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A Phase 1/2 Study of INCB000928 as Monotherapy or Combined With Ruxolitinib in Patients With Anemia due to Myelofibrosis

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Introduction

- Anemia occurs in more than one-third of patients at myelofibrosis (MF) diagnosis and can be exacerbated by currently available MF therapies[1,2]
- MF-related anemia is associated with poor prognosis[2,3] and reductions in health-related quality of life[4]
- Activation of activin receptor-like kinase (ALK)-2 (also known as ACVR1) may contribute to MF-associated anemia by upregulating hepcidin levels, leading to functional iron deficiency[2,5]

Objective

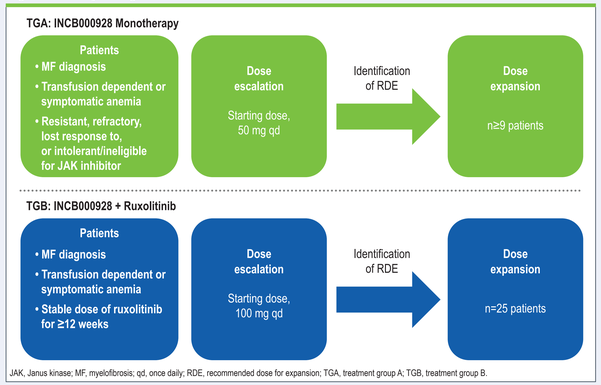
- To evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics of INCB000928, a potent and selective, oral ALK2 inhibitor, in patients with anemia due to MF

Methods

Study Design and Patients

- INCB 00928-104 (NCT04455841) is an ongoing open-label, multicenter, phase 1/2 dose-escalation and dose-expansion study evaluating INCB000928 alone (treatment group A [TGA]) or in combination with ruxolitinib (treatment group B [TGB]; **Figure 1**)

Figure 1. Study Design



JAK, Janus kinase; MF, myelofibrosis; qd, once daily; RDE, recommended dose for expansion; TGA, treatment group A; TGB, treatment group B.

- Eligible patients were ≥18 years old with histologically confirmed diagnosis of primary or post–polycythemia vera/essential thrombocythemia MF of intermediate (Int)-1 (TGB only) or Int-2/high-risk (TGA and TGB) per the Dynamic International Prognostic Scoring System
  - Patients were transfusion dependent (≥4 units of red blood cell transfusions during the 28 days or 8 weeks before Cycle (C) 1 Day (D) 1 for hemoglobin [Hb] <8.5 g/dL in the absence of bleeding or treatment-induced anemia) or presented with symptomatic anemia (Hb <10 g/dL during screening on 3 separate occasions ≥7 days apart)
  - In TGA, patients were resistant, refractory, or had lost response to Janus kinase (JAK) inhibitor treatment (≥12 weeks) or were intolerant of or not eligible for JAK inhibitor treatment
  - In TGB, patients were on a therapeutic and stable regimen of ruxolitinib for ≥12 weeks
- The TGA INCB000928 starting dose was 50 mg once daily (qd), with dose increases of ≤2-fold performed until a grade ≥2 toxicity with reasonable probability of being related to the treatment group was observed; subsequent dose increases were limited to ≤50% until the maximum tolerated dose (MTD) was reached or the recommended dose for expansion (RDE) was identified
- The TGB starting dose was 100 mg qd (half of the safe and tolerated dose, as determined in a study in healthy volunteers)

Endpoints

- The primary endpoint was safety and tolerability of INCB000928 ± ruxolitinib, including determination of dose-limiting toxicities (DLTs), MTD, and RDE
- Secondary endpoints include efficacy (as assessed by anemia response parameters), PK, and pharmacodynamics

Pharmacokinetics

- Blood sampling for PK analyses was performed at C1D1 and C1D15 (predose and 2, 4, and 6–8 hours postdose)
- Target thresholds include protein binding–adjusted 50% or 90% inhibitory concentration (IC_{50}/IC_{90}) values for inhibition of bone morphogenetic protein (BMP)-7–induced hepcidin in human primary hepatocytes and IC_{50} value for inhibition of pSMAD1 observed in an in vivo mouse model (target value shown is adjusted to correspond to human protein binding)
- Simulated data (Day 14–15, steady state) were obtained from simulation of various dose regimens (200–600 mg qd/twice daily [bid] for 28 days) based on a population PK model developed with data from healthy participants

