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Pharmacokinetics of Iron Isomaltoside1000 in Patients with Stage 5 Chronic Kidney Disease on Dialysis Therapy

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Abstract

Background: Iron deficiency anemia is common in patients with chronic kidney disease, and intravenous iron is the preferred treatment for those on dialysis. We investigated the pharmacokinetics, pharmacodynamics, and safety of three doses (100 mg, 200 mg, and 500 mg) of iron isomaltoside 1000administered as bolus injections in patients with stage 5 chronic kidney disease on dialysis therapy.

Methods: This prospective, randomized, open-label pharmacokinetic study was conducted in 18 patients at one center. Patients were randomly assigned in a 1:1:1 ratio to receive a single dose of 100 mg, 200 mg, or 500 mg intravenous bolus injection (6 patients each) of iron isomaltoside 1000 at baseline visit. The pharmacokinetic, pharmacodynamics, and safety parameters were assessed over seven days and increases in *serum*-iron was used as a surrogate for iron isomaltoside 1000.

Results: There was a dose-dependent increase in the geometric mean values of area under serum concentration-time curve (AUC) from injection to last measurable data point, area under serum concentration-time curve from injection to infinity (AUC_{0-t}), and maximum serum concentration (C_{max}), whereas time to reach maximum concentration (T_{max}) decreased with increasing doses of iron isomaltoside 1000. Thegeometric mean of half-life ($T_{½}$) was approximately 30 h and the elimination rate constant (K_e) remained similar across the three doses. *Serum*-iron, transferrin saturation, and *serum*-ferritin increased significantly, and the increases were related to iron dose. No major change was observed in the mean hemoglobin, reticulocyte count, reticulocyte hemoglobin content, ortotal iron binding capacity across the three doses. Three adverse events occurred of which one, asthma exacerbation, was considered probably related to the treatment.

Conclusions: The pharmacokinetic characteristics and simplicity of administration of iron isomaltoside 1000 suggest it to be a convenient iron replacement therapy over this dosage range.

Keywords: Sage 5 chronic kidney disease; Intravenous iron; Iron deficiency anemia; Iron isomaltoside 1000; Pharmacokinetics; Dialysis

Introduction

Iron deficiency anemia is the leading cause of anemia, affecting approximately 1.6 billion people worldwide [1]. It is often associated with many chronic diseases, including inflammatory bowel disease, chronic heart failure, cancer, and chronic kidney disease (CKD) [2-4]. Studies have shown that oral iron supplementation in patients with CKD, especially those on hemodialysis, is inferior to intravenous iron administration [5,6].

In CKD patients, several factors can lead to iron deficiency anemia. The use of erythropoiesis stimulating agents enhances iron requirements, iron losses increase due to procedural blood losses, and intestinal absorption of iron is frequently impaired by inflammation leading to elevated serum hepcidin, the regulator of iron absorption. Hence, intravenous iron therapy may be the preferred iron treatment in CKD patients.

Iron isomaltoside 1000 (Pharmacosmos A/S, Holbaek, Denmark) is a complex between iron and a carbohydrate moiety with an average molecular weight of 1000 Dalton.

While dextrans have an α-D-1,6-glucose-linked glucan with intermittent α-1-3 linked side-chains, iron isomaltoside 1000 has a purely linear structure of repeating α-(1-6) linked glucopyranose residues, averaging 5.2 glucose units to lower the potential for immunologic recognition.

Iron is strongly bound within the iron-isomaltoside formulation, reducing the risk of free iron toxicity [7]. This low content of free iron makes it possible to administer iron isomaltoside 1000 by rapid intravenous infusion or bolus injections. Various studies of iron isomaltoside 1000 have been reported and demonstrated efficacy and a good safety profile in patients with iron deficiency anemia [2-4].

In 2012, Nordfjeld and colleagues reported a pharmacokinetic study of iron isomaltoside 1000 in patients with inflammatory bowel disease and normal renal function. At the administered doses, iron isomaltoside 1000 showed first-order pharmacokinetics and they conclude that changes in total *serum* (*s*-) iron could be used as a surrogate for isomaltoside bound iron. Furthermore, the study did not raise safety concerns in patients with inflammatory bowel disease [4].

