JTZ-951, a Novel HIF-PHD Inhibitor, Demonstrates Increases in Hemoglobin, Iron Mobilization, Reproducible Pharmacokinetics, and Safety following Once daily Administration for 15 Days in Patients with Anemia Receiving Hemodialysis

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Abstract

INTRODUCTION AND AIMS: JTZ-951 is a potent inhibitor of hypoxia inducible factor prolyl hydroxylase with *in vitro* human IC_{50} of 0.106 µmol/L (HIF-PHD2). Phase 1 studies in healthy subjects showed dose-related increases in JTZ-951 plasma levels following single and once daily (QD) administration. The current study was conducted to characterize the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of JTZ-951 in patients with end-stage renal disease (ESRD) with anemia receiving hemodialysis (HD). The purpose was to define a dose/exposure range to enable dose-ranging trials in the target population.

METHODS: This was a single-blind, placebo-controlled, ascending dose study at 2, 5, 10, and 15 mg JTZ-951 QD (n=6 active, 2 placebo/dose) for 15 days. Key inclusion criteria were males and females (18-75 years) with ESRD on HD thrice weekly, hemoglobin (Hgb) ≥8.5 to ≤11.0 g/dL on Day -1 [baseline (BL)], erythropoiesis stimulating agent (ESA)-naïve, or a 7-day washout of epoetin alpha; exclusion criteria were transferrin saturation (TSAT) ≤20% or ferritin ≤200 ng/mL, hyporesponsiveness to ESAs, AST, ALT, or ALP >2x upper limit of normal (ULN), total bilirubin >1.5x ULN. IV iron was discontinued 30 days before JTZ-951 dosing. At appropriate intervals, laboratory safety tests, vitals, and 12-lead ECGs were assessed; blood samples were obtained for hematology (e.g., reticulocytes, Hgb), iron-related parameters, erythropoietin (EPO), and vascular endothelial growth factor (VEGF). Plasma and urine were quantified for JTZ-951 PK with validated methods.

RESULTS: JTZ-951 was rapidly absorbed with peak levels (C_{max}) at 0.5-1.5 hrs. Mean effective half-life ($t_{1/2(eff)}$) was ~11 hrs and was dose-independent demonstrating linear kinetics. JTZ-951 C_{max} and area under the curve (AUC) increased roughly dose proportionally, with minimal accumulation (~20%) on Day 15 (consistent with $t_{1/2(eff)}$), low inter-subject variability in AUC (CV%; ~30%), demonstrating reproducible kinetics in HD patients. EPO changes at 2 mg were similar to placebo; from 5 to 15 mg there were marginal, transient, dose dependent EPO increases that were similar on Days 1 and 15. Reticulocyte (Ret) counts increased with dose (5 to 15 mg) from Day 5 onwards. Mean Hgb levels at 2 mg declined over the 2-week period (similar to placebo); at 5 mg Hgb declined initially, then stabilized by Day 10, albeit without positive changes from BL on Day 16. At 10 mg, Hgb increased on Day 16, with mean 0.74 ± 1.1 g/dL (range: -0.7 to 2.3 g/dL; n=5) change from BL. At 15 mg, 2 subjects discontinued treatment prior to Day 15 based on Hgb increase and one was suspended dosing on Days 13 and 14 due to Hgb increase. In addition, one discontinued on Day 12 due to stenosis of fistula (not related to JTZ-951); in the remaining two subjects, Day 16 Hgb increases were 1.4 and 1.6 g/dL. Dose-dependent increases in Hgb were observed. Dose-dependent changes in ferritin, hepcidin, TIBC, and UIBC, with stable serum iron levels, indicated iron mobilization. There were no dose-related changes in VEGF, laboratory safety parameters, vital signs and ECGs. Daily JTZ-951 administration for 15 days was safe and well tolerated over the 2 to 15 mg dose range.

CONCLUSIONS: The study clearly demonstrated the efficacy of JTZ-951 (Hgb increase) based on its mechanism of action. The reproducible and predictable PK characteristics demonstrated exposure-related efficacy, and in conjunction with safety defined the systemic exposure/dose range for dose ranging trials in ESRD patients on hemodialysis.

