

# A Pilot Study of the Response of Oxidant Stress Induced Injury and Mitochondrial Dysfunction Biomarkers to Treatment with Iron Chelators: Ancillary Study of the Novartis ICL670 107 Open Label Phase III Trial

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## Synopsis:

Although the life expectancy for patients with  $\beta$ -thalassemia has greatly improved with the use of transfusions and iron chelation therapy, there continues to be significant mortality with death occurring by age 25 in most patients, most often as a result of heart disease. In addition, over 70% of teenagers and young adults in this group suffer from primary and secondary amenorrhea, hypogonadism, and multi-organ dysfunction. The mechanism for this ongoing organ injury in thalassemia, despite the introduction of aggressive iron chelation with DFO, is not known. Similar occurrence of severe organ injury has also been described in older patients with myelodysplasia receiving chronic transfusions but has not been reported frequently in iron overloaded patients with SCD. The mechanisms underlying these differences have not been established but may relate to differences in intestinal iron absorption, organ distribution of iron and storage mechanisms, disease-specific inflammatory response, response to oxidant stress such as the induction of the intrinsic pathway of apoptosis, and/or generation of toxic-nontransferrin bound iron (NTBI).

ICL670 is a new orally-active iron chelator that has been studied both *in vitro* and *in vivo* in animal toxicology and pharmacology studies. As of June 2002, three clinical studies have been initiated and 90 patients have received ICL670 for periods of up to 11 months. In recently reported results from a phase II trial, ICL670 at 20 mg/kg demonstrated negative iron balance comparable to deferoxamine at 40 mg/kg (Piga, A.ASH meeting, Philadelphia, PA, 2002).

The purpose of this ancillary study is to estimate the magnitude of response and variability in the response of biomarkers of oxidant-stress induced injury and mitochondrial dysfunction in  $\beta$ -thalassemia patients to treatment with ICL670 or deferoxamine (DFO). In parallel with this, we will determine the effect of body iron burden, inflammation, and antioxidant status on biomarkers of oxidant-stress induced injury and mitochondrial dysfunction.