POPULATION PHARMACOKINETICS AND RESPONSE OF ICL670, A NOVEL IRON CHELATOR, IN BETA-THALASSAEMIA PATIENTS

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Introduction

ICL670 is a novel oral iron chelator developed for the long-term treatment of iron overload. The purpose of this retrospective study was to determine the population pharmacokinetics and response of ICL670 in beta-thalassaemic patients with transfusional iron overload.

Objectives

- To develop a population pharmacokinetic model for ICL670 and the iron-complex Fe-$[ICL670]_2$.
- To explore the relationship between ICL670 exposure and the efficacy variable faecal iron excretion.

Data

This retrospective study utilised data from a previously performed Novartis clinical trial[1]. Plasma concentration-time data from 18 subjects randomised to receive daily oral doses of either 10, 20 or 40 mg/kg ICL670 for 12 days were available. Data rich plasma PK profiles were obtained on Days 1 and 12; and trough data was obtained on Days 4, 6, 8, 10 and 12. Daily faecal iron excretion data was also available.

There were 9 male and 9 female patients. Mean [range] demographics follow: weight (kg) 62.5 [45.7-118.4], height (cm) 160.9 [145.0-182.0], age (years) 26.4 [18-39].

Methods

Non-linear mixed-effects modelling in NONMEM (double precision, FO estimation) with a proportional error model for inter-subject and residual variability was performed. A three-compartment pharmacokinetic model (including two-compartments for ICL670 and one-compartment for Fe-$[ICL670]_2$ formation) was fitted to the plasma profiles. An empirical linear effect model was fitted to describe the relationship between exposure to ICL670 (daily ICL670 AUC) and daily faecal iron excretion.

Results

- No significant effects of demographic or clinical covariates were detected.

Table1 ICL670 population pharmacokinetic parameters

Parameter	Estimate [95% CI]	Precision [a]
CL/F (L/h)	2.94 [2.55-3.33]	6.6%
V_1/F (L)	31.6 [25.6-37.6]	9.5%
Q (L/h)	1.86 [1.43-2.29]	11.5%
V_2/F (L)	25.5 [15.0-36.0]	20.7%
D_1 (h)	1.40 [1.20-1.60]	7.3%
Inter-subject variability (CV%) [b]		
CL/F	39.2	21.9%
V_1/F	39.0	34.1%
Intra-subject variability (CV%) [b]		
	46.8 [41.6-51.5]	10.5%

[a] Precision was calculated as the SE divided by the parameter estimate x 100.
[b] The CV% for both inter-subject and intra-subject variability is an approximation taken as the square root of the variance x 100.

Figure 1 ICL670 observed and predicted (solid line mean, dashed line 95% prediction interval) plasma concentration versus time profile

