Draft Clinical Pharmacology and Biopharmaceutics Executive Summary

ICL670 is formulated as an immediate release tablet for oral suspension at 125, 250 and 500 mg dose strengths. The proposed maintenance dose is to be adjusted from the starting dose every 3-6 months in steps of 5 or 10 mg/kg based on serum ferritin levels. Doses of ICL670 should not exceed 30 mg/kg per day as there is limited clinical experience beyond this dose. ICL670 tablet is recommended to be taken once daily after dispersing the tablet in water or orange juice.

Data was submitted from nine Clinical Pharmacology and Biopharmaceutics-related studies investigating among others, relative bioavailability, mass balance, food-effect, dose proportionality, multiple dose Pharmacokinetics (PK) / Pharmacodynamics (PD), drug-drug interaction with digoxin, and cardiac safety (thorough QT study).

The mean %ICL670 chelated to iron in pharmacodynamic studies ranged from 15-32%. There was a dose-related negative iron balance for ICL670 in two pharmacodynamic studies. In addition, a correlation analysis between LIC and corresponding PK parameters in study 107 showed reasonable correlation between LIC (measured by liver biopsy) on one hand and Cmax and AUC of iron-complex ICL670 on the other.

The findings of *in vitro* and *in vivo* pre-clinical studies as well a definitive thorough QT study in healthy subjects indicate that ICL670 is not associated with QT prolongation effects on the cardiac system.

ICL670 is a poorly soluble, highly permeable drug (BCS Class II drug).

The mean absolute bioavailability of ICL670 tablet for suspension was determined to be 73%. Peak plasma levels of ICL670 were achieved 1 to 4 hrs following oral administration, while the mean Cmax and AUC values of ICL670 and the iron complex increased in a dose-related manner in the dose range of 2.5 to 80 mg/kg. Steady-state of ICL670 was achieved after 3 days of multiple QD dosing of ICL670 tablets with an accumulation factor of 1.8.

Three formulations of ICL670 tablet were utilized throughout the clinical development program. The formulations were linked using *in vitro* dissolution.

A significant food-effect was observed on the bioavailability of the ICL670 tablet, whereby the relative bioavailability of ICL670 is increased when administered within 5 minutes of a high-fat breakfast (1000 cal). Total exposure (AUC_{0-t}) was doubled while Cmax increased by 77% compared to administration of ICL670 under fasted conditions. Administration of ICL670 tablet 30 minutes before a high-fat breakfast (1000 cal) resulted in mean AUC_{0-t} and Cmax increases of 23% and 25%, respectively, relative to fasting conditions. Subsequently, ICL670 tablets were administered 30 min before a standard breakfast in the pivotal clinical trial (study 107).

Administration of ICL670 dispersed both in orange juice and in apple juice was studied as alternate administration options to dispersion in water. ICL670 tablets dispersed in orange juice and ICL670 tablets dispersed in water were bioequivalent. While ICL670 tablets dispersed in apple juice and ICL670 tablets dispersed in water were not bioequivalent, the observed PK differences are unlikely to be of clinical relevance.

ICL670 is highly bound to plasma proteins (99.5-99.7%) within a concentration range of 7-166 μg/mL. ICL670 is primarily bound to albumin in plasma.

In vitro metabolism studies in human liver microsomes as well as in human hepatocytes have shown that ICL670 is primarily metabolized by glucuronidation with the acyl-glucuronide (M3) being the major metabolite. Glucuronidation appears to be mediated predominantly by UGT1A1 and UGT1A3 isoforms. Up to 8% of an oral dose of ICL670 is metabolized by CYP450 enzymes, in particular, CYP1A1, CYP1A2 and CYP2D6.

In vitro metabolism studies have also shown that ICL670 is a weak inhibitor of CYP450 activities with IC_{50} values ranging from 100 to > 500 μM. Therefore, ICL670 is unlikely to inhibit the metabolism of CYP450 substrates.

A mass balance study using ^{14}C-radiolabeled ICL670 indicated that ICL670 was primarily excreted in feces (84% of the dose) with only 7.6% of the radioactivity excreted in the urine.

The terminal half-life of ICL670 following I.V. infusion was estimated at 4 hrs. However, following oral administration of ICL670, the apparent terminal half-life ranged from 12-18 hrs, likely due to enterohepatic recirculation.

As the renal excretion of ICL670 is limited (urinary excretion of ICL670 and its iron complex form account for < 0.1% of the administered ICL670 dose over 96 hrs post-dose), studies evaluating the PK of ICL670 in patients with renal impairment were not undertaken.

Data evaluating the PK of ICL670 in patients with hepatic impairment is not available. However, since patients with iron overload often have abnormal liver function tests due either to iron overload or concomitant viral hepatitis, patients with mild to moderate elevations in serum transaminase levels (up to 5 times the ULN) were enrolled in clinical studies and were treated with similar doses of ICL670 to patients without hepatic impairment. The general safety and efficacy profiles in these individuals were similar to the overall population. ICL670 is proposed to be used with caution in patients with hepatic impairment.

Co-administration of ICL670 with digoxin did not result in a significant PK interaction.

Females exhibit lower apparent clearance (by 17.5%) for ICL670 compared to males. However, as ICL670 is dosed by weight, those gender-related differences in PK are unlikely to be of clinical relevance.

A total of 292 pediatric patients aged 2 to 16 years were treated with ICL670 during the clinical development program. Children and adolescents demonstrate a lower exposure to ICL60 following single and multiple doses. The exposure of children aged 2 to 6 years is around half that of adults. Drug exposure gradually increases between ages 2 to 18 years to reach adult levels. There was generally a trend toward reduced efficacy in children age 2 to 6 years, consistent with the lower drug exposure in these patients. However, since ICL670 dosing is based upon titration to the individual patient response, the pharmacokinetic differences may not have significant clinical implications.

A total of 30 geriatric patients > 65 years of age were treated with ICL670 during the clinical development program. Pharmacokinetic data in geriatric patients is not available to allow comparison to young adults with respect to total exposure.