928-104; NCT04455841)

Zilurgisertib monotherapy
- Anemia due to MF
- Resistant, refractory, lost response to or intolerant/ineligible for JAKi

Dose escalation
50 mg qd (n=4)
100 mg qd (n=4)
200 mg qd (n=6)
400 mg qd (n=8)
600 mg qd (n=1)

Identify RDE(s)

Dose expansion
n≥9 patients planned

Zilurgisertib add-on to ruxolitinib
- Anemia due to MF
- Stable dose of ruxolitinib ≥12 weeks

Dose escalation
100 mg qd (n=4)
200 mg qd (n=8)
400 mg qd (n=9)
600 mg qd (n=1)

Identify RDE(s)

Dose expansion
n=25 patients planned

Zilurgisertib plus ruxolitinib in JAKi-naive patients
- Anemia due to MF
- No prior treatment with any JAKi

Dose escalation
Starting dose,
400 mg qd (n=1)*

Identify RDE(s)

Dose expansion
n=25 patients planned

Primary endpoint: safety and tolerability of zilurgisertib ± ruxolitinib

Secondary endpoints: anemia response
- If non–transfusion dependent at baseline: Hb increase ≥1.5 g/dL relative to baseline for any rolling 12-week period during Weeks 1–24
- If transfusion dependent at baseline: achieving transfusion independence for any rolling 12-week period during Weeks 1–24

Other secondary endpoints: PK and pharmacodynamics (erythropoiesis and iron metabolism parameters)

Anemia definitions
- **Transfusion dependent (TD):** ≥4 units of red blood cell transfusions during the 8 weeks before Cycle 1 Day 1 for Hb <8.5 g/dL in the absence of bleeding or treatment-induced anemia
- **Anemic, non–transfusion dependent (NTD):** Hb <10 g/dL during screening, confirmed on 3 separate occasions ≥7 days apart, and not meeting criteria for TD

Hb, hemoglobin; JAKi, Janus kinase inhibitor; MF, myelofibrosis; PK, pharmacokinetics; qd, once daily; RDE, recommended dose for expansion.
* Not included in the current data analysis.

Patient Demographics and Clinical Characteristics

- 46 patients were enrolled at the time of analysis (data cutoff date, August 1, 2023), including 1 in the cohort of zilurgisertib plus ruxolitinib in JAKi-naive patients (data not shown)

	Zilurgisertib Monotherapy (n=23)	Zilurgisertib Add-on to RUX (n=22)
Age, median (range), y	73.0 (53–84)	77.0 (54–85)
Male, n (%)	15 (65.2)	9 (40.9)
Time since MF diagnosis, median (range), y	2.0 (0.2–23.1)	5.5 (0.8–24.1)
Transfusion dependent, n (%)	11 (47.8)	5 (22.7)
DIPSS risk level, n (%)		
High	1 (4.3)	4 (18.2)
Intermediate-2	22 (95.7)	17 (77.3)
Intermediate-1	0	1 (4.5)
Prior MF therapy, n (%)		
Ruxolitinib	14 (60.9)	22 (100.0)
Other JAKi*	3 (13.0)	2 (9.1)
Other†	9 (39.1)	10 (45.5)
Ruxolitinib starting daily total dose during study, median (range), mg	—	20 (15–50)
Hb, median (range), ‡ g/dL	7.9 (6.5–9.7)	8.0 (5.2–9.1)
Hepcidin, median (range), § ng/mL	202 (18–535)	135 (7–421)

DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; JAKi, Janus kinase inhibitor; MF, myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.
* Other JAKi included pacritinib (n=3) and fedratinib (n=2). † Other prior MF therapy included erythropoiesis stimulating agents (n=13) investigational (n=10), hydroxyurea (n=7), anagrelide (n=3), danazol (n=9), prednisone (n=3), peginterferon alfa-2a (n=3), lenalidomide (n=2), umbralisib (n=1), azacitidine (n=1), luspatercept (n=4). Some patients had more than one prior MF therapy.
‡ Baseline Hb was determined as the average of values obtained during the 3 months prior to Cycle 1 Day 1 that met the following criteria: Hb value was obtained outside the 14-day washout period following an RBC transfusion or Hb value triggered an RBC transfusion (even if obtained within the 14-day period following a transfusion). § Normal range, 0–50 ng/mL.