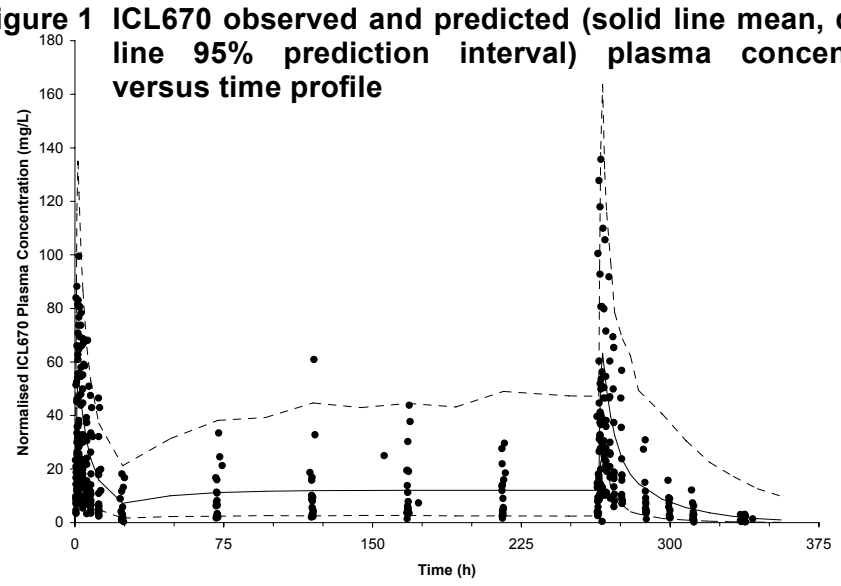


Figure 2 ICL670 model goodness of fit plot

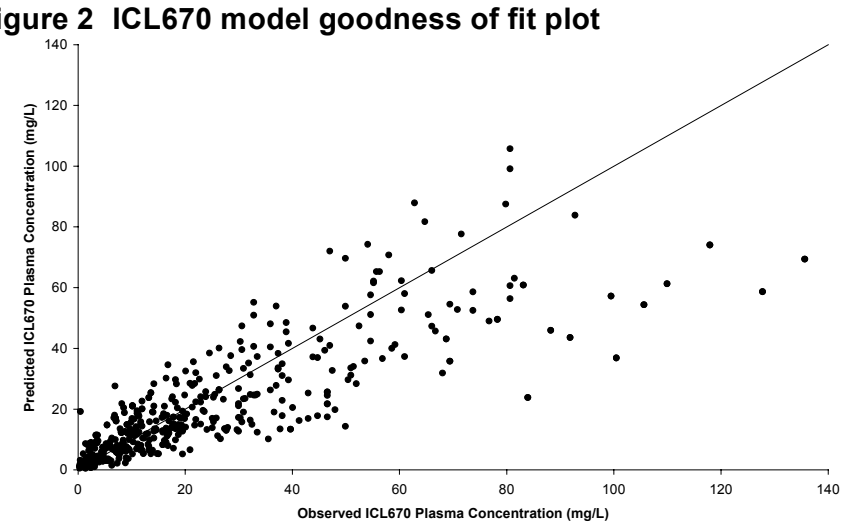


Table 2 Fe-$[ICL670]_2$ population pharmacokinetic parameters

Parameter	Estimate [95% CI]	Precision [a]
CL/Fm (L/h)	12.1 [10.4-13.8]	7.17%
V_3/F (L)	16.3 [8.82-23.8]	22.9%
Inter-subject variability (CV%) [b]		
CL/Fm	50.3	19.7%
V_3/F	107	33.4%
Intra-subject variability (CV%) [b]		
	59.2 [53.1-64.7]	9.8%

Figure 3 Fe-$[ICL670]_2$ observed and predicted (solid line mean, dashed line 95% prediction interval) plasma concentration versus time profile

