Synopsis

Title of Clinical Trial: A Prospective, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation With CELLECTRA™ 5PSP for the Treatment of HPV-16 and/or HPV-18 Related High-Grade Squamous Intraepithelial Lesion (HSIL) of the Cervix

Principal Investigator(s): Mark H Einstein, MD, MS.

Clinical Trial Center(s): This clinical trial was conducted at 96 clinical trial centers in the following countries: Argentina (4 centers), Belgium (4 centers), Canada (1 center), Czech Republic (4 centers), Estonia (3 centers), Finland (2 centers), Germany (2 centers), Italy (3 centers), Lithuania (3 centers), Mexico (2 centers), Peru (2 centers), Philippines (2 centers), Poland (4 centers), Portugal (4 centers), Slovakia (2 centers), South Africa (2 centers), Spain (5 centers), Thailand (2 centers), United Kingdom (2 centers), and United States (43 centers).

Publication(s) (Reference): None

Clinical Trial Period (Years): 28Jun2017 (First subject first visit) to 06Apr2021 (Last subject last visit)

Drug Development Phase: 3

Background and Rationale: The currently available prophylactic human papilloma virus (HPV) vaccines (Cervarix™, Gardasil™, and Gardasil™-9) are highly effective in preventing persistent infection and the subsequent development of high-grade cervical intraepithelial neoplasia (CIN) caused by HPV-16, HPV-18, and other HPV types; however, these prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia. This means that the large number of women who already have high-grade cervical dysplasia, either because they were too old to have received the prophylactic vaccine or they did not respond to vaccination, must currently rely upon surgery and the chance of spontaneous regression to treat their condition, and avoid progression to cancer. The current approaches to the management of cervical HSIL typically require surgery (i.e., loop electrosurgical excision procedure [LEEP]/large loop excision of the transformation zone [LLETZ], laser ablation, or conization); however, surgical excision does not necessarily address the underlying HPV infection and can adversely impact the reproductive health of women of childbearing age. Therefore, VGX-3100 is being developed as a nonsurgical

therapeutic option for the precancerous precursor to cervical cancer, cervical HSIL, and the underlying pathogenic HPV infection.

VGX-3100 contains plasmids that encode HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using Inovio Pharmaceuticals, Inc's (Inovio's) proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing deoxyribonucleic acid (DNA) inserts at the genetic level to allow high expression in human cells. VGX-3100 is delivered *in vivo* using the CELLECTRA™ 5PSP electroporation (EP) device. Electroporation is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electrical field at the injection-site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity.

This Phase 3 clinical trial, HPV-301, employed a prospective, randomized, double-blind, placebo-controlled design to demonstrate the safety and efficacy of VGX-3100 followed by EP in women with cervical HSIL associated with HPV-16 and/or HPV-18. The primary endpoint was histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36. A placebo-controlled design was selected for this clinical trial because it provided scientific rigor to distinguish a treatment effect, particularly in cervical HSIL for which spontaneous regression could occur.

Objectives and Endpoints:

The objectives and endpoints are given below.

Objectives	**Endpoints**
Primary	
Determine the efficacy of VGX-3100 compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18	Proportion of subjects with no evidence of cervical HSIL on histology (i.e., biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in cervical samples by type-specific HPV testing at Week 36 visit