Safety

- Dose escalation was ongoing in both treatment groups, and MTD had not been reached at the time of analysis
- One dose-limiting toxicity occurred (400 mg add-on therapy, grade 3 alveolar hemorrhage)
- TEAEs were mainly low grade and without apparent dose dependence
- One zilurgisertib-related TEAE led to study drug discontinuation (grade 2 hyperferritinemia; 200 mg add-on therapy)

Zilurgisertib Monotherapy (n=23)		
Event, n (%)	**Any grade**	**Grade ≥3**
Most common TEAE*		
Hyperuricemia	7 (30.4)	0
Nausea	5 (21.7)	0
Pruritus	5 (21.7)	0
Cough	4 (17.4)	0
Dyspnea	4 (17.4)	0
Edema peripheral	4 (17.4)	0
Thrombocytopenia	3 (13.0)	3 (13.0)
COVID-19	3 (13.0)	2 (8.7)
Asthenia	3 (13.0)	0
Constipation	3 (13.0)	0
Decreased appetite	3 (13.0)	0
Diarrhea	3 (13.0)	0
Dysphagia	3 (13.0)	0
Epistaxis	3 (13.0)	0
Fatigue	3 (13.0)	0
Headache	3 (13.0)	0
Myalgia	3 (13.0)	0
Vomiting	3 (13.0)	0
TRAE†	14 (60.9)	2 (8.7)

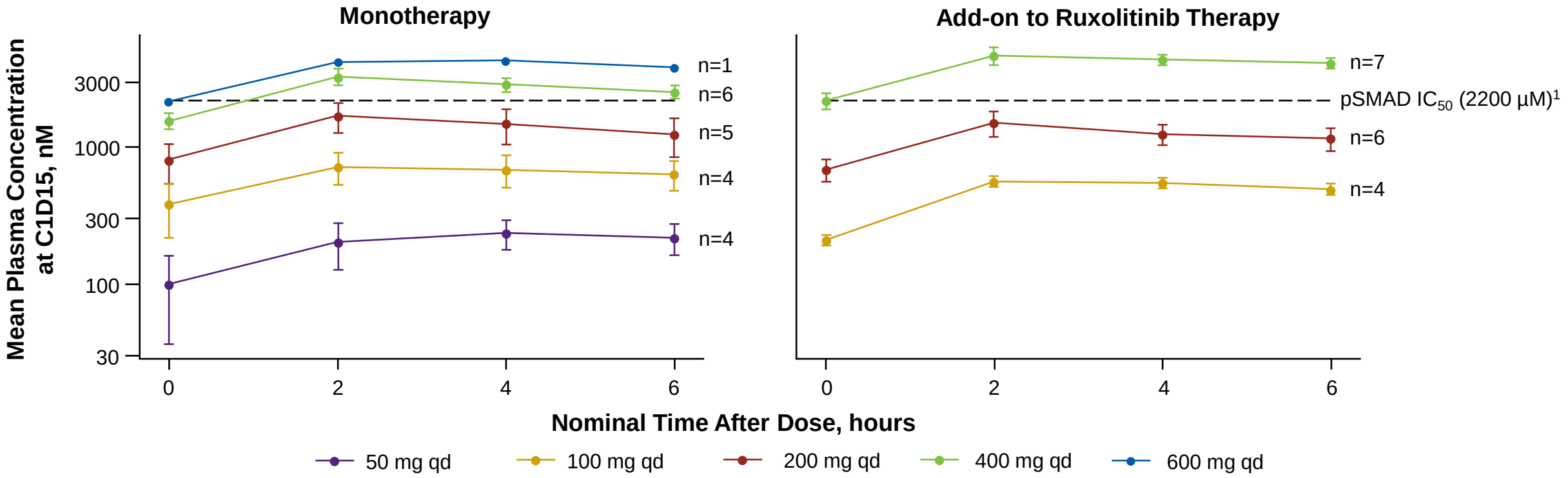
Zilurgisertib Add-on to Ruxolitinib (n=22)		
Event, n (%)	**Any grade**	**Grade ≥3**
Most common TEAE*		
Diarrhea	5 (22.7)	0
Hyperkalemia	5 (22.7)	0
Pain in extremity	4 (18.2)	0
Asthenia	3 (13.6)	1 (4.5)
Dizziness	3 (13.6)	1 (4.5)
Thrombocytopenia	3 (13.6)	1 (4.5)
Alopecia	3 (13.6)	0
Blood creatinine increased	3 (13.6)	0
Decreased appetite	3 (13.6)	0
Dyspnea	3 (13.6)	0
Edema peripheral	3 (13.6)	0
Muscular weakness	3 (13.6)	0
Urinary tract infection	3 (13.6)	0
TRAE†	12 (54.5)	1 (4.5)

MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
* Any grade occurring in ≥10% of patients. † Zilurgisertib-related per by study investigator.