Introduction

Renal Anemia Drugs and Its Limitation:

- Prior to the commercial availability of epoetin alfa, the first approved ESA in 1989, dialysis patients had symptomatic anemia with Hgb levels typically less than 8 g/dL and were dependent upon recurrent blood transfusions for anemia treatment. Early ESA trials demonstrated transfusion avoidance as a clinically meaningful benefit of treatment. Currently ESAs have been widely used worldwide as renal anemia drugs since 1989.
- However, some risks related to ESA use were identified such as thrombosis, hypertension and seizures in ESA trials. Also, whereas existing protein-based ESAs are effective for most renal anemia patients, there are a small number of patients who have developed anti-EPO antibody-mediated pure red cell aplasia.
- All existing ESAs are available only in injectable forms and therefore involve injection-specific issues (e.g., injection pain, drug management [cool storage, medical waste, coordination for injections, etc.], risk of infection).

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 utilization.
- 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 would offer different safety profiles from those observed in ESAs.

JTZ-951:

- JTZ-951 is a new orally-available HIF-PHD inhibitor.

Study Objectives:

- This study was conducted to investigate the safety, tolerability, PK, and PD of ascending doses of JTZ-951 administered QD for 15 days in anemic subjects with ESRD receiving hemodialysis.

Background

- JTZ-951 is a potent inhibitor of HIF-PHD with *in vitro* human IC_{50} of 0.106 µmol/L (HIF-PHD2).
- Phase 1 studies in healthy subjects showed dose-related increases in JTZ-951 plasma levels following single administration, and following QD administration for 14 days. Renal elimination of unchanged drug was significant following the single dose study and at steady state in the multiple dose study. Steady state was achieved by Day 4 with an $t_{1/2(eff)}$ of ~15 hours.
- Following administration of appropriate probe substrates in the multiple dose study in healthy subjects, it was determined that dose adjustment for drugs metabolized by CYP1A2, 2C9, 2C19, 2D6 and 3A4 is not necessary during JTZ-951 treatment.
- Based on its mechanism of action, EPO increases were observed following single administration at doses >50 mg, and at all doses following repeated administration with dose-related reticulocyte increases without, however, changes in Hgb levels.
- JTZ-951 was generally safe and well tolerated following single doses up to 400 mg and following 25 and 50 mg QD administered orally for 14 days in healthy subjects.
- In healthy subjects, co-administration of sevelamer carbonate resulted in a substantial reduction in the oral bioavailability of JTZ-951. Administration of JTZ-951 in a staggered manner relative to sevelamer carbonate had a minor effect on the drug's bioavailability.
- In a study in ESRD patients conducted to assess the effect of hemodialysis on JTZ-951 clearance, the drug was rapidly absorbed and eliminated with a mean half-life of 9 - 10 hours, which was similar in the presence and absence of hemodialysis.
- In ESRD patients, the plasma protein binding was high and hemodialysis cleared a only small fraction of the administered dose.
- The results of the hemodialysis clearance study showed that JTZ-951 can be administered regardless of dialysis schedule in ESRD patients, and that dose adjustment of JTZ-951 is unnecessary in such patients.

Study Design and Methods

Study Design: Randomized, single-blind, placebo-controlled, ascending dose study at 2, 5, 10, and 15 mg JTZ-951 QD (n=6 active, 2 placebo/dose) for 15 days.

Study Subjects:

