to metformin observed in the different Hb genotypes presented here as well as the lack of response in nonSCD patients in the previous report.[5]

Here we report the first *in vivo* evidence of using metformin in SCD patients. We demonstrate HbF increase was minimal in nonHb SS/Sβ^0 patients, consistent with the results in previous nonSCD patients.[5] Some HbF induction was observed in Hb SS/Sβ^0 genotype, and combination of HU with metformin might have additional benefits. Importantly, we did not find evidence that metformin increases anemia or lactic acidosis in SCD patients. Our report is limited by the sample size and variability in the patient baseline characteristics. The compliance to metformin is difficult to assess due to the retrospective design, which may also contribute to some of the inter-individual variation in the HbF response. Our findings require substantiation in prospective clinical trials to evaluate the safety and efficacy of metformin in SCD patients.

CONFLICT OF INTEREST

Nothing to report.

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REFERENCES

1. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med*. 1995;332(20):1317-1322.
2. Zhang Y, Paikari A, Sumazin P, et al. Metformin induces FOXO3-dependent fetal hemoglobin production in human primary erythroid cells. *Blood*. 2018; 132(3):321-333.
3. Vecchio S, Protti A. Metformin-induced lactic acidosis: no one left behind. *Crit Care*. 2011;15(1):107.
4. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab*. 2016;101(4): 1754-1761.
5. Boulassel MR, El-Hussain AI, Hassan MM, et al. Stability of fetal hemoglobin levels in patients receiving metformin therapy. *Haematologica*. 2018;103:e440-e442.
6. Charache S, Dover GJ, Moore RD, et al. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia. *Blood*. 1992; 79(10):2555-2565.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Predicting serum ferritin levels in patients with iron overload treated with the film-coated tablet of deferasirox during the ECLIPSE study

To the Editor:

The iron chelator, deferasirox, is generally effective and well tolerated, but issues around ease of use and palatability of dispersible tablets (DTs) may limit adherence, and by extension efficacy, in some patients. The ECLIPSE trial (NCT02125877) demonstrated that deferasirox film-coated tablets (FCTs) and DT formulations had similar safety profiles during 6 months of treatment, though fewer patients treated with FCT experienced severe gastrointestinal-related adverse events and patient-reported outcomes were more favorable with FCT than with DT.[1]

Absolute and relative serum ferritin changes from baseline in each treatment arm were evaluated monthly during ECLIPSE. While patients experienced similar exposure to active deferasirox with either DT or FCT, a greater reduction in serum ferritin levels from baseline to end of treatment was observed with FCT, with a geometric mean change of −431 compared with −153 ng/mL with DT.

In the absence of reported efficacy data beyond 6 months for the FCT in the clinical trial setting, this mathematical modeling analysis investigated whether the observed difference in serum ferritin levels between the 2 arms at month 6 of ECLIPSE would have translated into a sustained difference in treatment effect if the study had continued through 12 months.