Pharmacokinetic Profile

- t_{max} was 2–4 hours after zilurgisertib administration across dose groups
- Estimated $t_{1/2}$ in patients with MF was ~24 hours, consistent with that observed in healthy volunteer studies (mean of 24–27 hours across dose groups)
- Exposures above the preclinical target threshold were achieved at doses of 400 mg qd and 600 mg qd

Zilurgisertib PK Profile at Steady State



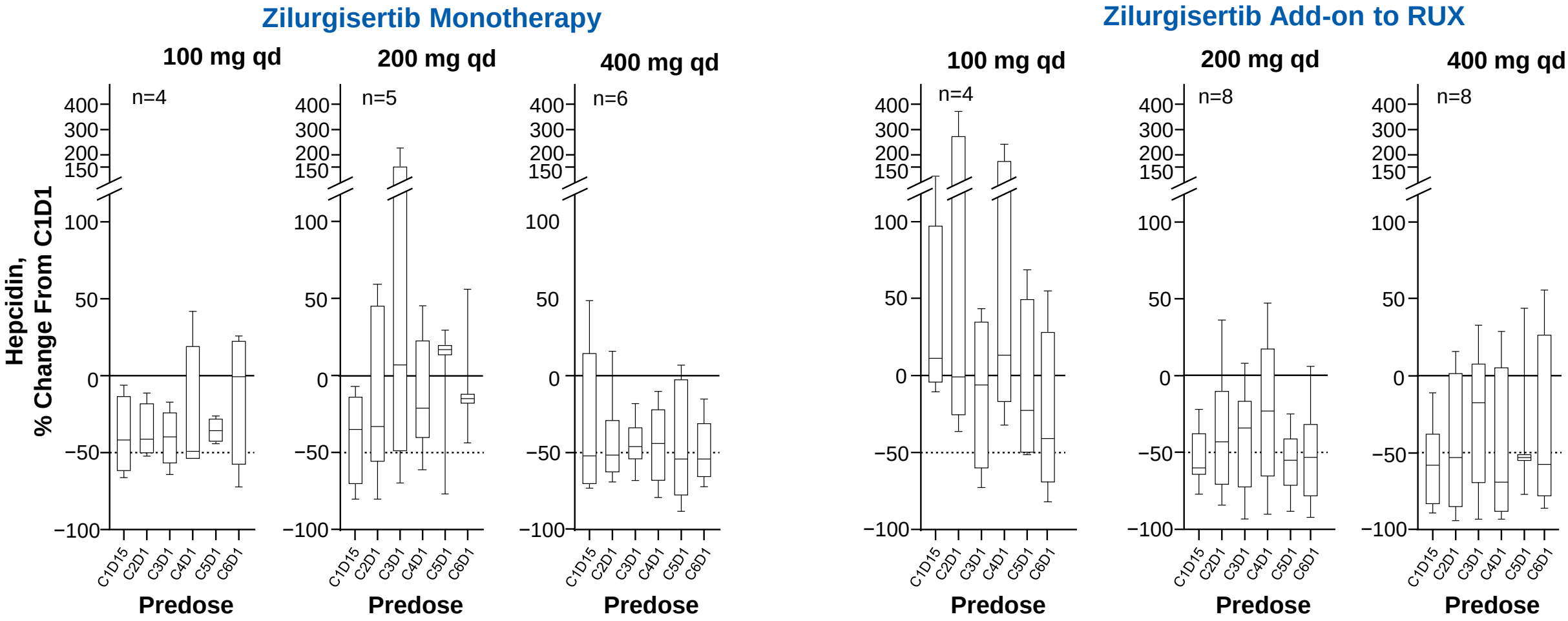
C, Cycle; D, Day; IC_{50}, 50% inhibitory concentration; MF, myelofibrosis; PK, pharmacokinetics; qd, once daily; $t_{1/2}$, half-life; t_{max}, time to maximum plasma concentration.