Objectives	Endpoints
Secondary	
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the clinical trial (through Week 88 visit) 1b. Incidence and severity of all AEs including SAEs (e.g., SUSAR, UADE, and other unexpected AEs) for the duration of the clinical trial (through Week 88 visit)
2. Determine VGX-3100 efficacy compared with placebo as measured by histopathologic regression of cervical HSIL	2. Proportion of subjects with no evidence of cervical HSIL on histology (i.e., biopsies or excisional treatment) at Week 36 visit
3. Determine VGX-3100 efficacy compared with placebo as measured by virologic clearance of HPV-16 and/or HPV-18	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in cervical samples by type-specific HPV testing at Week 36 visit
4. Determine VGX-3100 efficacy compared with placebo as measured by complete histopathologic regression of cervical HSIL to normal	4. Proportion of subjects with no evidence of LSIL or HSIL (i.e., no evidence of CIN1, CIN2, or CIN3) on histology (i.e., biopsies or excisional treatment) at Week 36 visit
5. Determine VGX-3100 efficacy compared with placebo as measured by both complete histopathologic regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18	5. Proportion of subjects with no evidence of LSIL or HSIL (i.e., no evidence of CIN1, CIN2, or CIN3) on histology (i.e., biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type-specific HPV testing at Week 36 visit
6. Determine the efficacy of VGX-3100 compared with placebo as measured by histopathologic nonprogression	6. Proportion of subjects with no progression of cervical HSIL to cervical carcinoma from baseline on histology (i.e., biopsies or excisional treatment) at Week 36 visit

Objectives	Endpoints
7. Describe the clearance of HPV-16 and/or HPV-18 infection from noncervical anatomic locations	7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from noncervical anatomic locations (oropharynx, vagina, and intra-anal) at Week 36 visit
8. Determine the humoral and cellular immune response to VGX-3100 compared with placebo at post dose three (3) and Week 36 visit as assessed relative to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Weeks 15 and 36 visits 8b. IFN-γ ELISpot response magnitudes at baseline and Weeks 15 and 36 visits 8c. Flow cytometry response magnitudes at baseline and Week 15 visits
Exploratory	
1. Evaluate tissue immune responses to VGX-3100 in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments could include visualization of granulysin, perforin, CD137, CD103, and PD-L1 in cervical tissue as sample allowed. Markers listed here could change as new relevant information became available
2. Describe association of miRNA profiles, DNA methylation profile, previous colposcopy, cytology, and HPV testing results with Week 36 histologic regression	2. Colposcopy, cytology, HPV test results (Weeks 8, 15, and 28 visits), miRNA profile (baseline and Week 8), and DNA methylation profile (baseline and Week 15) in conjunction with histologic regression of cervical HSIL at Week 36 visit
3. Describe the durability of virologic clearance of HPV-16 and/or HPV-18 for subjects treated with VGX-3100 compared with those treated with placebo	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 by type-specific HPV testing at Weeks 62 and 88 visits

Objectives	Endpoints
4. Describe the patient-reported outcomes for subjects treated with VGX-3100	4. Patient-reported outcome questionnaires were self-administered at baseline, Weeks 4 and 12, 8-14 days following each dose, and at Weeks 28, 36, 40, and 88 by subjects enrolled in US, Canada, Mexico, Germany, and UK
5. Determine whether a tissue-based score derived using immunologic markers (immunoscore) at baseline was predictive for histological and virological response to VGX-3100 at Week 36	5. Immunoscore results for VGX-3100 treated subjects in conjunction with histological and virological outcomes at Week 36

Abbreviations: AE: Adverse Event; CD: Cluster Of Differentiation; CIN: Cervical Intraepithelial Neoplasia; DNA: Deoxyribonucleic Acid; ELISpot: Enzyme-Linked Immune Absorbent Spot; EP: Electroporation; HPV: Human Papilloma Virus; HSIL: High-Grade Squamous Intraepithelial Lesion; IFN: Interferon; IM: Intramuscular; LSIL: Low-Grade Squamous Intraepithelial Lesion; miRNA: Microribonucleic Acid; PD-L1: Programmed Death Ligand 1; SAE: Serious Adverse Event; SUSAR: Suspected Unexpected Serious Adverse Reaction; UADE: Unanticipated Adverse Device Effect; UK: United Kingdom; US: United States.

Methodology:

This was a prospective, randomized, double-blind, placebo-controlled clinical trial to determine the efficacy, safety, and tolerability of intramuscular (IM) VGX-3100 injection followed by EP delivered with the CELLECTRA™ 5PSP device in adult women with histologically confirmed cervical HSIL (CIN2 and CIN3) associated with HPV-16 and/or HPV-18.