The present study was designed to evaluate the pharmacokinetics, pharmacodynamics, and safety of iron isomaltoside 1000 in patients with stage 5 CKD on dialysis therapy.

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Materials and Methods

Ethics

This study was conducted at the Chromalloy American Kidney Center, St. Louis, MO, USA in accordance with the "Declaration of Helsinki" and International Conference on Harmonization Guideline for Good Clinical Practice guidelines. Prior to conduct of the study, the study protocol and other relevant documents were reviewed and approved by the Washington University Human Studies committee. All patients signed an informed consent form before they were enrolled in the study.

Study design and patients

This was a prospective, randomized, open-label pharmacokinetic study of18 patients diagnosed with stage 5 CKD on dialysis therapy. All patients were randomly assigned in a 1:1:1 ratio to receive a single dose of 100 mg, 200 mg, or 500 mg intravenous bolus injection of iron isomaltoside 1000 (6 patients in each group). The dose was administered as an undiluted intravenous bolus injection over approximately 2 min. The randomization list was prepared centrally using a block randomization methodology using a validated computer program (SAS® version 9.1.3; PROC PLAN procedure). An envelope method was used to randomize eligible patients to the treatment.

Patients were enrolled during a period of 5 months. The study duration for the individual patient was 14-21 days and consisted of 5 visits: visit 1 (screening visit; visits1a and 1b were separated by at least 1 week), visit 2 (baseline and dosing visit; dosing was done within 1 week to 15 days from screening), visit 3 (48 h post-dose), visit 4 (72 h post-dose), and visit 5 (7 days post-dose). Blood samples for pharmacokinetic assessments were collected at baseline (30 min pre-dose and at drug administration time)and at 30 min, 1 h, 2 h, 3 h, 4 h, 8 h, 24 h, 48 h, 72 h, and 7 days post-dose. A total of 75 mL blood was collected from each individual patient during the study. The blood samples were drawn at the same time after dialysis.

Inclusion criteria were >18 years of age, patients with stage 5 CKD on dialysis for at least 90 days prior to inclusion, weight >50 kg, *s*-ferritin ≤800 ng/mL, transferrin saturation (TSAT) <35%, life expectancy beyond 12 months by investigator's judgment, hemoglobin(Hb) concentration ≥10.0 g/dL and ≤12.5 g/dL at screening visits 1a and 1b, and receiving a stable dose of erythropoietin stimulating agent and ≤100 mg/week of iron for 4 weeks prior to inclusion. Patients were excluded if they had anemia caused primarily by factors other than renal related anemia, iron overload or disturbances in utilization of iron (e.g. hemochromatosis and hemosiderosis), difference of Hb ≥ 1.0 g/dL between screening visits 1a and 1b, known hypersensitivity to any excipients in the investigational product, history of multiple allergies, decompensated liver cirrhosis and history of hepatitis B or C (alanine aminotransferase >3 times upper limit of normal), acute or chronic infections, rheumatoid arthritis with symptoms or signs of active joint inflammation, pregnant or nursing, blood transfusion within the previous 12 weeks, planned elective surgery during the study where significant blood loss was expected, participation in any other clinical study within 3 months prior to screening, untreated vitamin B_{12} or folate deficiency, or any other medical condition that, in the opinion of the investigator, would have caused the patient to be unsuitable for completion of the study or placed the patient at potential risk from being in the study.

Objectives and outcome measures

The primary objective of the study was to assess pharmacokinetic properties of clinical relevant dosages of 100 mg, 200 mg, and 500 mg iron isomaltoside 1000 in patients with stage 5 CKD on dialysis therapy. The secondary objective was to assess pharmacodynamic properties and safety of iron isomaltoside 1000.

In the study, total *s*-iron was used as a surrogate for iron isomaltoside 1000 for pharmacokinetic evaluation. Iron in iron isomaltoside 1000 is strongly bound within the matrix molecule, leading to low availability of free iron content. Therefore, the level of total *s*-iron is considered equivalent to total administered iron isomaltoside 1000 bound iron [4,7]. Since iron is already present in the body, the pre-dose concentrations (*s*-iron concentrations were available at 30 min pre-dose and at drug administration time) were subtracted from the post-dose concentrations in order to obtain more accurate pharmacokinetics results.

