JTZ-951, AN ORAL NOVEL HIF-PHD INHIBITOR, ELEVATES HEMOGLOBIN IN JAPANESE ANEMIC PATIENTS WITH CHRONIC KIDNEY DISEASE NOT ON DIALYSIS

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FP380

Background

HIF-PHD THERAPY FOR ANEMIA:

- Hypoxia inducible factor (HIF) is a transcription factor that plays a key role in adaptive response and cell survival under hypoxic condition. Stabilization of HIF with small molecule prolyl hydroxylase domain (PHD) induced activation of many erythropoietic genes, including EPO and EPO receptor, as well as those that promote iron absorption and recycling.
- An orally-available HIF-PHD inhibitor can be a new-type of ESA that would correct the erythropoietic capacity and improve the anemic state in patients with renal anemia, by stabilizing HIF-α in the kidney and liver followed by enhancing endogenous EPO production, and also is expected to offer a superior safety profiles from those observed in ESAs.

JTZ-951

- JTZ-951 was discovered at the Central Pharmaceutical Research Institute of Japan Tobacco Inc.
- JTZ-951 is a new orally-available HIF-PHD inhibitor.
- JTZ-951 is being developed for treatment of anemia both in chronic kidney disease (CKD) patients on and not requiring dialysis.
- The efficacy, safety, and pharmacokinetics of JTZ-951 were also evaluated after orally administered for 8 weeks in Japanese anemic patients with CKD receiving maintenance hemodialysis. (JapicCTI-132254)

Method

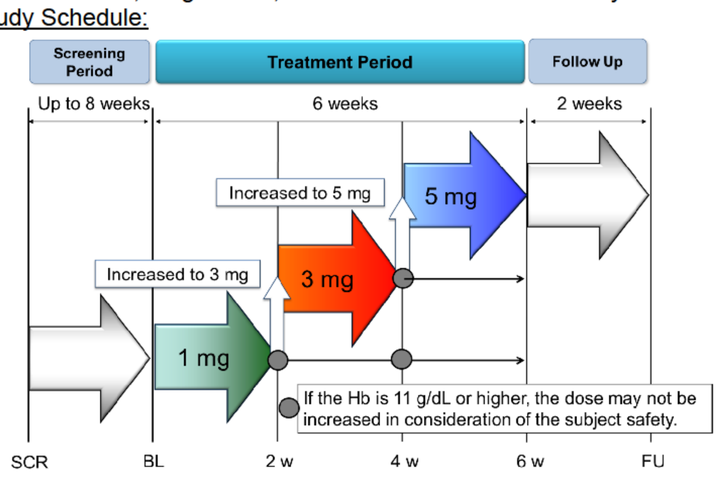
Study Objectives:

- This study was to assess the efficacy, safety, and pharmacokinetics of JTZ-951 orally administered once daily for 6 weeks in anemic patients with CKD not requiring dialysis. (JapicCTI-132295)

Study Design:

- Multi-center, Single-blind, Intra-Individual titration study

Study Schedule:



SCR: Screening Visit, BL: Baseline (Week 0), FU: Follow-up Visit

Key Inclusion Criteria:

- Japanese patients with CKD in stage G3a to G5; eGFR at screening, <60 mL/min/1.73 m^2
- Male or female 20 - 75 years of age (inclusive)
- Hb ≥9.0 g/dL to <10.0 g/dL at screening
- Hb decreased by ≥0.5 g/dL from screening to administration
- TSAT >20% or ferritin >100 ng/mL at screening

Key Exclusion Criteria:

- Patients who have been treated within 4 weeks prior to screening visit as follows,
  - ✓ IV iron: administration
  - ✓ Oral iron: new administration, discontinuation, or change of dose

Hb Discontinuation Criteria:

- Hb level
  - ✓ ≥13.0 g/dL
  - ✓ <8.0 g/dL
  - ✓ >2.0 g/dL within 4 weeks

Assessment:

- Efficacy:
  - ✓ Hb level was set as the primary endpoint.
- Safety:
  - ✓ Adverse events were determined by symptoms, physical findings, and abnormal changes in physiological tests and clinical laboratory tests.
- Pharmacokinetics:
  - ✓ Plasma concentration of JTZ-951 was measured at each observation time point.
- Other parameters:
  - ✓ The trough concentrations of EPO, VEGF, and iron-related parameters.

