Influence of patient-reported outcomes on the treatment effect of deferasirox film-coated and dispersible tablet formulations in the ECLIPSE trial: a *post-hoc* mediation analysis

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To the Editor:

Deferasirox dispersible tablets (DT), a once-daily, oral iron chelator, was approved by the US Food and Drug Administration in 2005. Deferasirox DT is typically dispersed in water or juice (20–30 mg/kg/day) and taken on an empty stomach ≥30 minutes before a meal.[1] For patients to receive the maximum therapeutic benefit from chelation therapy, adherence to the prescribed dosing regimen is essential. Treatment satisfaction can affect adherence and, thus, its ultimate effectiveness.[2] Deferasirox DT has been associated with better patient satisfaction and adherence (>80%), as well as lower impact on daily activities, than the previous standard iron chelator, deferoxamine.[3,4] However, barriers to optimal adherence exist, including the need to take medication on an empty stomach, palatability, and gastrointestinal (GI)-related side effects.

ECLIPSE was a 24-week, open-label, randomized study (NCT02125877) of DT and a new film-coated tablet (FCT) formulation of deferasirox (which can be taken with a light meal) among 173 iron chelation-naïve and -experienced patients with transfusion-dependent thalassaemia or myelodysplastic syndromes.[5] ECLIPSE showed that the safety profile of the two formulations were comparable, with FCT recipients experiencing fewer severe GI-related adverse events (AEs). Although not a study endpoint, serum ferritin was monitored to guide dosing. FCT patients had a higher median reduction in serum ferritin from baseline (–350.0 [FCT] vs. –85.5 ng/mL [DT]) to study end, suggesting a possible association between deferasirox formulation and observed efficacy. Furthermore, FCT patients had more favorable patient-reported outcomes (PROs) than DT recipients, reporting better adherence, satisfaction, and palatability, and fewer concerns about iron chelation therapy, as assessed using modified Satisfaction with Iron Chelation Therapy and palatability questionnaires. One explanatory factor of the observed difference in serum ferritin reduction could be better treatment adherence among FCT patients. The objective of this *post-hoc* analysis was to estimate the proportion of the observed difference in serum ferritin reduction between the two formulations mediated by PROs, with a focus on patient-reported

adherence. We assessed the proportion mediated (PM) by PROs in the overall population, as well as in subgroups with prior DT use ('DT non-naïve'), with thalassemia only, and in DT non-naïve patients with thalassaemia.

The mediation analysis was based on a method outlined previously.[6] Average PROs were calculated by taking the average of all available PRO domain scores over the treatment period for each patient. Three mediation frameworks with incremental increases in the number of mediators were considered: (1) average PRO adherence domain score; (2) all average PRO domain scores (adherence, satisfaction, concerns, palatability); and (3) all average PRO scores and frequency of severe GI-related AEs (**Supplementary Fig S1**).

Univariate and multivariate generalized linear models, with and without the mediator variables of interest as predictors, were used to model the association between treatment (FCT or DT) and change in serum ferritin from baseline to end of treatment. The multivariate models included the covariates age, sex, race, underlying disease, prior use of iron chelation therapy, level of iron overload severity at baseline, average planned dose, and number of blood transfusions while on treatment. The models without the mediator(s) of interest provided an estimate of the total association between treatment and change in serum ferritin, ie the association both *through* and *not through* the mediator(s). The models with the mediator(s) of interest provided an estimate of the association between treatment and serum ferritin change *not through* the mediator(s). Results are reported as PM, ie the proportion of the total association between exposure and outcomes that is operationalized *through* the mediator(s) of interest, calculated as one minus the ratio of the association that does *not* go through the mediator, divided by the total association. Analytical variables were log transformed or square-root transformed for normality, as required.

A total of 154 patients had at least one PRO assessment over the study period and were included in the analyses. Among these patients, the average patient-reported adherence score mediated 66.6% (P=0.012) of the association between treatment and change in serum ferritin (**Table 1**). Patient-reported adherence, satisfaction, concerns, palatability

scores, and frequency of severe GI-related AEs together mediated 90.1% of the association (*P*=0.014). In DT non-naïve patients, the PM by patient-reported adherence was 62.6% (*P*=0.014), and by patient-reported adherence and other PRO scores was 94.3% (*P*=0.012). In the DT non-naïve with thalassemia and thalassemia subgroups, similar trends were observed (**Table 1**).

In summary, these analyses found that PRO scores, specifically adherence, represent important mediators of the observed difference in serum ferritin reduction between the two treatment groups.

The PM was greatest among patients with prior experience with DT. One explanation, supported by a previous comparative analysis of iron chelation therapies,[3] is that patients with prior experience with DT have a reference frame for comparing the new FCT formulation with the standard formulation, and are better able to appreciate attributes of the new formulation.