The primary endpoint was to calculate total *s*-iron pharmacokinetic parameters: area under serum concentration-time curve (AUC) from injection to last measurable data point, area under serum concentration-time curve from injection to infinity (AUC_{0-t}), maximum serum concentration (C_{max}), time to reach maximum concentration (T_{max}), elimination rate constant (K_e; derived from each dosing episode profile by log-linear regression), and half-life ($T_{½}$) based upon data collected at baseline (30 min pre-dose and at drug administration time) and at 30 min, 1 h, 2 h, 3 h, 4 h, 8 h, 24 h, 48 h, 72 h, and 7 days post-dose. The secondary endpoint was to measure change in concentrations of Hb, reticulocyte count, reticulocyte hemoglobin content (CHr), *s*-ferritin, total iron binding capacity (TIBC), and TSAT from baseline to 4 h, 8 h, 24 h, 48 h, 72 h, and 7 days post-dose. The safety endpoints included adverse events, safety laboratory variables, physical examination, vital signs, and electrocardiogram.

Statistical methods

There was no formal sample size calculation. The primary and secondary analyses were conducted on the per-protocol population which comprised all patients who received the drug and did not have any major protocol deviations. All the continuous variables were summarized using descriptive statistics by treatment group. The categorical variables were summarized with counts and percentages. The pharmacokinetic parameters (AUC, AUC_{0-t}, C_{max}, T_{max}, K_e and $T_{½}$) were calculated using actual sampling time points for total *s*-iron using SAS® (version 9.1.3) software. AUC and AUC_{0-t} were calculated using trapezoidal rule to the last time of a non-missing concentration; the latter included the extrapolated area (using the terminal slope of the plasma concentration). The pharmacokinetic variables were presented by descriptive statistics. The pre-dose concentrations were subtracted from the post-dose concentrations and values greater than or equal to zero were considered for pharmacokinetic analysis.

Changes in concentrations of pharmacodynamic parameters (Hb, reticulocyte count, CHr, *s*-ferritin, TIBC, and TSAT) from baseline to 4 h, 8 h, 24 h, 48 h, 72 h, and 7 days post-dose were analyzed and tabulated.

The safety analysis was conducted on the safety population, which comprised all patients, who received the drug. All the safety parameters were presented by descriptive statistics. The adverse events and serious adverse events were coded by system organ class and preferred term using the latest Medical Drug Dictionary for Regulatory Activities

version 15.1 [8]. They were collected and evaluated for relatedness to the investigational product, seriousness, severity, and expectedness.

Results

Patients

Of31 patients screened, 12 were considered as screen failures, 1 withdrew consent, and the remaining 18 patients were randomized 1:1:1 to the 100 mg, 200 mg, and 500 mg intravenous bolus group. At the time of screening, all 31 patients were on maintenance iron therapy which was soon stopped after enrolment into the study. All 18 patients completed the study. Both the per-protocol and the safety population included 18 patients as no patient was excluded due to protocol deviations. The baseline demographic data were comparable between the three treatment groups (Table 1). All patients were receiving erythropoiesis-stimulating agent (ESA), and the other most common concomitant medications were ergocalciferol and paricalcitol.

Pharmacokinetic results

There was a dose-dependent increase in the mean (SD) and geometric mean of AUC, AUC_{0-t}, and $C_{max.,}$ and a dose-dependent decrease in T_{max}. Both $T_{½}$ and K_e remained similar across the three treatment groups (Table 2). The mean (SD) concentration of total *s*-iron at different time points of the study is provided in Figure 1.

