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CORRESPONDENCE

The safety and acceptability of twice-daily deferiprone for transfusional iron overload: A multicentre, open-label, phase 2 study

Lifelong iron chelation therapy is critical for patients with transfusion-dependent anaemias, and full adherence to therapy is essential to optimise long-term patient outcomes.[1,2] Deferiprone is an oral iron chelator with high efficiency in binding and removing excess intracellular and extracellular iron.[3,4] Owing to its elimination half-life of approximately 2 h, deferiprone is administered three times daily (t.i.d.) to promote longer extent of exposure and better control of labile iron.[5–7] Clinical trial data show adherence rates with deferiprone t.i.d. from 79% to 98%[8,9]; however, real-world adherence is generally lower than in clinical trials, as the t.i.d. regimen may be inconvenient and the midday dose may often be missed.[10–12]

The United States Food and Drug Administration recently approved a twice-a-day modified-release formulation of deferiprone (Ferriprox TAD 1000 mg tablet; manufactured by Apotex Inc., Toronto, Ontario, Canada) for the treatment of patients with transfusional iron overload due to thalassaemia syndromes, sickle cell disease or other anaemias.[13] In single-dose and multiple-dose pharmacokinetic studies of deferiprone in healthy volunteers (Tables S1 and S2), we found that the twice-daily (b.i.d.) formulation had equivalent 24-h drug exposure to the original immediate-release tablet administered t.i.d. (Figure S1), and exposure was not affected by administration with food (Table S3). Based on these pharmacokinetic data demonstrating that the deferiprone b.i.d. and immediate-release formulations provide equivalent 24-h drug exposure, it is anticipated that the two formulations will have similar safety and efficacy profiles.

We report the findings of a multicentre, open-label, phase 2 trial investigating the safety and acceptability of the b.i.d. formulation in patients with transfusion-dependent blood disorders who were already taking deferiprone immediate-release t.i.d. for the treatment of transfusional iron overload (NCT03802916; see Table S4 for eligibility criteria). Patients were switched from their current t.i.d. dosage to the equivalent daily dosage of deferiprone b.i.d. tablets for 28 days. Patients were assigned in a 1:1 ratio to groups defined as 'low standard dose' (Group A) or 'high standard dose' (Group B) based on whether their daily t.i.d. dose had been closer to 75 mg/kg or closer to 99 mg/kg respectively. Adherence was measured by

TABLE 1 Number of patients who experienced AEs while taking deferiprone b.i.d. (safety population, study LA61-0218).

	Group A (*n* = 15)	Group B (*n* = 14)	Overall (*N* = 29)
Patients with ≥1 AE, *n* (%)	10 (66·7)	9 (64·3)	19 (65·5)
Mild AEs	8 (53·3)	6 (42·9)	14 (48·3)
Moderate AEs	7 (46·7)	6 (42·9)	13 (44·8)
Severe AEs	1 (6·7)	0	1 (3·4)
SAEs	0	0	0
AEs seen in ≥2 patients, *n* (%)			
Headache	3 (20·0)	3 (21·4)	6 (20·7)
Arthralgia	3 (20·0)	1 (7·1)	4 (13·8)
Diarrhoea	0 (0·0)	3 (21·4)	3 (10·3)
Ear pain	1 (6·7)	1 (7·1)	2 (6·9)
Blepharitis	0 (0·0)	2 (14·3)	2 (6·9)
Pyrexia	1 (6·7)	1 (7·1)	2 (6·9)
Joint injury	2 (13·3)	0 (0·0)	2 (6·9)
Back pain	1 (6·7)	1 (7·1)	2 (6·9)
Sciatica	1 (6·7)	1 (7·1)	2 (6·9)
Gastrointestinal AEs seen in ≥1 patient, *n* (%)	3 (20·0)	3 (21·4)	6 (20·7)
Diarrhoea	0 (0·0)	3 (21·4)	3 (10·3)
Abdominal pain	1 (6·7)	0 (0·0)	1 (3·4)
Dyspepsia	1 (6·7)	0 (0·0)	1 (3·4)
Nausea/vomiting	1 (6·7)	0 (0·0)	1 (3·4)
Treatment-related AEs seen in ≥1 patient, *n* (%)	2 (13·3)	4 (28·6)	6 (20·7)
Diarrhoea	0 (0·0)	3 (21·4)	3 (10·3)
Arthralgia	1 (6·7)	1 (7·1)	2 (6·9)
Nausea	1 (6·7)	0 (0·0)	1 (3·4)
Vomiting	1 (6·7)	0 (0·0)	1 (3·4)
Pyrexia	0 (0·0)	1 (7·1)	1 (3·4)
Decreased neutrophil count	1 (6·7)	0 (0·0)	1 (3·4)
Headache	1 (6·7)	0 (0·0)	1 (3·4)
Renal colic	0 (0·0)	1 (7·1)	1 (3·4)