- Main inclusion criteria:
  - Have ESRD and receiving maintenance hemodialysis (thrice weekly) for at least 12 weeks prior to Screening Visit
  - Male or female age 18 to 75 years (inclusive)
  - Body weight (post-dialysis weight) greater than 45.0 kg and a BMI between 20.0 and 40.0 kg/m² (inclusive)
  - Hgb value:
    - ✓ ≥9.0 g/dL and ≤11.5 g/dL at the Screening Visit, and
    - ✓ ≥8.5 g/dL and ≤11.0 g/dL at Day -1, and
    - ✓ The difference between the Screening Visit and Day -1 must not be >2.0 g/dL
  - ESA therapy criteria:
    - ✓ The subject is ESA-naïve (defined as never taken an ESA agent or previously taken ESA agents but discontinued them at least 12 weeks prior to the Screening Visit), or
    - ✓ Current use of epoetin alfa (e.g., Epogen®, Procrit®)
- Main exclusion criteria:
  - Transferrin saturation (TSAT) ≤20% or ferritin ≤200 ng/mL at the Screening Visit
- Main stopping rule:
  - Any subject with a hemoglobin increase >1.0 g/dL (confirmed by repeat test) after initiation of JTZ-951 administration
  - Any subject with hemoglobin values ≥12.0 g/dL (confirmed by repeat test)
- Main Concomitant Medication Restrictions:
  - IV iron; at least 30 days prohibited prior to Day -1

Assessments

Safety:

- Adverse events, clinical laboratory safety test results (e.g., hematology, serum biochemistry, coagulation), vital signs, and ECGs
- Safety population consisted of randomized subjects who received at least one dose of JTZ-951 or placebo, including those who did not complete the duration of the study

PK:

- Single dose and steady state PK parameters: t_{max}, C_{max}, AUC_{tau}, $t_{1/2(eff)}$, AR_{Cmax}, AR_{AUCtau}, etc.
- PK population consisted of randomized subjects who received at least one dose of JTZ-951 and had sufficient plasma data to facilitate the calculation of PK parameters.

PD:

- EPO, VEGF, RBC count, Hgb, hematocrit, reticulocyte (Ret) count, TIBC, UIBC, serum iron, TSAT, hepcidin, and serum ferritin
- PD population is a subset of safety population including subjects who had at least one post-dose (JTZ-951 or placebo) PD measurement available for analysis.
- Both absolute value and the change from baseline were evaluated for each PD assessment

Subject Demographics

Table 1: Subject Demographics at Baseline

	Treatment					Total (n=29)
	Placebo (n=7)	JTZ-951 2 mg (n=4)	JTZ-951 5 mg (n=6)	JTZ-951 10 mg (n=6)	JTZ-951 15 mg (n=6)	
Gender: n (%)						
Male	3 (42.9)	1 (25.0)	5 (83.3)	5 (83.3)	2 (33.3)	16 (55.2)
Female	4 (57.1)	3 (75.0)	1 (16.7)	1 (16.7)	4 (66.7)	13 (44.8)
Race: n (%)						
White	0 (0.0)	1 (25.0)	1 (16.7)	2 (33.3)	1 (16.7)	5 (17.2)
Black or African American	7 (100.0)	3 (75.0)	4 (66.7)	4 (66.7)	5 (83.3)	23 (79.3)
Other: Hispanic	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.4)
Ethnicity: n (%)						
Hispanic or Latino	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	2 (6.9)
Not Hispanic or Latino	7 (100.0)	4 (100.0)	5 (83.3)	6 (100.0)	5 (83.3)	27 (93.1)
Age (years):						
Mean (SD)	47.29 (10.70)	48.00 (13.88)	50.67 (16.08)	53.00 (9.08)	56.50 (8.38)	51.17 (11.43)
BMI (kg/m²):						
Mean (SD)	28.31 (4.15)	30.15 (8.30)	29.05 (4.15)	30.35 (5.12)	26.22 (3.88)	28.71 (4.88)
Primary reason for CKD diagnosis						
Hypertension	5 (71.4)	2 (50.0)	4 (66.7)	4 (66.7)	3 (50.0)	18 (62.1)
Hypertension/diabetes	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Diabetes	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (6.9)
Diabetes mellitus type II	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.4)
Diabetes with renal manifestation	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.4)
Diabetes with renal manifestation type 2	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (3.4)
VATER syndrome	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Nephrocalcinosis	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Renal artery stenosis and IgA nephropathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (3.4)