Pharmacodynamic results

There was no major change in the mean Hb concentration, reticulocyte count, CHr, and TIBC from baseline to 4, 8, 24, 48, 72 h, and 7 days post-dose across 100 mg, 200 mg, and 500 mg intravenous bolus injection of iron isomaltoside 1000. An overall dose-dependent increase in mean *s*-ferritin concentration was observed from baseline to 4 h, 8 h, 24 h, 48 h, 72 h, and 7 days post-dose across the treatment groups. In addition, there was a sudden increase in the mean calculated TSAT concentration from baseline to 4 h post-dose followed by a gradual drop at 8 h, 24 h, 48 h, 72 h, and 7 days post-dose across the treatment groups (Table 3).

Safety results

Three patients reported 3 adverse events; bacterial arthritis (500 mg intravenous bolus group), asthma (500 mg intravenous bolus group), and rash (200 mg intravenous bolus group); rash was of mild intensity and bacterial arthritis and asthma were of moderate intensity. Both bacterial arthritis and rash were unlikely related and asthma was probably related to iron isomaltoside 1000. All 3 patients experiencing adverse events recovered and none of the patients withdrew due to an adverse event. Bacterial arthritis was considered as a serious adverse event. No safety issues were observed either in the shifts in iron status variables or laboratory data from baseline to 7 days post-dose. No patients developed hypophosphatemia, defined as a *s*-phosphate level lower than 2 mg/dL.

None of the patients reported abnormal clinically significant physical examination findings in any of the body systems or electrocardiogram results at 7 days post-dose. The vital signs were comparable between the treatment groups.

Discussion

Iron deficiency anemia is the most common cause of anemia worldwide. In addition to CKD, other disorders which predispose to iron deficiency anemia include inflammatory bowel disease and other gastrointestinal disorders, post-partum blood loss, autoimmune disorders, and major surgery [9]. Oral administration of iron is slow

	Treatment group		
	100 mg intravenous bolus (n=6)	**200 mg intravenous bolus (n=6)**	**500 mg intravenous bolus (n=6)**
Gender, n (%)			
Men	4 (66.7)	4 (66.7)	4 (66.7)
Women	2 (33.3)	2 (33.3)	2 (33.3)
Age (years)			
Mean (SD)	58 (17)	50 (18)	52 (8)
Race, n (%)			
African American	6 (100.0)	6 (100.0)	6 (100.0)
Weight (kg)			
Mean (SD)	92 (23)	91 (19)	105 (18)
Height (cm)			
Mean (SD)	171(7)	171(9)	173(10)
Smoking status, n (%)			
Yes	3 (50.0)	2 (33.3)	4 (66.7)
No	3 (50.0)	4 (66.7)	2 (33.3)

Table 1: Demographical characteristics of the treatment groups.

	Iron isomaltoside 1000 IV bolus doses					
	100 mg		**200 mg**		**500 mg**	
	Mean (SD)	**Geometric mean**	**Mean (SD)**	**Geometric mean**	**Mean (SD)**	**Geometric mean**
AUC_{0-t} (mg h/dL)	3.21 (1.17)	2.99	6.73 (2.48)	6.26	14.80(3.99)	14.34
AUC (mg h/dL)	4.69 (2.74)	4.00	9.44 (4.50)	8.54	19.51 (6.92)	18.61
C_{max}(mcg/dL)	101(23)	99	210 (60)	202	507 (175)	484
T_{max} (h)	1.42 (1.39)	1.00	1.35 (1.43)	0.91	0.59 (0.22)	0.57
K_e (1/h)	0.0273 (0.0144)	0.0240	0.0266 (0.0186)	0.0226	0.0230 (0.0058)	0.0223
$T_{1/2}$ (h)	33.07 (18.99)	28.86	35.14 (18.10)	30.72	32.35 (10.68)	31.14

Table 2: Pharmacokinetic parameters by treatment group for total *s*-iron.

