Single-Dose Pharmacokinetics of Deferiprone in Subjects with Various Degrees of Renal Impairment

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ABSTRACT

Statement of Purpose, Innovation or Hypothesis The primary objective of this study was to assess the impact of renal impairment on the pharmacokinetics (PK) of deferiprone and its metabolite.

Description of Methods and Materials The study was an open-label, multi-center, and parallel study in patients (n = 8 per group) with mild, moderate, and severe renal impairment (eGFR 60-89, 30-59, and 15-29 mL/min/1.73m^2, respectively) in comparison to healthy normal subjects (eGFR ≥ 90 mL/min/1.73m^2). Subjects received a single oral 33 mg/kg of deferiprone (Ferriprox™) under fasting conditions. Serum and urine samples were collected over 24 hours and were assayed for concentrations of deferiprone and its 3-*O*-glucuronide metabolite. Noncompartmental PK analysis was performed and a regression analysis was used to evaluate the relationship between renal function and the PK parameters. If the correlation was significant, an ANOVA was performed. Safety was monitored throughout the study.

Data and Results A decrease in the amount of deferiprone excreted over 24 hours was observed as the severity of renal impairment increased. Since the amount of deferiprone excreted in urine represented <5% of the dose, there was no significant impact on total body clearance. Systemic exposure to deferiprone, as indicated by C_{max} (mean 31-43 ug/mL) and AUC (mean 71-78 ug*h/mL), was not different among subjects. Tmax (median 0.5-1.0 h) and $T_{½}$ (mean 1.7-2.2 h) values were also not affected by renal impairment. Renal clearance of the inactive metabolite decreased with severity of renal function from 24 L/h in normals to 4 L/h in severe renal impairment, leading to increased C_{max} and AUCs, and longer T_{max} and $T_{½}$. Deferiprone was well tolerated in all groups and the severity of renal impairment was not associated with safety concerns. No SAEs were observed.

Interpretation, Conclusion or Significance Study results demonstrate that systemic exposure to orally administered deferiprone is not significantly altered by the presence or severity of renal impairment. These results indicate that impaired renal function does not require adjustment of the dosage of deferiprone.

PURPOSE

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is an orally active bidentate iron chelator that preferentially binds trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone:iron) complex. In 1999, deferiprone was first approved for the treatment of iron overload by the European Medicines Agency and it is currently approved in over 60 countries. This pharmacokinetic study was conducted as part of the post-marketing requirements of the FDA's accelerated approval of deferiprone tablet (Ferriprox™).

The primary objective of this study was to evaluate the effect of impaired renal function on the pharmacokinetics and safety of deferiprone (Ferriprox™) and its main metabolite.

METHODS

STUDY DESIGN

- The study design was chosen based on the FDA March 2010, Draft Guidance for Industry, 'Pharmacokinetics in Patients with Impaired Renal Function'.
- This was a Phase IV, multi-center, non-randomized, open-label, single-dose, parallel group study in a subject population comprised of adult male and female volunteers with various levels of renal function:

• Healthy volunteers (Normal renal function)	(eGFR ≥ 90 mL/min/1.73m^2)
• Mild renal impairment	(eGFR 60-89 mL/min/1.73m^2)
• Moderate renal impairment	(eGFR 30-59 mL/min/1.73m^2)
• Severe renal impairment	(eGFR 15-29 mL/min/1.73m^2)

- The degree of renal impairment was determined using the estimated glomerular filtration rate (eGFR) from the Modification of Diet in Renal Disease Study (MDRD).
- Subjects with renal impairment were recruited first, and healthy volunteers were matched by age (+/- 10 years), weight (+/- 15%), and tobacco use, to the extent possible.

Renal function/ impairment		Normal n=8	Mild n=8	Moderate n=8	Severe n=8	Overall n=32
Age (years)	Mean (SD)	56 (9)	64 (5)	59 (15)	58 (12)	59 (11)
	Min, Max	41, 65	60, 75	31, 73	34, 73	31, 75
Gender [n (%)]	Male	3 (37.5)	5 (62.5)	5 (62.5)	6 (75.0)	19 (59.4)
	Female	5 (62.5)	3 (37.5)	3 (37.5)	2 (25.0)	13 (40.6)
Weight (kg)	Mean (SD)	69.3 (8.5)	69.8 (11.6)	74.6 (12.6)	73.1 (13.2)	71.7 (11.3)
	Min, Max	60.0, 84.1	53.9, 86.6	58.8, 95.8	52.0, 94.6	52.0, 95.8
eGFR (mL/min/ 1.73 m^2)	Mean (SD)	99.76 (9.47)	75.43 (9.30)	45.88 (9.05)	22.50 (3.02)	-
	Min, Max	90.35, 120.88	60.03, 87.43	31.00, 55.00	19.00, 28.00	-

- All subjects received a single 33 mg/kg oral dose of Ferriprox™ under fasting conditions. Blood and urine samples for measurement of deferiprone and deferiprone 3-*O*-glucuronide concentrations were collected pre-dose and over a 24-hour period post-dose.
- Safety endpoints included the occurrence of adverse events (AEs), clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, and use of concomitant medications.