Group A, deferiprone b.i.d. dose closer to 75 mg/kg/day. Group B, deferiprone b.i.d. dose closer to 99 mg/kg/day. Abbreviations: AE, adverse event; SAE, serious adverse event; b.i.d., twice daily; t.i.d., three times daily.

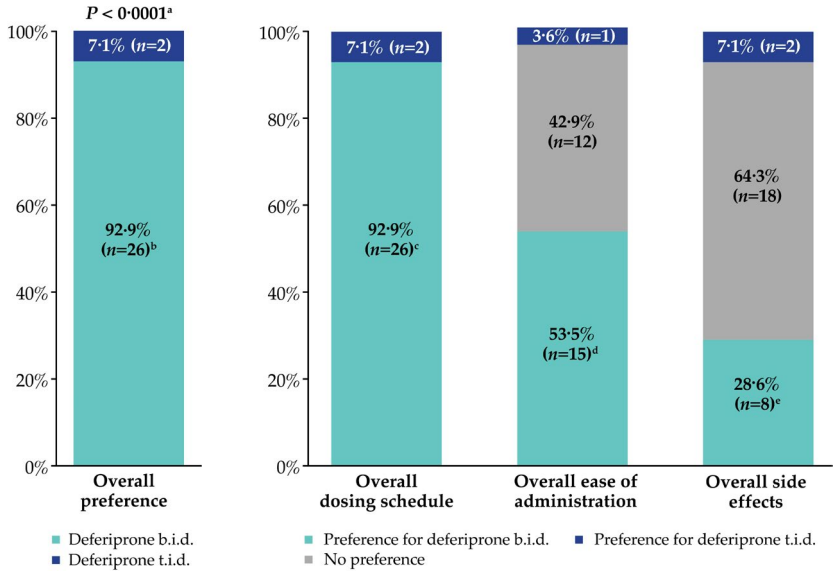

FIGURE 1 The acceptability of deferiprone b.i.d. in patients with transfusional iron overload (safety population, study LA61-0218). Acceptability was measured using a questionnaire administered on the last day of the study that asked about patients' preferences for deferiprone b.i.d. versus deferiprone t.i.d., with respect to (A) the overall preference of deferiprone b.i.d. versus deferiprone t.i.d. and (B) overall dosing schedule, overall ease of administration, and overall side effects of deferiprone b.i.d. *versus* deferiprone t.i.d. One of the 15 patients enrolled in Group A withdrew before completing the questionnaire, therefore responses are from 28 patients. [a]The one-sample proportion test to determine if the overall preference for deferiprone b.i.d. was greater than chance (i.e., a 50% preference for each formulation). [b]All 92.9% much preferred deferiprone b.i.d. [c]Patient preference was divided between much preferring deferiprone b.i.d. 64.3% (n = 18) and somewhat preferring deferiprone b.i.d. 28.6% (n = 8). [d]Patient preference was divided between much preferring deferiprone b.i.d. 46.4% (n = 13) and somewhat preferring deferiprone b.i.d. 7.1% (n = 2). [e]Patient preference was divided between much preferring deferiprone b.i.d. 25% (n = 7) and somewhat preferring deferiprone b.i.d. 3.6% (n = 1). b.i.d., twice daily; t.i.d., three times daily.

counting the remaining tablets at the end-of-study visit. Safety was assessed by monitoring adverse events (AEs) and serious AEs (SAEs), discontinuations due to AEs, and clinical laboratory tests. Acceptability was assessed using questionnaires about patients' preferences for the b.i.d and t.i.d formulations.

