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Considerations in the Design of the Preclinical Safety Program for PegIntron

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PegIntron is the pegylated form of human recombinant interferon alfa-2b (IFN α 2b). IFN α 2b, known as Intron A, has been in approved clinical use since the 1980's for various cancer indications, and for the treatment of Hepatitis C. In the mid 1990's, several clinical investigators reported that combination therapy with ribavirin and Intron A dramatically increased the therapeutic efficacy for treatment of Hepatitis C. Preclinical and clinical study programs necessary to demonstrate the safety and efficacy of this combination were carried out, leading to the first approvals of the combination of Intron A and ribavirin for the treatment of Hepatitis C in 1998.

Intron A is administered three times weekly by subcutaneous or intramuscular injection. PegIntron was developed to prolong the T1/2 of IFN α 2b and thereby to increase the efficacy by providing more continuous exposure to drug, and by improving patient comfort and compliance through reduction in the number of injections to once weekly. PegIntron was the first pegylated IFN to be developed. Therefore, the development program proceeded in two phases: proof of safety and efficacy of PegIntron monotherapy in Hepatitis C, then proof of safety and efficacy of the combination of PegIntron and ribavirin.

The preclinical development program design was heavily influenced by previous preclinical experience with the non-pegylated form of IFN α 2b, alone and in combination with ribavirin; the species-specific (human) nature of the IFN; the fact that PegIntron was the first-in-class as a pegylated IFN; and the need to establish preclinical safety in combination with ribavirin.

This presentation will describe the design of the preclinical program for PegIntron, alone

and in combination with ribavirin, with emphasis on how the program was influenced by the nature of the product (a human protein), the need to determine its effects in combination with ribavirin, the nature of the toxicities caused individually by PegIntron and ribavirin, the pegylated nature of the drug, and regulatory agency guidance.