Statement for FDA Bioequivalence Hearing:
Impact of T4 Dose on Babies with Congenital Hypothyroidism
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My name is Rosalind Brown. For 23 years I was at the University of Massachusetts Medical School where I was Professor of Pediatrics and Director of the Pediatric Endocrine Division. I have just relocated to Children's Hospital, Boston and Harvard Medical School where I am now the Director of Clinical Trials Research and where I am developing a program in Pediatric Thyroidology. My entire professional career has been devoted to the care and study of children with hormonal disorders with particular reference to children with abnormalities of the thyroid gland. I have published numerous original articles and book chapters and have held leadership positions in both the Lawson Wilkins Pediatric Endocrine Society and the American Thyroid Association.

I do not have any financial relationship with any company whose product might be affected by this discussion. However, I have received research support and honoraria for speaking engagements and have been on the Thyroid Research Advisory Council, a peer-review research review committee sponsored by Knoll Pharmaceuticals, in the past.

The purpose of my presentation is to emphasize the significant, irreversible impact of small dose changes in L-thyroxine on the brain development of small babies with congenital hypothyroidism.

Congenital hypothyroidism is a disorder caused most commonly either by failure of thyroid gland development or failure of thyroid hormone synthesis. The first slide demonstrates the devastating impact of this disorder on a small infant whose congenital hypothyroidism was undiagnosed and untreated. Because at birth affected babies have no symptoms and because for the best outcome treatment must be started as early as possible, screening programs for the detection of congenital hypothyroidism have been developed in the United States and throughout the world. We now know that the incidence of congenital hypothyroidism is 1 in 3,000 babies and, as such, this disorder is one of the most common *treatable* causes of mental retardation. In fact, congenital hypothyroidism is 3-4 times *more* common than PKU, for which newborn screening programs were originally developed.

The second slide demonstrates some data prior to the advent of newborn thyroid screening demonstrating the significant decrease in IQ of babies with congenital hypothyroidism (bottom panel) as compared with a control group of normal children (upper panel). An IQ of <85 is considered to be consistent with significant cognitive impairment. As can be seen, a majority of babies with congenital hypothyroidism indicated by the red arrow, but few of the normal babies had an IQ of 85 or less.

The third slide demonstrates the striking improvement and, in fact, the normalization of IQ in babies with congenital hypothyroidism (dark bars) as compared with control patients when the diagnosis was made by newborn screening and treatment was early and adequate.

Unfortunately, the IQ is only normal if treatment is adequate, and even small decreases in the dose of thyroxine replacement are associated with a significantly reduced prognosis. The fourth slide demonstrates a study in which the IQ of babies treated with 2 different starting doses was compared. It can be seen that babies treated with the higher dose, 10 ug/kg/day had a mean IQ that was 21 points higher than that of babies treated with 7 ug/kg/day, a difference that was highly significant statistically. Similar results have been reported by numerous other investigators. For example Rovet et al have noted a 4-5 point increase in IQ of CH infants when the dose of replacement was increased by as little as 1-2 ug/kg/day from 7-9 ug/kg/day to 8-10 ug/kg/day (data not shown).

These data clearly show that congenital hypothyroidism is associated with significant, irreversible cognitive impairment if treatment is inadequate. Relatively small differences in the dose of thyroxine replacement can have an enormous impact on the outcome of these babies. A potential difference of 33% in drug content is not acceptable for the optimal care of our patients. Bioequivalence should be determined by the serum TSH concentration which is a much more sensitive and physiologically meaningful assessment of bioequivalence than is the measure currently used to assess pharmacologic equivalence.