

## **Scientific Abstract**

The purpose of this Phase I dose escalation trial is to evaluate the safety and tolerability of escalating doses (0.6mg, 2 mg, and 6mg) of VGX-3100 administered by intramuscular injection in combination with electroporation to adult female subjects with a history of histologically diagnosed grade 2 or 3 cervical intraepithelial neoplasia (CIN). VGX-3100, HPV DNA plasmid vaccine is a combination of two plasmids in equal quantities, i.e., the 0.6 mg dose will deliver 0.3 mg each of pGX3001 (p16ConE6E7, a plasmid expressing a consensus E6 and E7 fusion antigen from HPV type 16) and pGX3002 (p18ConE6E7, a plasmid expressing a consensus E6 and E7 fusion antigen from HPV type 18) plasmids. Infection by HPV is characterized by ongoing viral replication and shedding and is associated with early pathologic changes (grade 1 cervical intraepithelial neoplasia; CIN1). Most cases of genital HPV infection clear spontaneously, but persistent infection with an oncogenic type can result in conversion of the viral genome from an episomal form to an integrated form. Persistent infection leads to the development of precancerous lesions (CIN grade 2/3) and eventually to invasive cancer of the cervix. The basis for these changes can be traced to effects of the viral proteins E6 and E7. They interact with the cell cycle regulation proteins p53 and pRb and can cause immortalization of the infected cells. E6 and E7 are produced constitutively by these immortalized cells. While the currently available prophylactic HPV vaccine (Gardasil®, Merck, and Cervarix™, GSK) is highly effective in preventing infection and the development of high-grade CIN caused by HPV types 16 and 18, it is of no value for women already infected with these oncogenic types. The standard of care for women with HPV related grade 2 or 3 is surgical removal of the affected tissue by cone biopsy or a loop electrical excision procedure (LEEP). Invasive cervical cancer is usually treated by hysterectomy. This study is based on pre-clinical results that show that boosting HPV type-specific cell-mediated immune responses might lead to elimination of immortalized cells and so prevent the development of cervical cancer.