Table 2: Pharmacodynamic Values at Baseline

	Treatment				
	Placebo (n=7)	JTZ-951 2 mg (n=4)	JTZ-951 5 mg (n=6)	JTZ-951 10 mg (n=6)	JTZ-951 15 mg (n=6)
Baseline EPO (mIU/mL): Mean (SD)	8.01 (11.72)	10.90 (5.22)	11.17 (8.08)	20.56 (14.32)	16.28 (11.34)
Baseline VEGF (pg/mL): Mean (SD)	75.57 (18.47)	104.50 (86.97)	91.00 (40.62)	94.67 (33.40)	81.00 (15.77)
Baseline Ret Counts (10^6/µL): Mean (SD)	0.03 (0.02)	0.04 (0.01)	0.03 (0.02)	0.05 (0.02)	0.06 (0.03)
Baseline Hgb (g/dL): Mean (SD)	9.71 (0.60)	9.83 (0.68)	10.00 (0.54)	9.92 (0.81)	9.73 (0.41)
Baseline ferritin (ng/mL): Mean (SD)	1270.71 (608.14)	1160.75 (333.03)	1095.83 (537.12)	873.00 (356.93)	1415.33 (338.99)
Baseline TSAT (%): Mean (SD)	37.29 (25.24)	46.00 (30.74)	39.33 (22.64)	38.83 (16.14)	46.33 (19.44)
Baseline Serum Iron(µg/dL): Mean (SD)	88.00 (71.45)	98.50 (38.91)	79.50 (46.90)	84.17 (36.23)	95.50 (32.89)
Baseline TIBC (µg/dL): Mean (SD)	222.86 (44.83)	235.50 (50.81)	205.17 (44.18)	216.33 (22.32)	214.33 (29.75)
Baseline UIBC (µg/dL): Mean (SD)	134.86 (56.51)	137.00 (81.83)	125.67 (58.78)	132.17 (35.54)	118.83 (54.19)
Baseline Hepcidin (ng/mL): Mean (SD)	746.56 (327.81)	680.65 (199.01)	563.75 (204.31)	411.97 (132.18)	728.33 (269.99)

Results

Table 3: Overall Summary of Treatment-Emergent Adverse Events (TEAEs)

	Placebo (N=7) n (%)	JTZ-951 2 mg (N=4) n (%)	JTZ-951 5 mg (N=6) n (%)	JTZ-951 10 mg (N=6) n (%)	JTZ-951 15 mg (N=6) n (%)
Number of TEAEs	12	11	15	5	5
Number of subjects with TEAEs	3 (42.9)	3 (75.0)	4 (66.7)	3 (50.0)	4 (66.7)
Severe TEAEs	2 (28.6)	1 (25.0)	1 (16.7)	1 (16.7)	0 (0.0)
Related TEAEs	1 (14.3)	3 (75.0)	3 (50.0)	1 (16.7)	1 (16.7)
TEAEs that led to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects with serious TEAEs	1 (14.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Related serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- ❖ There were no deaths, related SAEs
- ❖ TEAEs were evenly distributed across all cohorts without apparent dose-dependent trend
- ❖ The only TEAEs occurring in more than one subject in any JTZ-951 treatment group were headache and feeling hot
- ❖ There were no JTZ-951 related TEAEs leading to withdrawal
- ❖ The majority of TEAEs were mild to moderate in severity
- ❖ No apparent clinically meaningful mean changes from baseline in vital sign parameters were noted throughout the study
- ❖ No trends or clinically significant mean changes were observed with respect to any ECG parameter throughout the study

- ➢ JTZ-951 2, 5, 10 and 15 mg administered QD for 15 days was generally safe and well tolerated in anemic subjects with ESRD receiving hemodialysis