Subject Demographics & Baseline

		N=22
Age (years)	Mean (SD)	60.7 (12.2)
Gender (Male)	N (%)	11 (50.0)
BMI (kg/m^2)	Mean (SD)	23.38 (3.63)
eGFR (mL/min/1.73m^2)	N (%)	
<15		13 (59.1)
>=15		9 (40.9)
Underlying disease of CKD	N (%)	
Diabetic nephropathy		8 (36.4)
Chronic glomerulonephritis		5 (22.7)
Nephrosclerosis		4 (18.2)
Other		5 (22.7)
ESA treated patients	N (%)	10 (45.5)
Baseline Hb (g/dL)	Mean (SD)	9.44 (0.44)
Baseline Serum iron (μg/dL)	Mean (SD)	71.0 (31.1)
Baseline Ferritin (ng/mL)	Mean (SD)	164.16 (117.90)
Baseline TIBC (μg/dL)	Mean (SD)	253.7 (49.3)
Baseline TSAT (%)	Mean (SD)	28.61 (14.01)
Baseline Hepcidin (ng/mL)	Mean (SD)	82.786 (58.639)

Information

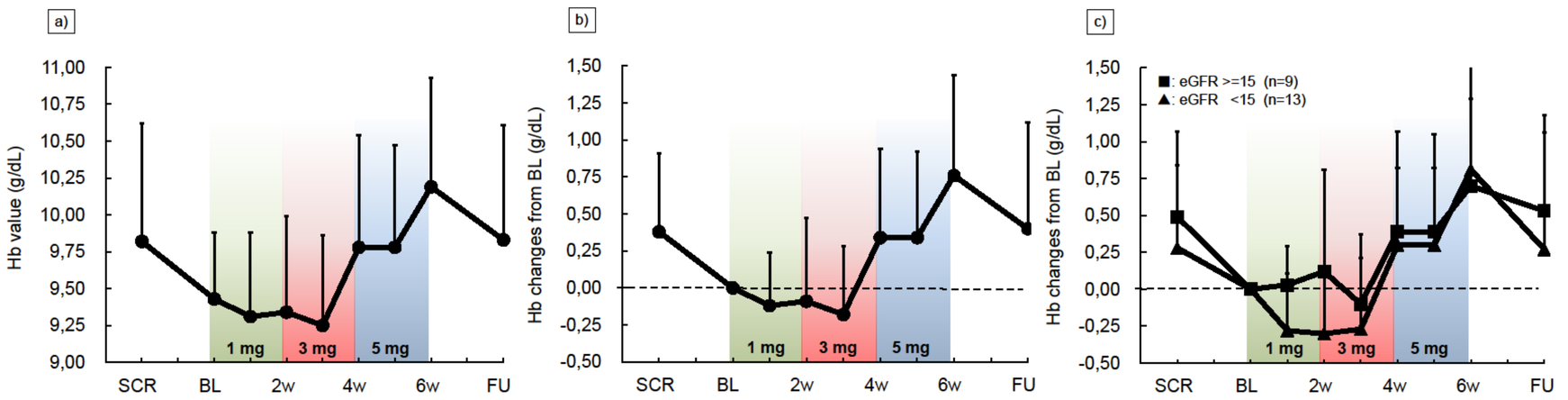
The results of the following three clinical studies with JTZ-951 are presented at this 52nd ERA-EDTA Congress:

1. Phase 2a, Japanese anemic patients with CKD Receiving Maintenance Hemodialysis (#FO019)
2. Phase 2a, Japanese anemic patients with CKD not on Dialysis (#FP380: This Poster)
3. Phase 1, Patients with Anemia Receiving Hemodialysis (# FP658)

Results

Efficacy

Time course of a) Hb value, b) Hb changes from BL and c) Hb changes from BL divided by eGFR in 2 groups.



- Mean Hb increase at week 6 was 0.76 g/dL [SD 0.68, 95%CI (0.42, 1.10)].
- There were no apparent differences in Hb changes from baseline between "eGFR: >=15" and "eGFR: <15" population from when dose was up-titrated to 3 mg of JTZ-951.