BIOANALYTICAL AND STATISTICAL ANALYSIS

- Samples were quantified for serum and urine deferiprone and its metabolite using validated LC-MS/MS methods.
- Noncompartmental PK analysis was performed (Phoenix® WinNonlin® 6.3) and a regression analysis was used to evaluate the impact of impaired renal function on the relevant PK parameters. If any trend observed was significant, an ANOVA would be performed to assess individual differences between groups (SAS® 9.2, Proc MIXED).

RESULTS

RECRUITMENT

- The enrollment of the 24 patients with varying degrees of renal impairment was completed in approximately 3 months and 8 healthy volunteers in approximately 1,5 months.
- Healthy subjects and subjects with mild renal impairment were recruited and dosed at Algorithme Pharma and subjects with moderate and severe renal impairment were enrolled at Hôpital Maisonneuve-Rosemont.

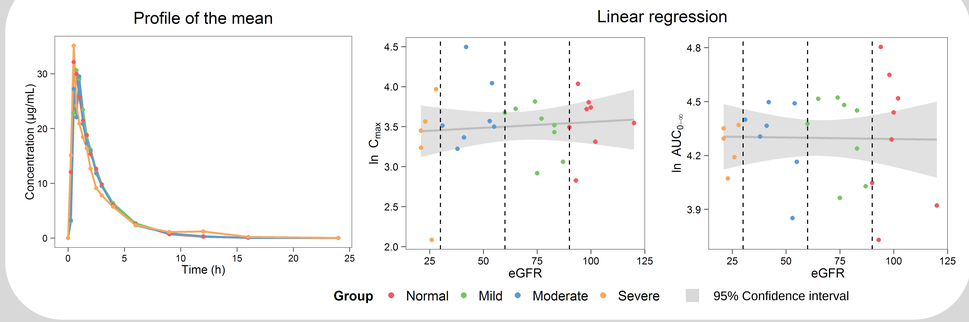
DEFERIPRONE

- The results showed similar C_{max} for subjects with renal impairment (mean C_{max} ranged 31-43 µg/mL) compared to healthy subjects (mean C_{max} 37 µg/mL).
- No overall group effect was noted for the exposure (AUC), (mean $AUC_{0-\infty}$ ranged 71-78 ug*h/mL).
- Deferiprone was rapidly absorbed with a median T_{max} of 0.5-1 hour for all subjects.
- No significant differences in elimination half-life of the drug between healthy volunteers and renally impaired subjects were observed in all pairwise comparisons, with a $T_{½}$ ranging 1.7-2.2 hours among groups.

Serum Deferiprone

	Renal function / impairment							
	Normal n=8		Mild n=8		Moderate n=7		Severe n=5	
Variable	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
C_{max} (µg/mL)	37.1	32.4	33.4	28.3	43.3	52.9	30.6	53.0
T_{max} (h)*	0.50	0.25-1.00	0.75	0.50-1.00	1.00	0.50-2.00	0.75	0.25-4.00
AUC_{0-t} (µg*h/mL)	77.8	35.7	76.5	20.5	74.0	20.1	70.1	12.7
$AUC_{0-\infty}$ (µg*h/mL)	78.1	35.5	76.9	20.4	74.9	20.1	70.9	12.0
$T_{1/2}$ (h)	1.68	16.0	1.77	9.6	2.03	15.9	2.20	41.2
Cl/F (L/h)	33.4	47.0	31.5	23.8	34.8	20.9	34.0	20.9
CLr (L/h)	0.999	20.3	0.905	22.2	0.485†	27.7	0.326†	44.0
Vd/F (L)	77.7	38.2	79.8	22.8	103	26.1	114	57.1