The clinical trial consisted of a screening period (up to 10 weeks), treatment and follow-up period (36 weeks), and long-term follow-up period (52 weeks). The total duration of participation in the clinical trial for each subject was up to 98 weeks.

Approximately 198 eligible subjects were to be randomly assigned to receive either 6 mg (in 1 mL) VGX-3100 or placebo (ratio 2:1), IM followed by EP. Subjects were to be randomly assigned in a stratified manner according to: 1) CIN severity observed in the biopsy specimens at screening (CIN2 vs. CIN3), 2) body mass index (BMI) category ($\leq$25 kg/m^2 vs. >25 kg/m^2) on Day 0, and 3) age category (<25 years vs. $\geq$25 years) on Day 0. To ensure CIN2 disease was not overrepresented in the clinical trial, the percentage of subjects enrolled with CIN2

were to not exceed 50% of the total enrolled. Each participating country was designated a group of sequential allocation numbers for use.

Screening Period

All screening evaluations were to be completed within 10 weeks of first dose of clinical trial treatment (Day 0), except for the safety laboratory assessments, which were to be performed within 45 days prior to Day 0.

Treatment and Long-Term Follow-Up Periods

Eligible subjects received three (3) 6-mg doses of VGX-3100 refrigerated formulation or placebo, IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device. The first clinical trial treatment was administered on Day 0, the second at Week 4, and the third (final) at Week 12. The first clinical trial treatment was given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16 and/or HPV-18 status but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the Pathology Adjudication Committee (PAC) during screening, contemporaneous with the positive testing for HPV-16 and/or HPV-18.

The injection site was assessed by clinical trial personnel prior to and at least 30 minutes after each clinical trial treatment and at 2 to 4 weeks after clinical trial treatment. Participant Diary Cards (PDCs) were distributed to subjects on the day of clinical trial treatment. Subjects were advised to record local and systemic adverse events (AEs) for 7 days in the PDC after each clinical trial treatment. Subjects were followed up by a phone call at 8 to 14 days after each clinical trial treatment for PDC review of AEs and injection-site reactions.

Efficacy assessments included histology (i.e., biopsy or excisional treatment), colposcopy, cytology, and HPV testing at screening and at specified visits on and after Day 0. Digital photographs of the cervix following application of acetic acid were used to document colposcopic exam findings. Tissue to be analyzed for evidence of histopathologic regression was obtained at Week 36 either by excision (e.g., LEEP, LLETZ, cold knife conization) or by biopsy (4-quadrant biopsy or 4-quadrant biopsy with endocervical curettage), based upon the assessment at Week 28 of cytology, high-risk HPV status, and colposcopic findings.

All subjects were to undergo a long-term follow-up planned for safety, cytology, and HPV-16 and/or HPV-18 testing at 6 months and 1 year following the Week 36 histopathologic assessment.

Safety was assessed throughout the clinical trial and included monitoring of local and systemic AEs for 7 days following each clinical trial treatment as noted on the PDC and all AEs including serious AEs (SAEs), unanticipated adverse device effects, and other unexpected AEs throughout the clinical trial.

An independent Data and Safety Monitoring Board (DSMB) provided safety oversight. The DSMB was to be scheduled to meet quarterly. The DSMB was responsible for advising the sponsor if there appeared to be a safety issue and if it appeared that the proportion of the subjects with regression in the VGX-3100 group was unacceptably low compared with the placebo group; no formal interim analysis was to be performed for this purpose.

Immunogenicity assessments included humoral and cell-mediated immune responses in response to VGX-3100 treatment in blood samples and evidence of elevated immune responses in the cervical tissue samples.

Number of Subjects (Planned and Analyzed):

A total of 198 subjects were planned to be randomized to receive either 6 mg VGX-3100 or placebo IM followed by EP in a 2:1 ratio.