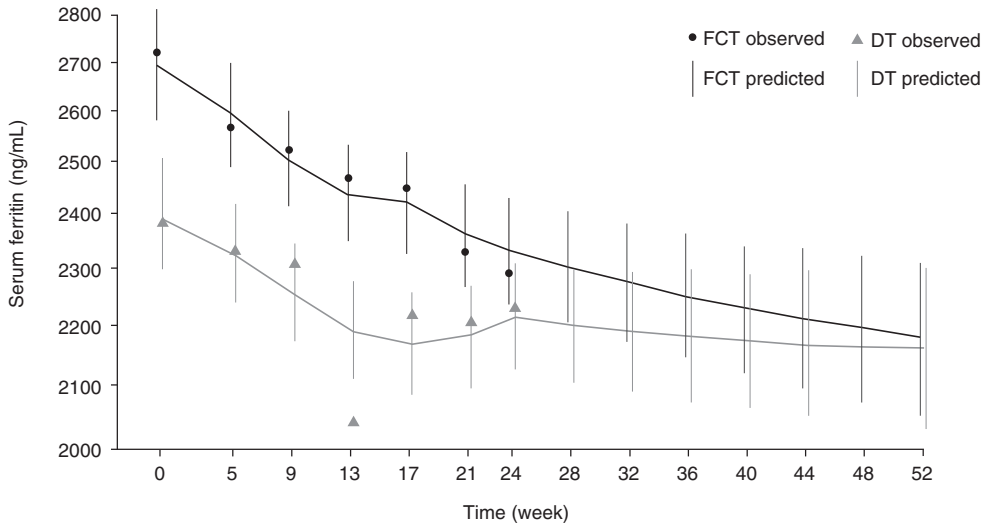

FIGURE 1 Serum ferritin with model prediction for completers of the ECLIPSE trial. Circle and triangle data points represent actual geometric mean serum ferritin value observed during the ECLIPSE trial. Solid lines represent model prediction for serum ferritin values with error bars showing 90% CIs of the predicted geometric mean. Abbreviations: DT, dispersible tablet; FCT, film-coated tablet

The ECLIPSE study design is described in detail elsewhere.[1] Briefly, ECLIPSE was a randomized, open-label, multicenter, Phase II study in which male or female patients aged ≥10 years with transfusion-dependent thalassemia or International Prognostic Scoring System lower-risk myelodysplastic syndromes (MDS) received deferasirox DT (starting dose: 20 mg/kg/d) or FCT (starting dose: 14 mg/kg/d) for 24 weeks. Improved bioavailability of the FCT formulation means that equivalent deferasirox doses are 30% lower for the FCT than the DT formulation.[2]

Initial exploratory graphical analyses were conducted to understand the distribution of serum ferritin and of key covariates at baseline including weight and age.

Two candidate models, using the 12-month data from the controlled registration study ICL670A108 (NCT00061763),[3] were evaluated to describe changes from baseline in serum ferritin with deferasirox; both use log transformed serum ferritin measurement:

(1) simple exponential model (random intercept and slope model of log[serum ferritin]), where treatment effect is on lambda.

$$\mathrm{SF}(t) = \mathrm{SF\_0}^{*} \exp\left(-\mathrm{lambda}^{*} t\right) <=> \log(\mathrm{SF}(t)) = \log(\mathrm{SF\_0}) - \mathrm{lambda}^{*} t.$$

(2) Verhulst model that has a saturation effect after an initial exponential decrease, where treatment effect is on gamma.[4]

$$\mathrm{SF}(t) = \mathrm{SF\_0}^{*}\,\mathrm{gamma}^{*} \exp\left(\mathrm{lambda}^{*} t\right) / \left(\mathrm{gamma} - 1 + \exp\left(\mathrm{lambda}^{*} t\right)\right).$$

The 1-year prospective, multicenter, and Phase II ICL670A108 study evaluated deferasirox efficacy in transfusion-dependent patients with MDS (n = 47), β-thalassemia (n = 85), Diamond-Blackfan anemia (n = 30), or other rare anemias (n = 22). Patients in this study were deferasirox-naïve, unlike most ECLIPSE patients who had received prior deferasirox. After discarding the first 3-month serum ferritin data from ICL670A108, patients were considered nondeferasirox-naive, and the subsequent serum ferritin data from months 4 to 10 were used to fit the models, and those from months 11 to 12 served to test model prediction accuracy.

The final model was selected by comparing model performance based on prediction accuracy and using out-of-sample information criteria.[5] The population and individual level predictive properties of the final model on the out-of-sample data, including coverage, bias, and root mean square error (RMSE), were also evaluated.

In ECLIPSE, 86 patients were randomized to receive DT, and 87 patients to receive FCT. Mean (SD) patient age was 34.9 (19.3) years, and 90% had previously received iron chelation therapy. Over 24 weeks, the mean (SD) actual daily deferasirox dose was 27.5 (7.7) mg/kg/day in the DT group, and 20.8 (5.4) mg/kg/day in the FCT group, indicating similar deferasirox exposure. At baseline, geometric mean serum ferritin was 2381 and 2721 ng/mL in the DT and FCT arms, respectively.