Pharmacodynamics: Hepcidin Measurement

- Hepcidin concentration was measured from plasma isolated from blood collected in a sodium heparin tube at C1D1 and C1D15 (predose and 2, 4, and 6–8 hours postdose)
- Plasma hepcidin was measured using a validated fluorometric immunoassay (ProteinSimple hepcidin assay, Ella automated system; Biotechne, Minneapolis, MN)

Results

Baseline Characteristics

- A total of 18 patients enrolled at the time of analysis (data cutoff date, August 23, 2022), including 14 in TGA and 4 in TGB (**Table 1**)
  - High baseline hepcidin was observed in both treatment groups
  - Mean monthly transfusion burden during the 12 weeks before first dose of study treatment was 1.4 units (range, 0–6)
  - In TGB, ruxolitinib doses included 10 mg bid in 3 patients and 10 mg every morning and 15 mg every evening in 1 patient

Safety

- At the time of analysis, dose escalation was ongoing in both treatment groups
- No DLTs or study drug–related serious adverse events (AEs) occurred in either treatment group
- The MTD had not been reached at the time of analysis
- Treatment-emergent AEs were mainly low grade (**Table 2**)
- Few grade ≥3 treatment-related AEs were observed, including thrombocytopenia in 2 patients with baseline grade 2 thrombocytopenia, and neutropenia in 1 patient with baseline grade 2 neutropenia (**Table 3**)
- No treatment-related AEs led to study drug discontinuation

Pharmacokinetic Profile

- Supra proportionality was observed from 50–200 mg qd for maximum observed concentration (C_{max}) and area under the curve from time 0 to last measurable time point at steady state (**Figure 2**)
- Time to C_{max} (t_{max}) was attained at 2–4 hours following INCB000928 administration across dose groups
- Observed half-life ($t_{½}$) was consistent with that determined in previous healthy volunteer studies, with mean $t_{½}$ of 24–27 hours across dose groups
- Interpatient variability was low at 50 and 100 mg qd and increased at 200 mg qd
- Modeling of higher INCB000928 monotherapy doses indicates that a dose of 600 mg qd should provide exposure above the target threshold (**Figure 2**)

Pharmacodynamic Activity

- Reduction in hepcidin following INCB000928 dosing was observed at all dose levels (**Figure 3**)
  - The greatest hepcidin reductions were observed in the monotherapy cohort at the highest dose tested and in the ruxolitinib combination therapy cohort

Anemia Responses

- Three patients achieved an initial anemia response of Hb increase ≥1.5 g/dL relative to baseline (protocol defined endpoint of 12 weeks for anemia response not yet reached at the time of data cut-off; all 3 patients continue on study)
- In the monotherapy cohort, Hb increase was observed in 1 patient at INCB000928 dose of 200 mg qd (n=6 for this cohort), with response starting during Cycle 1 and subsequently maintained (patient in Cycle 2 of treatment; **Figure 4A**)
- In the combination cohort, Hb increases were observed in 2 patients at INCB000928 dose of 100 mg plus ruxolitinib (n=4 for this cohort), with response starting during Cycles 2 and 3 and subsequently maintained (patients in Cycle 5 and 6 of treatment, respectively; **Figure 4B** and **C**)