This analysis is subject to several limitations. During ECLIPSE, a larger proportion of FCT patients received a higher-than-recommended dose or were not dose adjusted during management of AEs, which could have contributed to the observed serum ferritin reduction.[5] In addition, serum ferritin levels in the deferasirox FCT arm were higher than in the DT arm at baseline (2983 vs. 2485 ng/mL). Furthermore, these results may not be generalizable outside the context of ECLIPSE because of the stringent inclusion/exclusion criteria. Although multivariate models were used to adjust for baseline covariates, the effect estimates between treatment group and serum ferritin reduction should be interpreted as associations, and the estimates of mediation by PROs should be interpreted as statistical mediation and not necessarily as causal.

In conclusion, this *post-hoc* analysis supports the importance of considering PROs in determining the efficacy of chelation therapy for iron overload. Owing to its better palatability and ease of use, deferasirox FCT may be a superior therapy to DT for some patients with iron overload by increasing adherence to therapy.

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AUTHORSHIP CONTRIBUTIONS

ATT, RO, SP, AK, KB, and JBP served as investigators in the ECLIPSE trial, enrolling patients. VH, JH, and AB contributed to the interpretation and reporting of this analysis. PB and MSD conducted the analysis for this study. All authors contributed to data interpretation, reviewed, and provided their comments on this manuscript, and approved the final version.

PREVIOUS PRESENTATION

A synopsis of the current research was submitted for presentation at the European Hematology Association Congress in Madrid, Spain, 22–25 June 2017, at the Thalassemia International Federation congress in Thessaloniki, Greece, 17–19 November 2017, and at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Prague, Czech Republic, 22–26 August 2018.

DISCLOSURES AND COMPETING INTERESTS STATEMENT

Funding for this research was provided by Novartis. VH, JH, and AB are employees of Novartis and own stock/stock options. PB and MSD are employees of Analysis Group, Inc, which has received consultancy fees from Novartis. ATT reports receiving research funding and honoraria from Novartis and research funding from Celgene and Roche, and consultancy from Vifor. RO reports receiving honoraria from Novartis and Apopharma and for being part of the Italian advisory board for BlueBird Bio. SP reports receiving research

funding and honoraria from Novartis and research funding from Acceleron. AK reports receiving honoraria from Novartis, Amgen, and Janssen and consultancy for Gilead, Roche, and Celgene. KB has no disclosures or conflicts of interest to report. JBP reports consultancy, research grant funding, and honoraria from Novartis, consultancy and honoraria from Agios Pharmaceuticals and Shire, and consultancy from Bluebird Bio and Celgene; JBP is supported by the NIHR University College London Hospitals Biomedical Research Centre.

DATA SHARING

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. This trial data availability is in accordance with the criteria and process described on www.clinicalstudydatarequest.com.

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TABLE LEGEND

Table 1. Multiple mediators of the effect of treatment group (FCT vs DT) on absolute change in serum ferritin levels from baseline at the end of treatment, overall and by subgroup

*P<0.05.

[1]Models adjusted for age, sex, race, underlying disease, level of iron overload severity at baseline, average planned dose and number of blood transfusions while on treatment.

[2]PM calculated as the ratio of the indirect effect (effect through the mediator) to the total effect (effect both through and not through the mediator).

[3]Satisfaction, concerns and palatability scores.

[4]PM calculated to be >100%; in instances with multiple mediators, because of the interaction between them, the PM may be calculated to be >100%.

AE, adverse event; DT, dispersible tablet; FCT, film-coated tablet; GI, gastrointestinal; PM, proportion mediated; PRO, patient-reported outcome.

Table 1. Multiple mediators of the effect of treatment group (FCT vs DT) on absolute change in serum ferritin levels from baseline at the end of treatment, overall and by subgroup

Mediators	Overall population				DT non-naïve patients				Patients with thalassaemia				DT non-naïve patients with thalassaemia			
	Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]	
	PM[2] (%)	*P*	PM[2] (%)	*P*	PM[2] (%)	*P*	PM[2] (%)	*P*	PM[2] (%)	*P*	PM[2] (%)	*P*	PM[2] (%)	*P*	PM[2] (%)	*P*
Adherence, assessed by average adherence PRO score	36.0	0.041*	66.6	0.012*	62.6	0.014*	62.6	0.014*	34.4	0.084	45.0	0.090	65.1	0.014*	68.1	0.025*
Adherence, assessed by average adherence PRO score + other PRO scores[3]	58.0	0.049*	77.0	0.020*	94.3	0.012*	94.3	0.012*	36.2	0.1626	56.1	0.125	68.9	0.050	66.1	0.093
Adherence, assessed by average adherence PRO score + other PRO scores[3] and severe GI-related AEs	58.4	0.060	90.1	0.014*	–[4]	–	–[4]	–	36.8	0.1472	69.5	0.074	75.7	0.032*	85.1	0.044*

*$P<0.05$.

[1]Models adjusted for age, sex, race, underlying disease, level of iron overload severity at baseline, average planned dose and number of blood transfusions while on treatment.

[2]PM calculated as the ratio of the indirect effect (effect through the mediator) to the total effect (effect both through and not through the mediator).

[3]Satisfaction, concerns and palatability scores.

[4]PM calculated to be >100%; in instances with multiple mediators, because of the interaction between them, the PM may be calculated to be >100%.

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