Model diagnostics showed that the difference in the information metric between the 2 models was greater than 100 points in favor of the Verhulst model, suggesting the latter has superior leave-one-out predictive performance and, therefore, was suitable for predicting new data with acceptable accuracy. However, some degree of overfitting was observed with the ICL670A108 data (high shrinkage on slope and residual error term; inflated 50% coverage). Additionally, the out-of-sample performance metrics showed that the individual level model resulted in lower RMSE and allowed for less bias compared with the population level model, suggesting that serum ferritin value forecasting for the ECLIPSE patient population was best achieved using individual level model predictions.

The final model predictions yielded a close approximation of the ECLIPSE data; the predicted geometric mean serum ferritin values during the first 6 treatment months were similar to the actual serum ferritin values observed during the trial (Figure 1). Importantly, the model predicted that geometric mean serum ferritin would continue to decrease over the subsequent 6 months with both deferasirox DT and FCT, reaching 2162 ng/mL (90% CI 2029-2304) with deferasirox DT, and 2180 ng/mL (90% CI 2054-2311) with deferasirox FCT after

12 months of treatment. The predicted relative serum ferritin reduction at 12 months was 10% (90% CI 2-17) with deferasirox DT, and 19% (90% CI 12-25) with deferasirox FCT. It is important to note that mean actual deferasirox dose remained stable throughout the 6-month study with both DT (27.1-28.2 mg/kg/day) and FCT (20.1-21.6 mg/kg/day).

According to the predicted results from the proposed model, and with a similar exposure to deferasirox, patients treated with FCT would have had a greater reduction in serum ferritin at 12 months than patients treated with DT. Although it cannot be excluded that other factors might have influenced the trajectories of this model, such as the higher baseline serum ferritin values in the FCT group, this greater serum ferritin reduction with deferasirox FCT could be attributed to better treatment adherence. Previous analyses have indicated that improved patient-reported outcomes, especially increased adherence, are significant mediators of the association between treatment with deferasirox DT vs FCT, and the reduction from baseline in serum ferritin achieved over 6 months of treatment.[6] Further exploration of long-term efficacy outcomes and their associated factors is needed to confirm improved efficacy with deferasirox FCT.

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CONFLICT OF INTEREST

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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 anonymized 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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REFERENCES

1. Taher AT, Origa R, Perrotta S, et al. New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: results of the randomized, phase II ECLIPSE study. *Am J Hematol*. 2017;92:420-428.
2. Novartis Pharmaceuticals. Exjade film-coated tablets - summary of product characteristics. 2018. Available at: www.medicines.org.uk/emc/print-document?documentId=32428.
3. Porter J, Galanello R, Saglio G, et al. Relative response of patients with myelodysplastic syndromes and other transfusion-dependent anaemias to deferasirox (ICL670): a 1-yr prospective study. *Eur J Haematol*. 2008;80:168-176.
4. Verhulst P-F. Recherches mathématiques sur la loi d'accroissement de la population. *Nouveaux Mémoires de l'Académie Royale des Sciences et Belles-Lettres de Bruxelles*. 1845;18:1-42.
5. Vehtari A, Gelman A, Gabry J. Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. 2016. Available at: https://arxiv.org/pdf/1507.04544.pdf.
6. Taher AT, Origa R, Perrotta A, et al. Mediation by patient-reported outcomes on the association between film-coated versus dispersible formulations of deferasirox and serum ferritin reduction: a post hoc analysis of the ECLIPSE trial. *Haematologica*. 2017;102(s2):abst P286.

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Carfilzomib weekly 20/56 mg/m^2, lenalidomide and dexamethasone for early relapsed refractory multiple myeloma

To the Editor:

Triplet-based lenalidomide plus dexamethasone combinations have become a new standard of care for early relapsed refractory multiple myeloma (RRMM),[1] improving the outcome of MM over the past