1. Yang Y et al, Presented at AACR 2023. Abstract CT243.

Pharmacodynamic Activity

Hepcidin Level Predose on Day 1 of Each Cycle

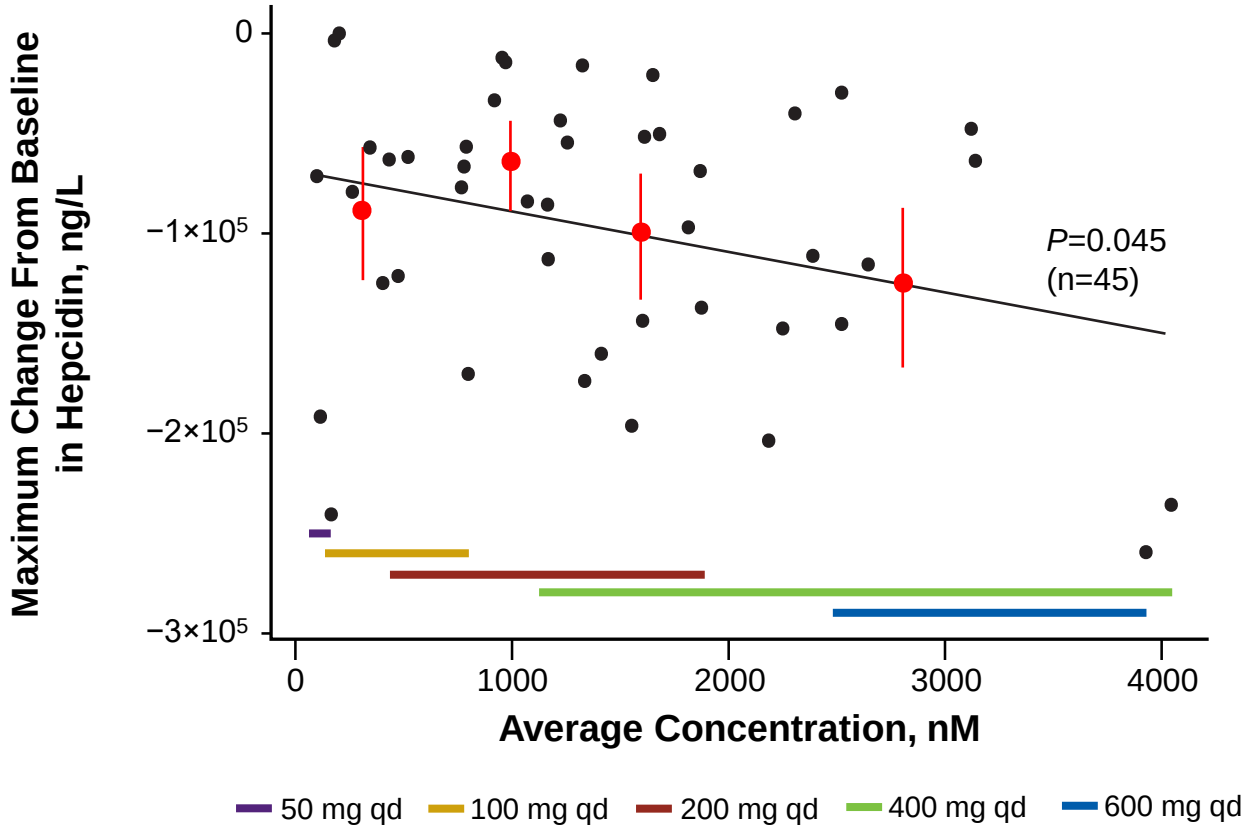
- Hepcidin suppression was observed in both treatment groups, with greater control of hepcidin over time observed at higher doses



C, Cycle; D, Day; qd, once daily.
Data shown for patients who completed ≥1 treatment cycle.