Table 1. Demographics and Clinical Characteristics at Baseline

	TGA				TGB
	50 mg qd (n=4)	100 mg qd (n=4)	200 mg qd (n=6)	Total (n=14)	100 mg qd + Ruxolitinib (n=4)
Age, median (range), y	73.5 (53–84)	63.0 (60–72)	70.5 (63–75)	70.0 (53–84)	75.5 (68–79)
Men, n (%)	3 (75.0)	2 (50.0)	4 (66.7)	9 (64.3)	2 (50.0)
Race, n (%)					
White	4 (100)	2 (50.0)	4 (66.7)	10 (71.4)	2 (50.0)
Black	0	1 (25.0)	0	1 (7.1)	0
Asian	0	1 (25.0)	2 (33.3)	3 (21.4)	0
Other	0	0	0	0	2 (50.0)
Time since first MF diagnosis, median (range), y	4.2 (2.6–10.3)	3.0 (0.2–8.1)	2.1 (0.6–23.1)	2.7 (0.2–23.1)	11.6 (9.3–14.3)
DIPSS risk level, n (%)					
High	0	0	1 (16.7)	1 (7.1)	1 (25.0)
Intermediate-2	4 (100)	4 (100)	5 (83.3)	13 (92.9)	3 (75.0)
Prior MF therapy, n (%)					
Ruxolitinib	4 (100)	2 (50.0)	5 (83.3)	11 (78.6)	4 (100)
Other	2 (50.0)	2 (50.0)	3 (50.0)	7 (50.0)	3 (75.0)
Transfusion dependent,* n (%)	3 (75.0)	2 (50.0)	4 (66.7)	9 (64.3)	1 (25.0)
Hb, median (range),† g/dL	8.3 (7.0–8.7)	7.4 (6.4–8.3)	7.5 (6.6–9.2)	7.7 (6.4–9.2)	8.3 (7.9–8.7)
Hepcidin, median (range),‡ ng/mL	374 (318–535)	158 (85–275)	133 (79–275)	235 (79–535)	157 (6.9–250)

C1D1, Cycle 1 Day1; DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; MF, myelofibrosis; qd, once daily; RBC, red blood cell; TGA, treatment group A; TGB, treatment group B.
* Defined as patients who have received ≥4 units of RBC transfusions during the 28 days before C1D1, or have received ≥4 units of RBC in the 8 weeks before C1D1 for an Hb level of <8.5 g/dL in the absence of bleeding or treatment-induced anemia; the most recent transfusion must have occurred within 28 days before C1D1.
† Baseline Hb was determined as the average of values obtained during the 3 months prior to C1D1 which met the following criteria: Hb value was obtained outside the 14-day washout period following a RBC transfusion or Hb value triggered a RBC transfusion (even if obtained within the 14-day period following a transfusion).
‡ Normal range, 0–50 ng/mL.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥2 Patients Across Groups

	TGA				TGB
Event, n (%)	50 mg qd (n=4)	100 mg qd (n=4)	200 mg qd (n=6)	Total (n=14)	100 mg qd + Ruxolitinib (n=4)
Skin and subcutaneous tissue disorders					
Pruritus	1 (25.0)	0	2 (33.3)	3 (21.4)	0
Metabolism and nutrition disorders					
Hyperkalemia	1 (25.0)	1 (25.0)	0	2 (14.3)	1 (25.0)
Hyperuricemia	1 (25.0)	2 (50.0)	0	3 (21.4)	0
Hypocalcemia	2 (50.0)	0	0	2 (14.3)	1 (25.0)
Hyponatremia	1 (25.0)	0	1 (16.7)	2 (14.3)	0
Blood and lymphatic					
Thrombocytopenia	1 (25.0)	0	1 (16.7)	2 (14.3)	0
Gastrointestinal disorders					
Abdominal distention	0	1 (25.0)	1 (16.7)	2 (14.3)	0
Diarrhea	1 (25.0)	0	0	1 (7.1)	1 (25.0)
Dysphagia	1 (25.0)	1 (25.0)	0	2 (14.3)	0
Vomiting	0	0	1 (16.7)	1 (7.1)	1 (25.0)
General disorders and administration site conditions					
Asthenia	1 (25.0)	0	1 (16.7)	2 (14.3)	0
Edema peripheral	1 (25.0)	0	1 (16.7)	2 (14.3)	0
Pyrexia	1 (25.0)	0	1 (16.7)	2 (14.3)	0
Infections and infestations					
Urinary tract infection	0	1 (25.0)	0	1 (7.1)	1 (25.0)
Investigations					
Blood alkaline phosphatase increased	2 (50.0)	0	0	2 (14.3)	0
C-reactive protein increased	2 (50.0)	0	0	2 (14.3)	0
Musculoskeletal and connective tissue disorders					
Bone pain	2 (50.0)	0	0	2 (14.3)	0
Myalgia	1 (25.0)	0	1 (16.7)	2 (14.3)	0
Nervous system disorders					
Headache	1 (25.0)	1 (25.0)	0	2 (14.3)	0
Psychiatric disorders					
Insomnia	1 (25.0)	1 (25.0)	0	2 (14.3)	0
Respiratory, thoracic, and mediastinal disorders					
Cough	1 (25.0)	1 (25.0)	0	2 (14.3)	0
Dyspnea	0	1 (25.0)	1 (16.7)	2 (14.3)	0