A total of 201 subjects were randomly assigned to receive either VGX-3100 + EP (138 subjects) or placebo + EP (63 subjects).

The percentage of subjects in each analysis set are summarized in Table S1.

Table S1: Analysis Sets

Analysis Sets	VGX-3100 + EP (N=138)	Placebo + EP (N=63)	Total (N=201)
Intent-to-Treat (ITT)	138	63	201
Modified ITT (mITT)	134 (97.1)	63 (100)	197 (98.0)
Per Protocol	124 (89.9)	60 (95.2)	184 (91.5)
Safety	136 (98.6)	63 (100)	199 (99.0)

Note: There were 2 subjects who were randomized to VGX-3100 + EP group but not treated.
Note: Denominator used in the percentage calculations was randomized subjects in each treatment.
Abbreviations: EP: Electroporation; ITT: Intent-to-Treat; N: Sample Size for the Group; n: Number of Subjects.

Diagnosis and Main Criteria for Inclusion and Exclusion:

To be eligible for the clinical trial, subjects were to be at least 18 years of age, provide consent to participate, and have cervical biopsy/biopsies of the cervical lesion(s) at the time of screening. Slides of the biopsy were to be sent to a central pathology laboratory for review by the PAC in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for randomization, the PAC was to assign the histologic diagnosis of cervical HSIL. Subjects were to also have a cervical ThinPrep™ specimen test positive for HPV-16 and/or HPV-18 by cobas™ HPV test. Subjects were required to provide informed consent for use of any information collected prior to consenting and before any additional clinical trial-specific procedures could be performed.

Test Product, Dose and Mode of Administration, Batch Number(s):

The test product, VGX-3100, was provided as a solution containing 6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate. VGX-3100 drug product was presented in clear glass cartridges and was injected IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device.

The lot numbers of VGX-3100 used in the clinical trial were 1622-035 and 1816-045.

Control Product, Dose and Mode of Administration, Batch Number(s):

The control product, placebo, consisted of a mixture of 150 mM sodium chloride and 15 mM sodium citrate. Placebo was presented in clear glass cartridges and was injected IM (deltoid [preferred site] or anterolateral quadriceps [alternate site]), followed immediately by EP with the CELLECTRA™ 5PSP device.

The lot number of placebo used in the clinical trial was 1622-066.

Duration of Treatment:

Treatment was administered over 12 weeks. The first clinical trial treatment was administered on Day 0, the second at Week 4, and the third (final) at Week 12.

Estimands and Intercurrent Events:

Estimands and intercurrent events were not defined in the clinical trial protocol or in the statistical analysis plan (SAP).

Statistical Methods:

Sample Size

A total of 198 subjects were planned to be randomized to receive either 6 mg VGX-3100 or placebo IM followed by EP in a 2:1 ratio. This sample size provided 90% power to declare VGX-3100 superior to placebo, assuming the true proportion of subjects who achieved the primary endpoint was 35% and 14% for VGX-3100 and placebo, respectively. These proportions also incorporated missing data (~10%) classified as nonregressors (failures). The assumptions were based on the Phase 2 clinical trial results.

Analysis Sets

The analysis sets were defined as follows:

Intent-to-Treat (ITT) Set: The ITT set included all subjects who were randomized. Subjects in this sample were grouped to treatment as randomized. The ITT set was used for the primary analysis of efficacy in this clinical trial. Missing data was considered as nonregressors (failures) for the ITT efficacy analysis. A subject's regression outcome was missing if her CIN grade and

HPV clearance for the Week 36 timeframe could not be determined. The ITT set was also used for summaries of demographics, baseline characteristics, disposition, and protocol deviations.

Modified Intent-to-Treat (mITT) Set: The mITT set included all subjects who received at least one (1) dose of clinical trial treatment and who had the analysis endpoint of interest. Subjects in this sample were grouped to treatment as randomized. Analysis of the mITT set was considered supportive for the corresponding ITT set for the analysis of efficacy and also served as sensitivity analyses regarding missing data.