Fig. 1: Plasma C-T Profiles of JTZ-951 on Day 15

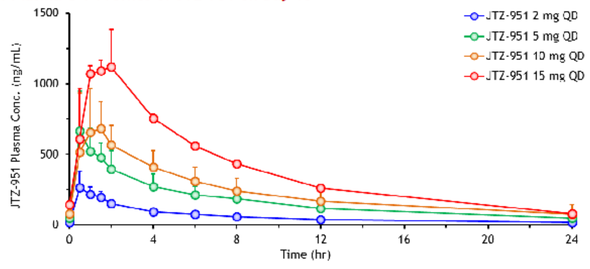


Table 4: Plasma PK Parameters of JTZ-951 on Day 15

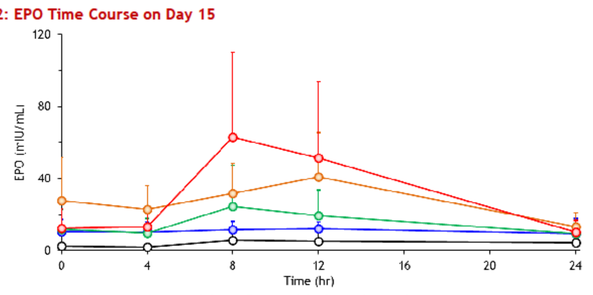
Plasma PK parameters	Treatment: JTZ-951 2 mg (N=4)	JTZ-951 5 mg (N=6)	JTZ-951 10 mg (N=6)	JTZ-951 15 mg (N=2)
t_{max} (hr)	0.500 [0.500-1.00]	0.500 [0.500-1.00]	1.50 [0.500-2.00]	1.50 [1.00-2.00]
C_{max} (ng/mL)	271 ± 105	683 ± 266	772 ± 283	1170 ± 191
AUC_{tau} (ng•hr/mL)	1400 ± 374	3940 ± 1370	5460 ± 2000	8990 ± 723
$t_{1/2(eff)}$ (hr)	8.97 ± 2.68†	10.8 ± 2.83††	11.3 ± 8.02‡	9.16††
AR_{Cmax}	1.03 ± 0.171	1.12 ± 0.169	1.21 ± 0.778	1.18 ± 0.754
AR_{AUCtau}	1.11 ± 0.186	1.21 ± 0.200	1.18 ± 0.402	0.976 ± 0.309

Mean ± SD, †: Median [Min-Max], ‡: N = 3, ††: N = 5, ‡‡: N = 4, ‡‡‡: N = 1

- ❖ Roughly dose-proportional increases in drug exposure over 2 to 15 mg
- ❖ Steady-state exposure was achieved by Day 4
- ❖ Minimal accumulation with 15-day QD dosing
- ❖ Most of the ESRD subjects in this study were unable to provide urine samples
- ❖ Despite the near absence of renal excretion, JTZ-951 was eliminated relatively rapidly in ESRD subjects on hemodialysis

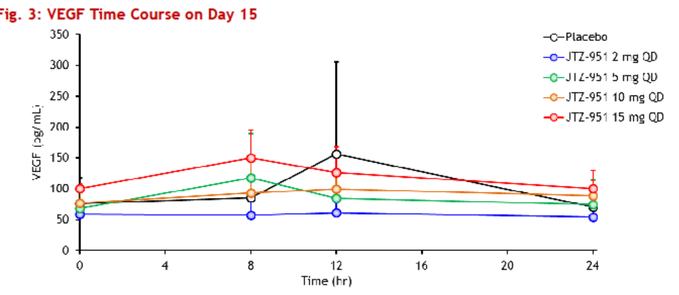
- ➢ This study results demonstrated reproducible and predictable PK of JTZ-951 in ESRD subjects on hemodialysis and provided a basis to develop dose/dosing regimens in future trials in this population

Fig. 2: EPO Time Course on Day 15



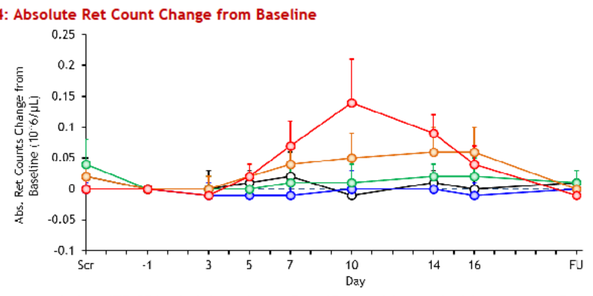
- ❖ Increases in EPO were observed from 5 mg with dose-dependent response
- ❖ There was no accumulation of EPO levels following repeated daily doses