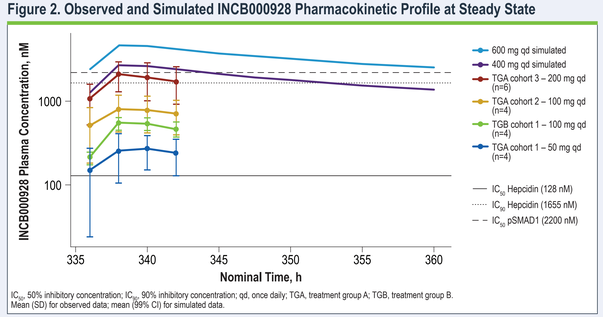
qd, once daily; TGA, treatment group A; TGB, treatment group B.

Table 3. All Grade 3/4 Treatment-Emergent Adverse Events

	TGA				TGB
Event, n (%)*	50 mg qd (n=4)	100 mg qd (n=4)	200 mg qd (n=6)	Total (n=14)	100 mg qd + Ruxolitinib (n=4)
Thrombocytopenia	1 (25.0)	0	1 (16.7)	2 (14.3)	0
COVID-19	0	0	1 (16.7)	1 (7.1)	0
Neutropenia	0	0	1 (16.7)	1 (7.1)	0
Pneumonia	1 (25.0)	0	0	1 (7.1)	0

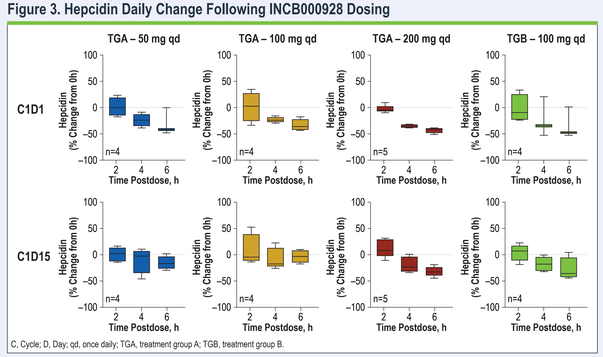
qd, once daily; TGA, treatment group A; TGB, treatment group B.

Figure 2. Observed and Simulated INCB000928 Pharmacokinetic Profile at Steady State



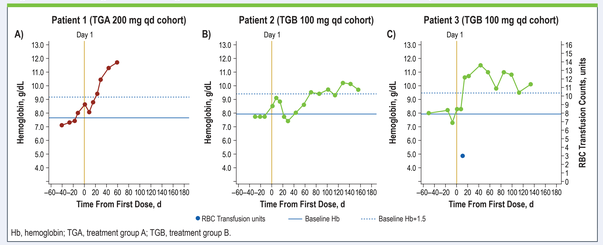
IC_{50}, 50% inhibitory concentration; IC_{90}, 90% inhibitory concentration; qd, once daily; TGA, treatment group A; TGB, treatment group B. Mean (SD) for observed data; mean (99% CI) for simulated data.

Figure 3. Hepcidin Daily Change Following INCB000928 Dosing



C, Cycle; D, Day; qd, once daily; TGA, treatment group A; TGB, treatment group B.

Figure 4. Hemoglobin Changes Over Time in Patients With Anemia Improvement



Hb, hemoglobin; TGA, treatment group A; TGB, treatment group B.

Conclusions

- **Treatment with INCB000928 monotherapy or in combination with ruxolitinib in patients with MF-associated anemia was generally well tolerated, with predominantly grade 1/2 treatment-emergent AEs and no DLTs**
- **Results from the PK analysis support once-daily dosing and continued dose escalation to achieve optimal exposure**
- **Reduction in postdose hepcidin levels was observed at all dose levels**
- **Improvements in anemia have been observed among patients treated in both the monotherapy and combination cohorts, suggesting potential for therapeutic activity, even at this early dose-escalation stage**

References

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