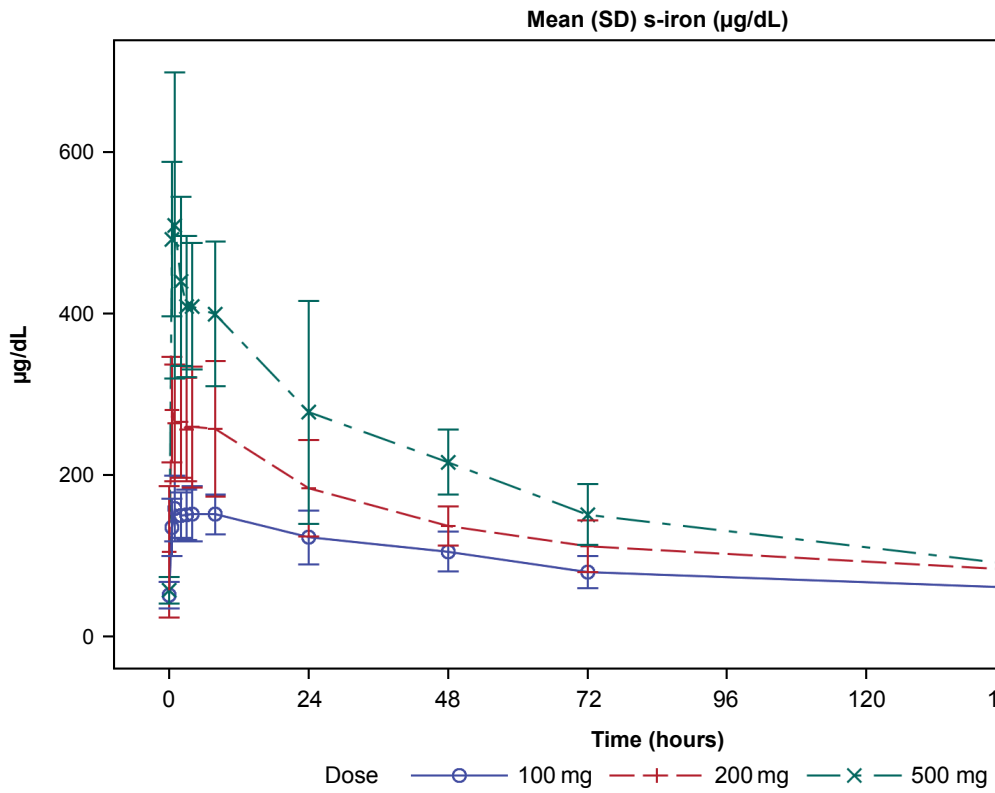

Figure 1: Mean (± SD) concentration of total *s*-iron versus time for each treatment group.

