unanticipated pharmacological effects in other organ systems. At clinically relevant exposure levels, repaglinide failed to elicit any significant effects on central nervous system, cardiovascular, respiratory, gastrointestinal or smooth muscle systems.

Lagan binding assays such as possible effects on the N and L calcium channels and potassium channels revealed no inhibitory activity except for the effects on the ATP sensitive channels described by Dr. Fuhlendorff. Increases were seen in diuresis and sodium excretion at single doses that are 100 times the proposed clinical regimen. The multiple cardiovascular evaluations indicated that adverse effects have not been seen at intravenous doses of 1,000 micrograms per kilogram.

An extensive program of acute and chronic toxicity studies has been performed including carcinogenicity evaluation in two species and studies evaluating the potential effects on all aspects of the reproductive process. Teratology studies have been carried out in two species and a complete ICH compliant genotoxicity evaluation was performed as well as immunogenicity evaluations.

Chronic toxicological evaluations in

rats and dogs have been performed at duration treatments of up to one year. In the rat, the no effect dose is 16 milligrams per kilogram which results in plasma concentrations that are 38 to 85 times the human exposure level. At higher doses, alkaline phosphatase levels are increased without histopathological effects. Dogs are sensitive to the hypoglycemic effects of repaglinide which is responsible for most of the effects in this species. At 50 milligrams per kilogram there were elevated hepatic enzymes with histological evidence of periportal enlargement with no evidence of hepatocyte degeneration. Thus, compared to the human dose of 0.32 milligrams per kilogram per day, there are no clinically relevant laboratory or histopathological changes.

The drug is not mutagenic in a battery of six genotoxicity studies. Four immunogenicity studies have revealed no evidence of immunologic responses or allergic reactions. In reproduction studies, repaglinide failed to produce an effect on fertility. It is not teratogenic when administered to rats and rabbits during the first trimester period of organogenesis. There is a developmental effect which is seen when the drug is administered

in late gestation and early lactation. I'll describe that in more detail later.

Carcinogenicity studies have shown no tumorigenic responses at doses that are more than 50 and 100 times the clinical exposure level in males and females respectively. I'll discuss that more later, also.

In the reproduction findings, there are limb deformations that are developed in the offspring of females that are treated later, beginning with the third trimester of gestation. This was initially observed in animals that were eight to ten weeks of age with an observation of altered ability to walk correctly. It came about as a result of the behavioral evaluations that have been performed in these animals, an evaluation that is relatively new in preclinical development.

Subsequent studies have revealed that this effect is due to an altered structure of the limbs. Mechanistic studies that have been performed that have been designed to identify the specific period of effect have shown that this effect does not occur if the animals are treated in the first or second trimester, and is limited to the third trimester of gestation and the early period of

nursing. There is histological evidence of chondromalacia and an inhibition of the end growth of osteogenic buds.

Glucose levels are significantly reduced in maternal animals during this period of gestation and studies have identified that the offspring also have decreased glucose levels. Studies have identified that repaglinide can be transferred to the offspring via milk as evidenced by the fact that cross-fostering of offspring with untreated mothers also elicits this effect.

In summary, these are developmental changes as opposed to teratogenic effects and they've only been seen at doses that are significant multiples of the human exposure level and have not been seen at doses that are six times the human exposure level. In the carcinogenicity evaluation, repaglinide was not tumorigenic in the mouse at exposure levels that run from 71 to 160 times, 169 times the human AUC in males and females.

This is a bar graph in the rat carcinogenicity study that describes the exposure margins for the four treatment groups of males and females. I call your attention here. These numbers at the top of the bar graph represent the multiples

in excess of the human AUC that resulted from the exposure of animals at these four doses. I point out to you that in this study at these two doses here, the two lowest doses, which represent 51 and in excess of 100 times the human exposure level, there are no tumorigenic effects.

There is at the doses that result in 90 to 200 times the human AUC, an increase in benign thyroid tumors in the males. It's interesting to note that these benign thyroid tumors were not seen in the females even though the females' plasma concentrations were significantly higher than those of the males. At the very highest dose only that results in a 200 fold margin of the human AUC, there is an increase in the spontaneous rate of benign liver tumors in these male animals. It is again interesting to note that females who were exposed to higher plasma concentrations of repaglinide at that same dose, these tumors did not develop. This tumor type spontaneously occurs in rats and in this study were only seen at an increased incidence.

A study was done to elucidate the mechanism for the development of the thyroid tumors in the male rats. It was identified through these studies is that animals that are treated at those

two higher dosage levels develop a decrease in plasma T3 levels. The decrease in the plasma T3 levels result in increased levels of TSH and that results in an enhanced proliferation within the thyroid gland. That phenomenon of the increased TSH resulting in an increase in proliferation is a known phenomenon that has been seen with other drugs such as phenobarbital and some of the phenothiazine antidepressants. The current state of knowledge would suggest that that mechanism is not comparable to anything that is seen in humans. In the clinical program that will be described later, there were no changes in T3 uptake, T4 or TSH levels during the clinical program.

So, with regard to the conclusions from the carcinogenicity evaluation, we can say that repaglinide is not genotoxic. That there is a high exposure safety margin within these studies. That the development of the thyroid tumors is a mechanism that is specific for rats. That the mouse carcinogenicity study is negative and the conclusion would be that there is no clinical risk as a result of this information.

With regard to non-clinical pharmacokinetics, repaglinide in all of the animal

species study is rapidly absorbed with peak concentrations achieved in less than one hour. The drug is highly bound to plasma proteins exceeding 95 percent in all species examined. That in rodents, plasma levels in females are two to three times higher than those seen in males and that is a situation that is frequently seen in rodent studies. The drug is highly excreted by the bile with only eight percent of radiolabeled repaglinide excreted in the urine. The drug is metabolized by glucuronidation and/or oxidative pathways within the liver. The metabolite profile in the preclinical species are similar to those seen in man.

In conclusion, the preclinical safety assessment of repaglinide has shown a favorable safety profile with no suggestion of potential adverse toxicity at clinically relevant doses. That's described on the enhancement of the slide that was shown to you by Dr. Fuhlendorff.

Now I'd like to introduce to you Dr. Poul Strange who will discuss with you the clinical pharmacology and the clinical efficacy of repaglinide.

DR. STRANGE: Thank you.

As in animals, repaglinide is rapidly