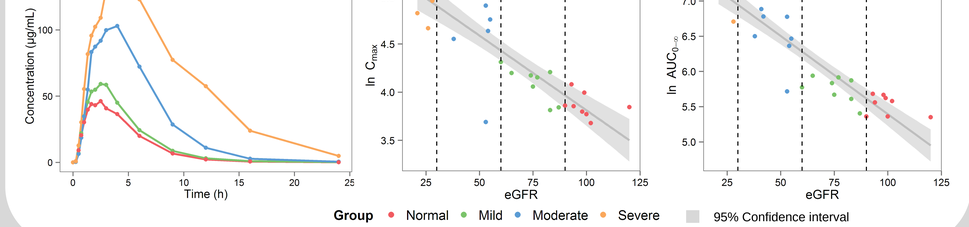
* For this parameter, the median and the range are presented
† p < 0.0001 compared to normal



Serum Deferiprone-3-*O*-Glucuronide

	Renal function / impairment							
	Normal n=8		Mild n=8		Moderate n=7		Severe n=6	
Variable	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
C_{max} (µg/mL)	47.8	13.0	60.8†	16.9	119†	40.6	151†	21.5
T_{max} (h)*	2.50	1.33-3.00	2.50	2.00-3.00	3.00	2.00-6.00	4.00†	2.00-6.00
AUC_{0-t} (µg*h/mL)	252	14.1	318†	17.0	698†	32.5	1410†	23.2
$AUC_{0-\infty}$ (µg*h/mL)	253	14.0	319†	16.9	703†	32.6	1440†	23.3
$T_{1/2}$ (h)	2.14	14.9	2.58	17.6	2.58	14.9	3.35†	14.3
CLr (L/h)	23.7	17.1	20.8	20.4	9.27†	33.7	3.84†	47.4

* For this parameter, the median and the range are presented
† p < 0.05 compared to normal

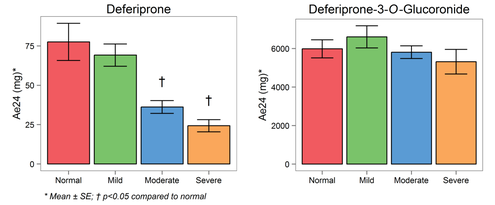


- A significant decrease was noted for the renal clearance (CL_r) and for the amount excreted over 24 hours (Ae_{24}) in renal impaired groups (an approximate 3-fold decrease was observed for severe impaired subjects when compared to healthy subjects). Since the amount of deferiprone excreted in urine represented < 5% of the dose, there was no significant impact on total body clearance.

DEFERIPRONE 3-*O*-GLUCURONIDE

- The C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ parameters were significantly increased following administration of deferiprone to subjects with various degrees of impaired renal function; a 3.2-fold increase in Cmax and a 5.6-fold increase in AUC were observed between healthy and severely impaired subjects.
- A prolonged T_{max} by 1.5 hour was observed for severe impaired subjects when compared to healthy subjects.
- The results also showed a slightly prolonged $T_{½}$ compared to normal subjects.
- There were no significant differences in Ae_{24} among subjects with renal impairment and healthy volunteers.
- Renal clearance of the inactive metabolite decreased with severity of renal function from 24 L/h in normals to 4 L/h in severe renal impairment, leading to increased C_{max} and AUCs, and longer T_{max} and $T_{1/2}$.

Amount excreted in urine over 24 h



** Mean ± SE; † p<0.05 compared to normal*

SAFETY

- The majority of the AEs were mild in severity and all AEs were transient in nature (lasting less than 24 hours) and resolved prior to subject discharge. The most commonly reported AEs were somnolence and headache, experienced by 4 subjects (12.5%) each. No AEs led to discontinuation from the study.
- Overall, increase in severity of renal impairment did not result in significant increase in incidence of AEs.
- There were no SAEs and no deaths. No clinically significant effects on laboratory values, vital signs, ECGs, or physical examinations were noted during this study.

CONCLUSION

The study results demonstrate that systemic exposure, as indicated by C_{max} and AUCs, to orally administered deferiprone is not significantly altered by the presence of renal impairment, even in severely impaired patients.

Conversely, systemic exposure of the 3-*O*-glucuronide metabolite was significantly impacted following administration of deferiprone to subjects with different degrees of impaired renal function, when compared to subjects with normal renal function. The exposure of deferiprone 3-*O*-glucuronide increased as eGFR decreased, with a greater rate of increase in patient with more severe renal impairment.

Irrespective of the severity of renal impairment, the majority of the orally administered dose of Ferriprox was excreted in urine over the first 24 hours as 3-*O*-glucuronide metabolite.

Ferriprox™ was well tolerated by the subjects included in this study.

Adjustment of the Ferriprox ™ dosage regimen in patients with impaired renal function is concluded to be unnecessary as there were no significant changes in systemic exposure of deferiprone, unless other factors warrant it.