	Hb (g/dL)	Reticulocyte count (10^3/µL)	CHr (pg)	TIBC (µg/dL)	*S*-ferritin (ng/mL)	TSAT(%)
100 mg iron isomaltoside 1000, mean (SD)						
Baseline	11.20 (0.60)	52.57 (12.28)	31.92 (2.08)	244.00 (25.88)	564.20 (136.66)	18.80 (6.38)
4 h	0.30 (0.38)	1.45 (9.48)	-0.17 (0.30)	-12.80 (17.40)	-29.80(86.90)	37.60 (8.91)
8 h	0.25 (0.2)	5.08 (8.94)	-0.07 (0.23)	-8.60 (22.65)	7.80 (23.40)	36.00 (4.69)
24 h	-0.15 (0.49)	-8.20 (10.11)	-0.48 (0.42)	-7.40 (20.82)	41.0 (84.68)	25.20 (10.08)
48 h	0.33 (0.32)	0.55 (16.0)	-0.47 (0.74)	-3.20 (20.74)	83.60 (67.33)	18.40 (3.36)
72 h	-0.07 (0.36)	-5.78 (15.67)	-0.02 (0.80)	-6.20 (16.78)	32.60 (39.32)	10.20 (8.87)
7 days	-0.30 (0.55)	-0.58 (11.70)	0.23 (0.64)	-11.0 (22.27)	29.80 (32.28)	-0.20 (3.27)
200 mg iron isomaltoside 1000, mean (SD)						
Baseline	10.73 (0.40)	41.45 (10.44)	31.92 (1.59)	233.67 (36.48)	698.33 (69.76)	37.33 (22.63)
4 h	0.32 (0.44)	6.87 (8.37)	0.23 (0.53)	2.83 (9.64)	37.50 (50.68)	61.17 (40.20)
8 h	0.60 (0.36)	8.50 (5.09)	0.22 (0.19)	13.17 (6.91)	117.83 (108.06)	53.67 (42.87)
24 h	0.20 (0.22)	5.75 (7.98)	0.37 (0.50)	7.83 (10.61)	37.50 (73.52)	31.33 (34.56)
48 h	0.75 (0.48)	2.42 (8.29)	0.12 (0.32)	15.67 (9.40)	169.83 (176.50)	11.00 (27.52)
72 h	0.43 (0.38)	0.72 (20.18)	0.35 (1.23)	10.33 (10.95)	168.83 (94.09)	2.17 (29.31)
7 days	-0.07 (0.54)	11.23 (19.27)	0.72 (1.04)	6.17 (11.81)	83.67 (96.18)	-10.33 (28.37)
500 mg iron isomaltoside 1000, mean (SD)						
Baseline	11.22 (0.84)	85.20 (49.85)	30.98 (1.20)	232.33 (32.87)	369.67 (205.19)	21.83 (6.24)
4 h	0.40 (0.52)	-2.32 (30.30)	0.28 (0.37)	-10.00 (28.19)	4.5 (66.79)	140.50 (39.01)
8 h	0.50 (0.36)	-5.42 (32.28)	0.32 (0.45)	7.17 (14.93)	-3.5 (28.24)	133.00 (43.23)
24 h	-0.00 (0.77)	-7.27 (24.08)	0.43 (0.74)	-29.83 (95.14)	-0.83 (95.18)	98.50 (29.75)
48 h	0.37 (0.56)	-29.67 (32.21)	0.43 (0.81)	34.17 (52.69)	155.83 (59.18)	58.67 (22.42)
72 h	0.07 (0.36)	-22.85 (26.19)	0.95 (0.42)	4.67 (4.03)	156.50 (104.57)	35.17 (16.22)
7 days	0.02 (0.64)	-11.87 (30.54)	1.43 (2.22)	10.33 (23.19)	216.67 (116.66)	4.33 (8.24)

CHr: Reticulocyte hemoglobin count; Hb: hemoglobin; TIBC: total iron binding capacity; TSAT: transferrin saturation

Table 3: Baseline values and change in concentrations of pharmacodynamic parameters from baseline to 4 h, 8 h, 24 h, 48 h, 72 h and 7 days post-dose.

and variably effective for treatment for iron deficiency anemia, and it has gastrointestinal side effects which limit compliance. Additionally, inflammation increases serum hepcidin levels, which in turn down-regulates intestinal absorption of iron. Several studies in CKD and other populations indicate that intravenous iron is as effective or superior to oral iron therapy.

This was a prospective, single center, open-label, 1:1:1 randomized, pharmacokinetic study of iron isomaltoside 1000 conducted in 18 patients with stage 5 CKD. In 2012, Nordfjeld and coworkers demonstrated that pharmacokinetic parameters for isomaltoside bound iron were close to that of total *s*-iron, and they conclude that total s-iron is a good surrogate for isomaltoside bound iron [4]. Hence, in the present study, *s*-iron was used as a surrogate marker for pharmacokinetic assessments.

In the present study, there was a dose-dependent reduction in the geometric mean of T_{max}. All bolus injections were administered over 2 min, hence the reduced T_{max} seen with the 500 mg bolus could not be explained by the different injection times. The reason for the differences observed in T_{max} among the dosages is unclear. Nordfjeld and coworkers [4] also observed a shorter T_{max} with a higher dose of isomaltoside in patients with inflammatory bowel disease. Further investigation of this observation is needed.

The dose-dependent increase in the mean AUC, $AUC_{0\text{-}t}$, and C_{max} of *s*-iron in this study was in concordance to an Australian Public Assessment Report (AusPAR) for iron carboxymaltose, another intravenous iron, where four treatment groups of iron carboxymaltose (100 mg, 500 mg, 800 mg, and 1000 mg) were compared in a randomized, double-blind, placebo-controlled, single-dose escalation study involving 32 men and women aged 18-45 years with mild iron deficiency anemia ($9.0 \leq Hb < 12.0$ g/dL, women; $9.0 \leq Hb < 13.0$ g/dL, men), *s*-ferritin < 20 µg/L, and TSAT< 16% at baseline [10]. The study showed a rapid increase in (total) *s*-iron levels in 24 out of 32 anemic patients with administration of iron carboxymaltose. Kowalczyk and coworkers also reported similar finding with fermoxytol showing a dose-dependent increase in C_{max} in healthy subjects and in patients with CKD stage 5 on hemodialysis [11].