Thirty patients with transfusional iron overload were enrolled in the study (15 patients per dosage group). One patient in Group B withdrew before receiving deferiprone b.i.d. and was not included in the analyses. Another patient in Group B reported a mild AE of renal colic, which occurred one day after initiating deferiprone b.i.d., was deemed possibly treatment-related and resulted in withdrawal from the study. The mean (standard deviation) age of patients was 41 (8) years, and about half (16 of 29) of the patients were men (Table S5). Twenty-seven patients had a primary diagnosis of thalassaemia major, one patient had α-thalassaemia/haemoglobin H disease and one patient had sickle β-thalassaemia. Treatment adherence was very high in both groups (mean, 99%).

A total of 49 AEs were reported by 10 patients in Group A and by nine patients in Group B (Table 1). Fourteen patients reported mild AEs, 13 patients reported moderate AEs and one patient reported a severe AE. There were no reports of SAEs. Additional details on the most frequent AEs and their severity are also reported in Table 1. Overall, the incidence of gastrointestinal AEs was low across both groups. Liver enzyme levels remained generally stable in both groups, and no patients had post-dose increases of clinical concern.

Thirteen AEs deemed at least possibly related to treatment were identified in six patients (two in Group A, four in Group B; Table 1). One patient in Group A reported three AEs that were judged by the investigator as definitely related to treatment: one event of severe arthralgia (elbow pain), one event of moderate elbow pain and one event of mild decreased absolute neutrophil count, which returned to within normal range the following day.

For the 28 patients who completed the acceptability questionnaire, there was a strong overall preference for deferiprone b.i.d. over deferiprone t.i.d. [26 (92·9%) vs 2 (7·1%), respectively; $p < 0.0001$; Figure 1]. Patients indicated a preference for the b.i.d. dosing schedule *versus* the t.i.d. dosing schedule [26 (92·9%) vs 2 (7·1%)]. Concerning ease of administration, patients were divided between preferring deferiprone b.i.d. [15 (53·5%)] and having no preference [12 (42·9%)]; only one patient preferred deferiprone t.i.d. (3·6%). Approximately two-thirds of respondents [18 (64·3%)] indicated no preference related to side effects, eight patients (28·6%) favoured deferiprone b.i.d. and two patients (7·1%) indicated a preference for deferiprone t.i.d.

Limitations of the study include the small sample size, short treatment period and exclusion of paediatric patients. Furthermore, neither deferiprone-naïve patients nor patients on combination therapy with another chelator were included in this study. Safety outcomes may differ compared with patients who have not been previously treated with deferiprone. The safety and tolerability profiles of the b.i.d. formulation, as assessed in this study, appear similar to those of the t.i.d. formulation.[5–7] AEs reported during deferiprone b.i.d. therapy were no different from those previously reported with

deferiprone t.i.d.[5–7] There were no new safety concerns, no SAEs such as agranulocytosis and no clinically concerning liver enzyme increases. Further studies are needed to assess the long-term safety and efficacy of deferiprone b.i.d. and treatment compliance.

Given the equivalent drug exposure of the two formulations, it is anticipated they would be comparable with respect to safety and efficacy. Our data show that the b.i.d. formulation is strongly preferred by patients. Given that appropriate long-term iron chelation is essential in the treatment of transfusion-dependent anaemias,[14,15] deferiprone b.i.d. has the potential to improve treatment adherence and health outcomes in patients with transfusional iron overload.

KEYWORDS
iron overload, anaemia, iron chelation, deferiprone, safety.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

BD, ES, CF, FT, YT: conceptualization, methodology and resources; FZ, YT: software, validation, and formal analysis; SB, AK, HE, BD, ES, SS, AP: investigation; all authors: reviewing and editing; CF, FT: supervision; CF, FT: project administration. All authors have read and agreed to the published version of the manuscript.

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SUPPORTING INFORMATION

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