Mean + SD
SCR: Screening Visit
BL: Baseline (Week 0)
FU: Follow-up Visit

Safety

Treatment-Emergent Adverse Events (TEAEs)

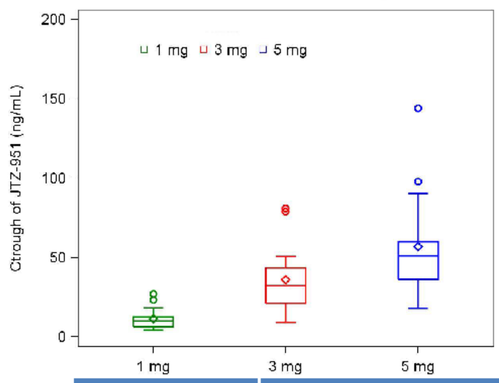
	N=22	
	N	%
Adverse Events	12	54.5
Drug-related Adverse Events	4	18.2
Serious Adverse Events	4	18.2
• interstitial lung disease*	1	4.5
• cardiac failure congestive	1	4.5
• cardiac failure	1	4.5
• vomiting*	1	4.5
Deaths	0	0
Discontinuation for Adverse Events**	0	0

*: drug-related
**: except subjects with discontinuation for SAE

- There were no clinically significant changes in laboratory test values, vital signs, physical findings, and other observations related to safety.

Pharmacokinetics

C_{trough} of JTZ-951



- Diamond: Mean value
- Line within box: Median value
- Bottom edge of box: 25th percentiles (Q1)
- Top edge of box: 75th percentiles (Q3)
- Lower adjacent value: Min value above Q1 - 1.5*IQR
- Upper adjacent value: Max value above Q3 + 1.5*IQR

(IQR: interquartile range)

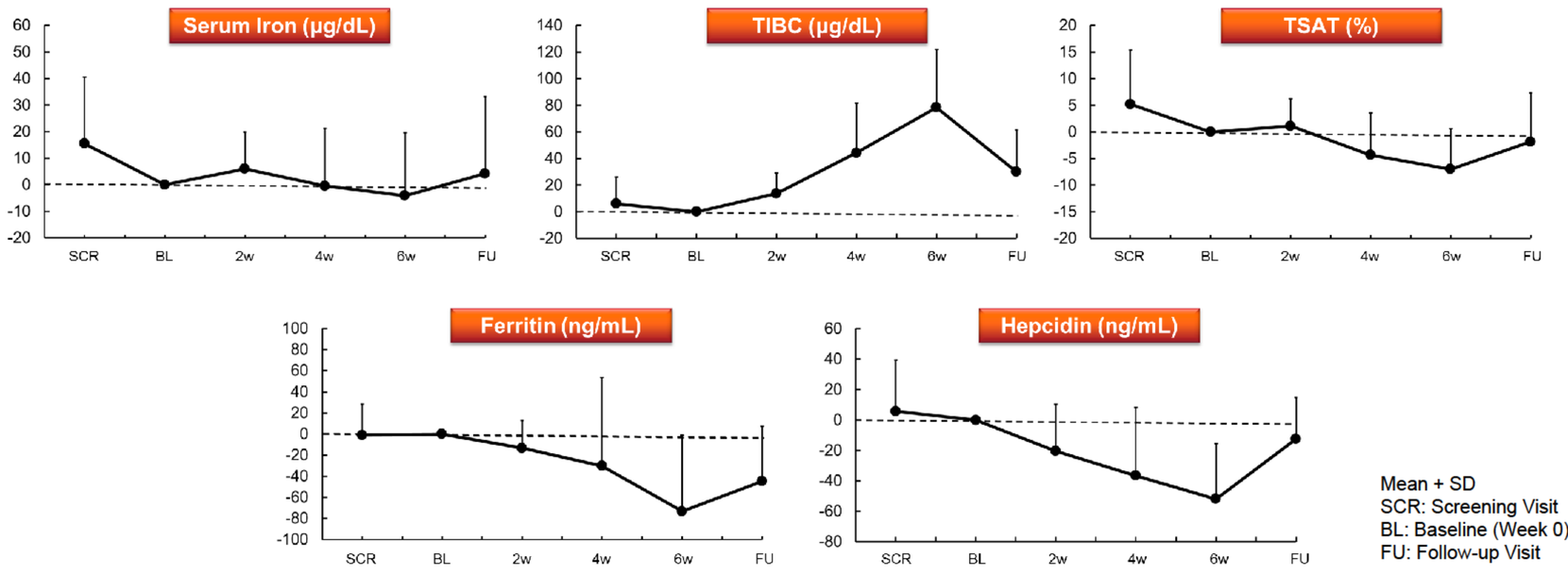
	Dose		
	1 mg	3 mg	5 mg
N	16	17	14
Mean* (SD)	11.43 (6.436)	36.17 (20.63)	56.84 (34.23)
Ratio to 1 mg	1.00	3.16	4.97

*: ng/mL

- C_{trough} increased in a dose dependent manner in ND-CKD patients.