The geometric mean of K_e and $T_{½}$ was comparable across the 3 treatment groups. Despite our patients being all African American and heavier, our findings were analogous to a pharmacokinetic study by Nordfjeld and coworkers in Caucasians where the geometric mean of K_e and $T_{½}$ remained similar with escalating doses of iron isomaltoside 1000 [4]. However, it is in contrast to the pharmacokinetic results of ferumoxytol where increasing doses led to a significant decline in K_e and increase in $T_{½}$. In addition the AUC increased out of proportion to the dose increase [12].

All patients were on maintenance iron prior to being enrolled into the study with an aim of maintaining a stable Hb. As expected, no major change in Hb, reticulocyte count, or CHr level was observed across the treatment groups at 7 days post-dose.

S-ferritin is an indicator of the storage iron in the reticuloendothelial system, and is acutely increased following intravenous iron administration. For this reason, clinical guidelines recommend delaying *s*-ferritin assessment at least 2 weeks following intravenous iron loading. Consistent with this, we observed a dose-dependent increase in *s*-ferritin following iron administration. The *s*-ferritin level peaked at 48 h post dose with 100 mg and 200 mg doses and at 7 days post-dose with the 500 mg dose. Similar results were observed in a study of iron carboxymaltose where an increase in *s*-ferritin was found to be dose-dependent but not strictly dose-linear [10].

TIBC indicates the maximum amount of iron needed to saturate plasma or serum transferrin, which is the primary iron transport protein [13]. The TIBC is an indicator of iron status, as TIBC level is elevated when iron stores are low and declines during iron repletion [14]. In the present study there was no major change in the mean TIBC concentration from baseline to 7 days post-dose across the 3 treatment groups.

Reduced calculated TSAT level is a marker of inadequate iron supply to the developing erythrocytes and serves as an indirect measure of the extent of iron utilization. Various studies have reported a dose-dependent increase in calculated TSAT in patients with different clinical conditions [15]. In this study, an initial increase in calculated TSAT at 4 h post-dose was followed by a gradual decrease at 8 h, 24 h, 48 h, 72 h, and 7 days post-dose across all three treatment groups. Of note in this aspect intravenous iron is a carbohydrate complex and may not bind to transferrin in the same way as free iron.

Three adverse events (bacterial arthritis, asthma, and rash) were reported of which asthma was thought to be probable related to the current drug. All the patients recovered from the adverse events. Our findings were in line with previous reported studies where no significant safety issues were observed with iron isomaltoside 1000 in doses up to 1800 mg in patients with CKD receiving dialysis or pre-dialysis care [3,16] and chronic heart failure patients with mild anemia [2].

No patients reported hypophosphatemia, defined as a *s*-phosphate level lower than 2 mg/dL, which is consistent with two interim analyses of other studies where no clinically significant hypophosphatemia was observed in 25 patients with cancer (NCT 01145638) and in 50 patients with non-dialysis dependent CKD (NCT 01102413) [9]. Other iron products, including iron carboxymaltose have previously been shown to be associated with hypophosphatemia [9].

In conclusion, pharmacokinetic study of bolus injections of iron isomaltoside 1000 over 2 min up to 500 mg found proportional increases in C_{max} and AUC, with no prolongation of the $T_{1/2}$. Rapid injection of doses over this range may be of significant clinical utility for the treatment of iron deficiency anemia in CKD patients.

Acknowledgements and Disclosure

LLT is an employee at Pharmacosmos A/S. DWC is a consultant for Pharmacosmos A/S, and has been a speaker for Pharmacosmos A/S, Watson Pharmaceuticals, and AMAG, which make intravenous iron products. DRG and DSL report no conflicts of interest. The study was funded by Pharmacosmos A/S.

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