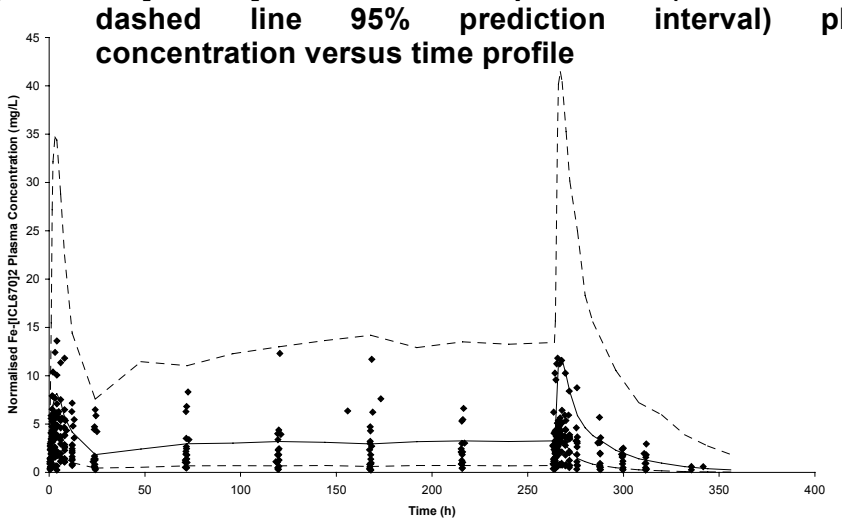


Figure 4 Fe-$[ICL670]_2$ model goodness of fit plot

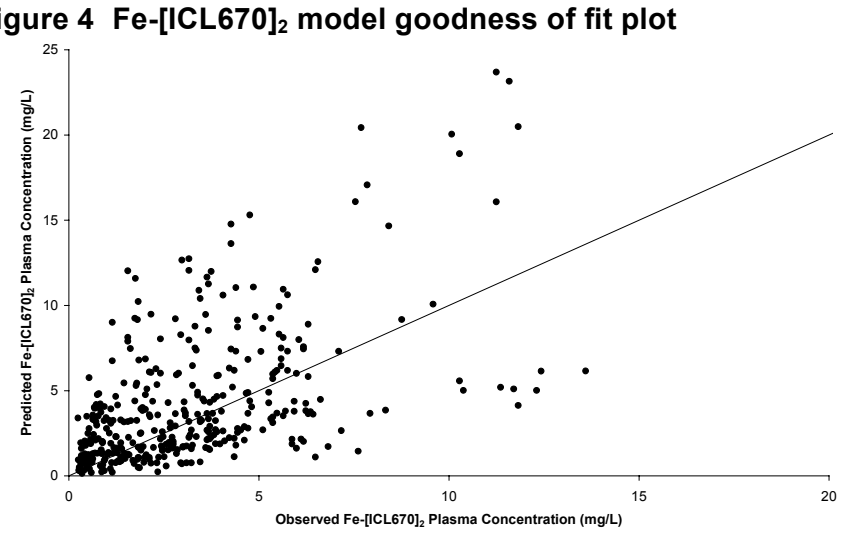
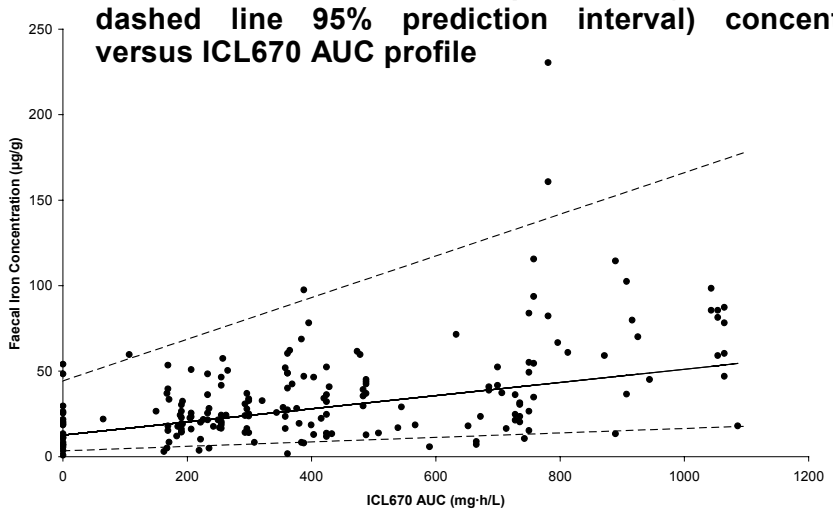


Table 3 Faecal iron population pharmacokinetic parameters

Parameter	Estimate [95% CI]	Precision [a]
Intercept	2.53 [2.1-2.9]	7.6%
Slope	-3.26 [-3.5- -3.0]	-3.5%
Inter-subject variability (CV%) [b]		
Intercept	31.3	<100%
Slope	0	<100%
Intra-subject variability (CV%) [b]		
	69.9 [56.7-81.0]	17.1%

Figure 5 Faecal iron observed and predicted (solid line mean, dashed line 95% prediction interval) concentration versus ICL670 AUC profile



Conclusions

The analysis provides a model which characterises the pharmacokinetics of ICL670 and Fe-$[ICL670]_2$ in plasma and the effect of ICL670 administration on faecal iron excretion in beta-thalassaemia patients.

Acknowledgement

We wish to thank Novartis Pharma for providing us access to the data used in this study.

References

1. Nisbet-Brown E., Olivieri N.F., Giardina P.J., Grady R.W., Neufeld E.J., Sechaud R., Krebs-Brown A.J., Anderson J.R., Alberti D., Sizer K.C., Nathan D.G. Effectiveness and safety of Icl670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet 2003; 361: 1597-1602.
2. NONMEM: Nonlinear-Mixed Effects Modelling, NONMEM Project Group, UCSF, San Francisco, CA, USA.

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