Fig. 3: VEGF Time Course on Day 15



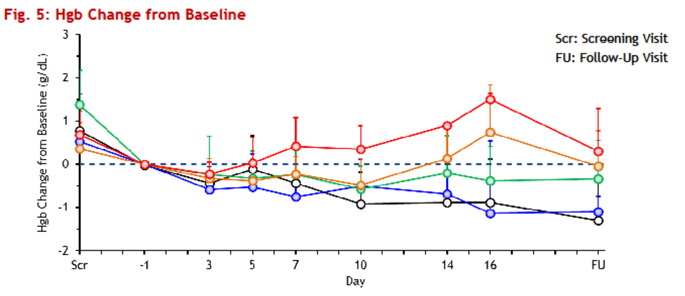
- ❖ JTZ-951 QD dosing at 2-15 mg had no effect on plasma VEGF concentrations

Fig. 4: Absolute Ret Count Change from Baseline



- ❖ Ret responded to JTZ-951 administration at 5 to 15 mg with marginal increases at 5 mg
- ❖ The Ret counts increased with the increase of dose, starting on Day 5
- ❖ Ret counts returned to baseline level at follow-up visit

Fig. 5: Hgb Change from Baseline



- ❖ At 5 mg, Hgb levels initially declined and then stabilized by Day 10 and remained relatively stable thereafter, albeit without positive changes from baseline on Day 16, which did not overlap with those treated with a 2-mg dose of JTZ-951 or placebo.
- ❖ Hgb responded positively to the elevation of Ret count at 10 and 15 mg.
- ❖ At 15 mg, three of six subjects discontinued early due to Hgb increase. In addition, one subject discontinued dosing on Days 13 and 14 to monitor any changes in elevated Hgb status.
- ❖ Dose-dependent increases in Hgb were observed following 15 days of QD dosing of JTZ-951