Exposure-Response

Maximum Decrease in Hepcidin



A population PK model was used to simulate the average concentration (C_{avg}) using the actual doses the patients received over the period from study start until the maximum change

- Zilurgisertib exposure is a statistically significant predictor for maximum hepcidin decrease using a univariate linear regression model

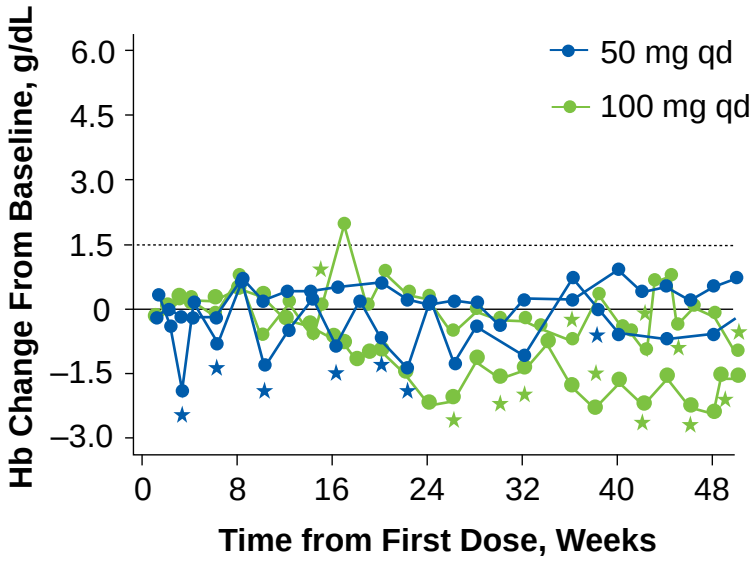
PK, pharmacokinetics; qd, once daily.

Anemia Response

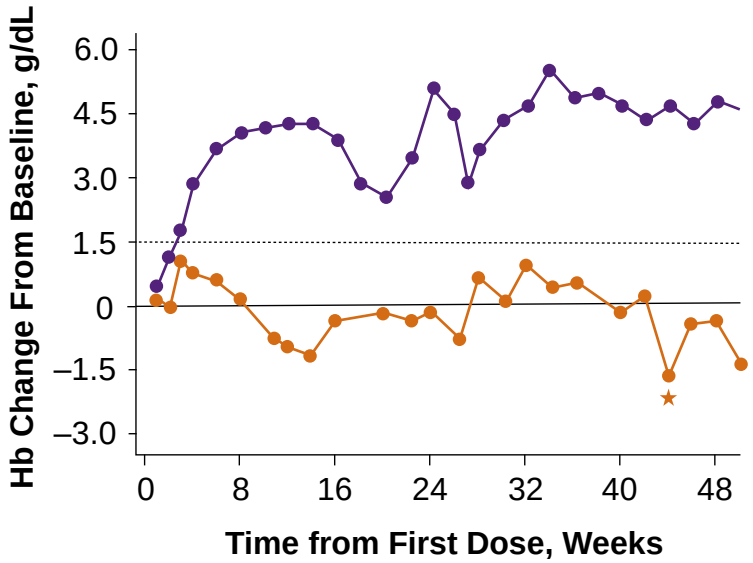
Monotherapy Population

- Among the 7 NTD patients who completed 24 weeks of treatment, anemia improvement (Hb increase ≥1.5 g/dL from baseline) was observed in 2 patients (200-mg and 400-mg cohorts)
  - Both patients achieved Week 24 anemia response (Hb increase ≥1.5 g/dL from baseline for any rolling 12-week period during Weeks 1–24)

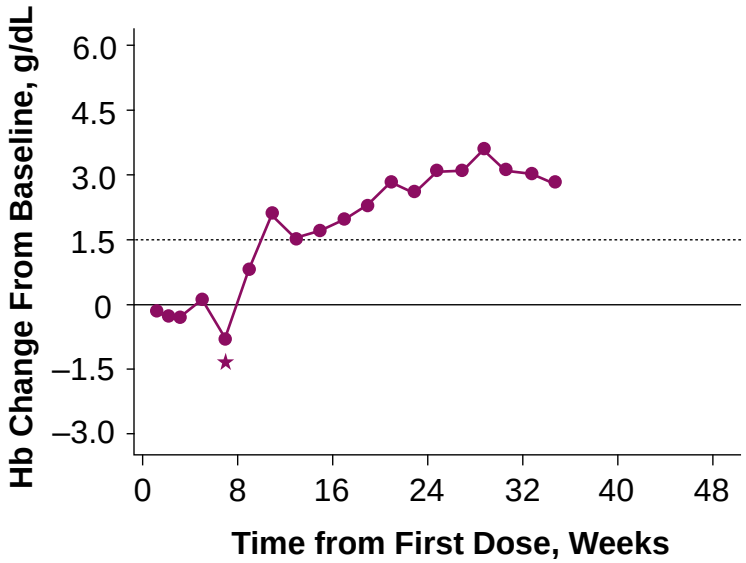
Zilurgisertib Monotherapy 50 & 100 mg qd