Other Parameters

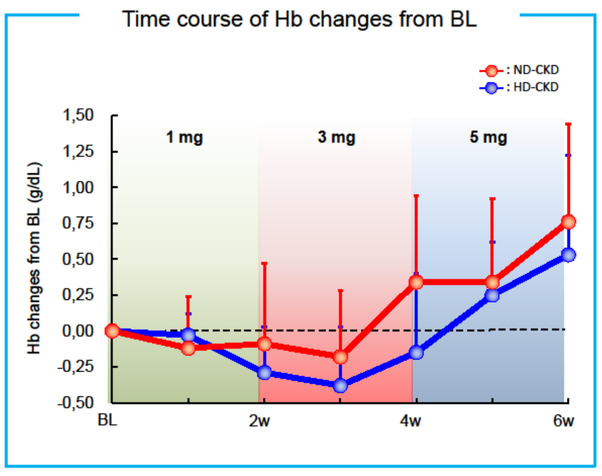
Time course of changes in iron-related parameters from BL



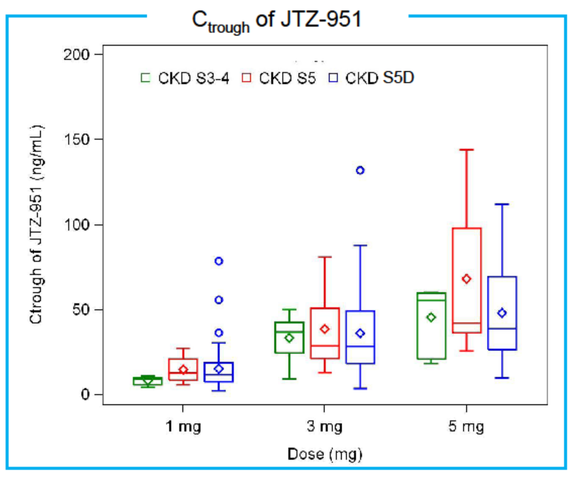
Mean + SD
SCR: Screening Visit
BL: Baseline (Week 0)
FU: Follow-up Visit

Comparison between ND- and HD-CKD Patients

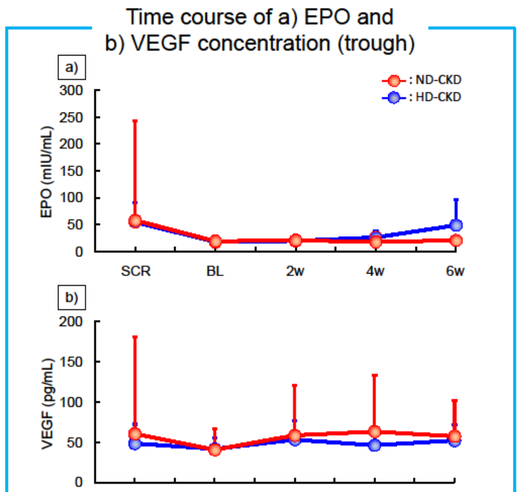
Time course of Hb changes from BL



C_{trough} of JTZ-951



Time course of a) EPO and b) VEGF concentration (trough)



Mean + SD
HD: Hemodialysis, ND: Not requiring dialysis
SCR: Screening Visit, BL: Baseline (Week 0)

Discussion & Conclusion

The efficacy, safety, and pharmacokinetics of JTZ-951 were assessed after administration for 6 weeks to anemic patients with CKD not requiring dialysis in up-titrated doses within a range of 1 mg to 5 mg.

Efficacy

- The Hb level at Week 6 was significantly increased from baseline. The changes in Hb level from baseline at Week 6 was 0.76 g/dL (95% CI: 0.42 to 1.10 g/dL).
- Similarly, reticulocyte count, hematocrit value, and red blood cell count increased. In contrast, there were no clinically meaningful changes in MCV, MCH, or MCHC (data not shown).

Safety

- JTZ-951 was considered to be tolerable at doses of up to 5 mg.

Pharmacokinetics

- Trough plasma concentrations of JTZ-951 increased in a dose-dependent manner.

Other parameters

- There were no significant changes in trough EPO and VEGF following the administration of JTZ-951.
- The changes of the iron-related parameters were considered to be reasonable phenomena for hematopoiesis following the administration of JTZ-951.

Result of this study indicated that JTZ-951 effectively corrects anemia with CKD in conjunction with iron mobilization, and is considered to be tolerated in anemic patients with CKD not requiring dialysis.

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J4) Chronic Kidney Disease. Anaemia.

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