Fig. 6: Ferritin Change from Baseline

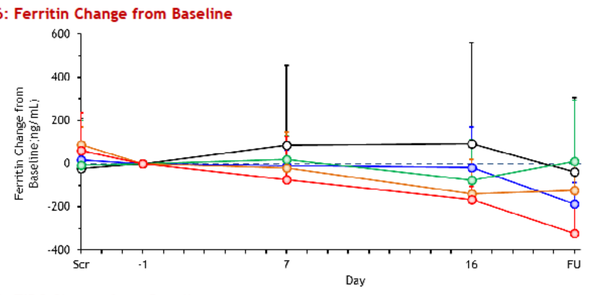


Fig. 7: TSAT Change from Baseline

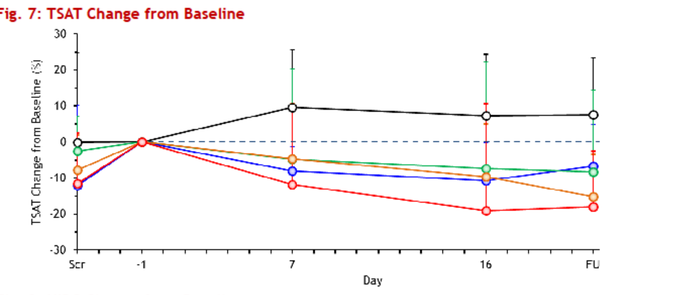


Fig. 8: TIBC Change from Baseline

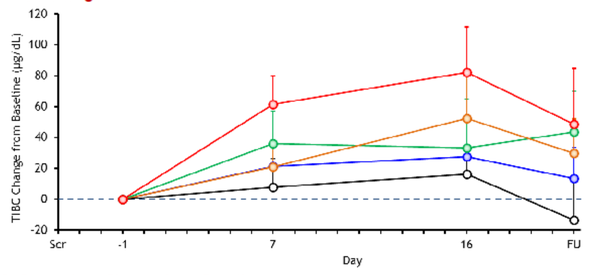


Fig. 9: UIBC Change from Baseline

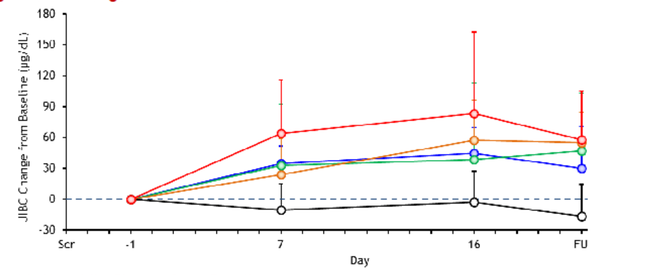


Fig. 10: Serum Iron Change from Baseline

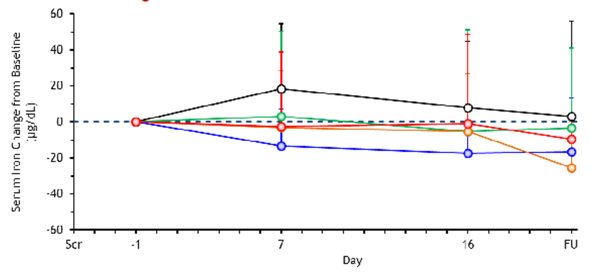
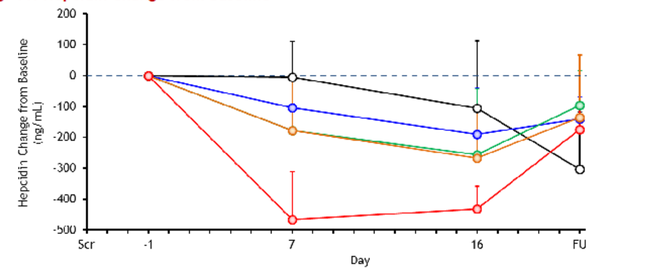


Fig. 11: Hepcidin Change from Baseline



- ❖ Stable serum iron levels with concurrent increases in Hgb was observed
- ❖ Dose-dependent increases in TIBC and UIBC were observed
- ❖ The concentrations of ferritin and hepcidin declined with JTZ-951 treatment in a dose-dependent fashion

- ➢ Dose related changes in iron-related parameters were observed with relatively stable serum iron levels, while Hgb increased positively at 10 and 15 mg doses

Conclusions

Safety

- ➢ JTZ-951 2, 5, 10, and 15 mg administered QD for 15 days was generally safe and well-tolerated in anemic subjects with ESRD receiving hemodialysis
- ➢ No dose-related trends in labs, vital signs, or ECGs were observed

Pharmacokinetics

- ➢ PK was characterized by dose-dependent increases in JTZ-951 exposure over 2 to 15 mg, with low to moderate inter-subject variability and minimal accumulation following QD dosing

Pharmacodynamics

- ➢ Marginal and transient changes from baseline in EPO were observed from 5 mg
- ➢ In response to EPO production, Ret increased followed by positive changes in Hgb from 10 mg
- ➢ Dose-related iron mobilization was observed

- ❑ **This study indicated that JTZ-951 effectively corrects anemia with CKD in conjunction with iron mobilization, and is safe and well-tolerated in anemic patients with CKD receiving maintenance hemodialysis.**
- ❑ **JTZ-951 is a promising new drug, and will be a safer and more effective treatment option for anemia in CKD patients than currently available agents.**

ClinicalTrials.gov Identifier: *NCT01971164*

Contact: pai@akrospharma.com

Information

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

1. JTZ-951, AN ORAL NOVEL HIF-PHD INHIBITOR, ELEVATES HEMOGLOBIN IN JAPANESE ANEMIC PATIENTS WITH CHRONIC KIDNEY DISEASE RECEIVING MAINTENANCE HEMODIALYSIS (#FO019)
2. JTZ-951, AN ORAL NOVEL HIF-PHD INHIBITOR, ELEVATES HEMOGLOBIN IN JAPANESE ANEMIC PATIENTS WITH CHRONIC KIDNEY DISEASE NOT ON DIALYSIS (#FP380)
3. JTZ-951, A NOVEL HIF-PHD INHIBITOR, DEMONSTRATES INCREASES IN HEMOGLOBIN, IRON MOBILIZATION, REPRODUCIBLE PHARMACOKINETICS, AND SAFETY FOLLOWING ONCE DAILY ADMINISTRATION FOR 15 DAYS IN PATIENTS WITH ANEMIA RECEIVING HEMODIALYSIS (# FP658: **This Presentation**)

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