

Double-Blind, Vehicle-Controlled Rising Dose Tolerance Study of ISIS 2105, A Phosphorothioate Oligonucleotide for Treatment of Condyloma Acuminatum

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ISIS 2105 is a phosphorothioate oligonucleotide with a chain length of 20 nucleotides designed to bind the AUG region of the HPV-11 E2 transactivator mRNA, thus leading to inhibition of the virus. ISIS 2105 solution for injection and its vehicle (PBS) were randomly assigned to ninety healthy male subjects, ten subjects per dose level. Following screening to assure that medical history, physical examination, and routine hemogram, serum chemistries, and urinalysis did not reveal abnormalities that would preclude subject participation in the study, 0.1 cc of the test articles was intradermally injected at 3 or 6 sites on the ventral surface of the forearms. Seven subjects at each dose level received ISIS 2105 at all injection sites on one arm and vehicle at the injection sites of the contralateral arm. Three subjects at each dose level received vehicle injections at all sites. Dose levels were 0.1, 0.25, 0.5, 1.25, 2.5, 3.75, 5.0, 7.5, and 10.0 mg; each dose below 5.0 mg was divided by one-third prior to injection whereas the top three doses were each divided by one-sixth. Subjects were evaluated for local injection site reactions (pain on injection, persistent pain, erythema, induration, erosion, ulceration, bruising, and desquamation) and adverse experiences during a 33 hour inpatient phase and followed for two weeks post-treatment. ISIS 2105 was well tolerated at all dose levels. There were no clinically significant abnormal laboratory values for subjects who received ISIS 2105. There was no evidence of desquamation, erosion, ulceration, or bruising at the injection sites. The most common local side effects were mild erythema and induration at the injection sites that occurred in a dose-dependent fashion 4 – 8 hours post-injection with complete resolution apparent in most cases by the next day. The most frequently reported adverse experiences included headache, asthenia, sore throat, and pallor following injection. Intradermal injection of ISIS 2105, the first antisense compound administered to man, was well tolerated at doses up to 10mg or 1.67mg/injection.