Zilurgisertib Monotherapy 200 mg qd



Zilurgisertib Monotherapy 400 mg qd



Baseline Baseline + 1.5 g/dL ★ Transfusion

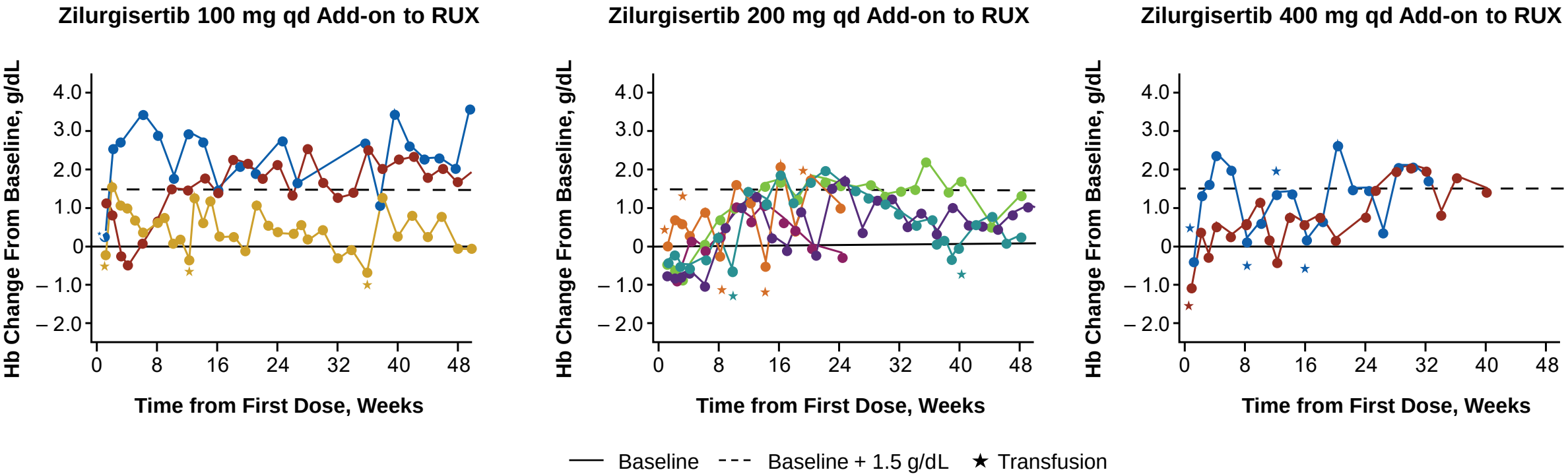
- None of the 6 TD patients who completed 24 weeks of treatment achieved transfusion independence

Hb, hemoglobin; NTD, non–transfusion dependent; TD, transfusion dependent.

Anemia Response

Combination Therapy Population

- Among the 10 NTD patients who completed 24 weeks of treatment, anemia improvement (Hb increase ≥1.5 g/dL from baseline) was observed in 2 patients (100-mg cohort)
  - One patient achieved Week 24 anemia response (Hb increase ≥1.5 g/dL from baseline for any rolling 12-week period during Weeks 1–24), and one patient achieved anemia response by Week 48



- The one TD patient who completed 24 weeks of treatment did not achieve transfusion independence

Hb, hemoglobin; NTD, non–transfusion dependent; qd, once daily; RUX, ruxolitinib; TD, transfusion dependent.

Conclusions

- Treatment with zilurgisertib monotherapy or as add-on to ruxolitinib in this patient population was generally well tolerated, with predominantly grade 1/2 TEAEs and only 1 DLT
- Greater hepcidin reduction was associated with higher zilurgisertib exposure in the exposure-response analysis, and greater control of hepcidin over time was observed at higher doses in both treatment groups
- Preliminary improvements in anemia were observed in non–transfusion-dependent patients, which suggests potential for therapeutic activity
- An additional cohort is currently enrolling, which is evaluating zilurgisertib plus ruxolitinib combination as first-line treatment in JAK inhibitor–naive patients with MF and anemia

DLT, dose-limiting toxicity; JAK, Janus kinase; MF, myelofibrosis; TEAE, treatment-emergent adverse event.

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