Per-Protocol (PP) Set: The PP set was comprised of subjects who received all doses of clinical trial treatments, had no protocol violations, and had the analysis endpoint of interest. Subjects in this sample were grouped to treatment as randomized. Analyses on the PP set was considered supportive of the corresponding ITT set for the analysis of efficacy. Additional efficacy analyses on the PP set utilized the Week 36 timeframe result regardless of any procedure performed before the Week 36 timeframe, thus serving as sensitivity analyses regarding early intervention. Subjects excluded from the PP set were identified and documented prior to unblinding of the clinical trial database.

Safety Set: The safety set included all subjects who received at least one (1) dose of clinical trial treatment. Subjects were analyzed as to the treatment they actually received.

Efficacy Analyses

Main Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was no evidence of cervical HSIL (i.e., no evidence of CIN2 and CIN3) on histology (i.e., biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in cervical samples by type-specific HPV testing at the Week 36 timeframe.

The primary hypothesis of superiority was:

H0: $\delta \leq 0$ vs. H1: $\delta > 0$,

where $\delta = P_v - P_p$, and P_v and P_p denoted the true population probabilities of the primary endpoint for VGX-3100 and placebo, respectively. The proportion in each treatment group was calculated by the number of responders divided by the total number of responders and nonresponders in the clinical trial population of the corresponding treatment group.

For the primary endpoint, Week 36 histology was evaluated based on the first biopsy or surgical excision procedure on or after Day 238; in case of multiple results on the same day, the one with worst grade was to be used. The virology result used for analysis was to be the latest result that was on or before the same date as the histology result and was taken on or after Day 238. If a subject underwent excision or cervical biopsy at any time on or after Day 1 and before Day 238, the subject was considered as nonresponder.

Number of responders and nonresponders, proportion of responders in each treatment group, and difference of proportions between the two (2) treatment groups were presented. A p-value of superiority based on a test of risk difference and corresponding 95% confidence interval (CI) using the method of Miettinen and Nurminen were computed. Superiority was concluded if the one-sided p-value was <0.025 and the corresponding lower bound of the 95% CI exceeded zero (0).

Responder proportion was also summarized based on the stratification factors separately.

Analyses of primary efficacy endpoint with the mITT and PP set served as sensitivity analyses and were considered supportive of the corresponding analysis with the ITT set.

Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoint analyses methods were the same as those for primary efficacy endpoint analysis, including the sensitivity analyses, but no p-values were computed for the secondary efficacy endpoint analyses.

Immunogenicity Analyses

The immunogenicity analyses were performed on the mITT set with at least one (1) immunogenicity measurement.

Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations and interferon-γ enzyme-linked immunosorbent spot (ELISpot) response magnitudes were assessed from sera and peripheral blood mononuclear cells (PBMCs) isolated from whole blood, respectively, collected at baseline, Week 15, and Week 36. Flow cytometry response magnitudes were assessed from PBMCs isolated from whole blood collected at baseline and Week 15.

All of the endpoints were summarized as continuous variables at each visit. Increases from baseline for each postbaseline visit from ELISpot and flow cytometry, and titers for each postbaseline visit from enzyme-linked immunosorbent assay were compared between treatment groups. These comparisons were analyzed with differences in medians and associated exact nonparametric 95% CIs.

Exploratory Endpoints Analyses

The relationship between the histologic regression of cervical HSIL with virologic clearance at Week 36 visit (yes, no) and a) microribonucleic acid (miRNA) results, b) DNA methylation results, c) colposcopy results, d) cytology results, e) HPV results, and f) baseline immunoscore results (tissue-based score derived using immunologic markers) were examined using separate logistic regression models for each result, with histologic regression of cervical HSIL with virologic clearance as the response variable and each of the results and treatment group as regressor variables. Odds ratios and corresponding 95% CIs were provided for the regressor variables. Durability, as measured by clearance of HPV-16 and/or HPV-18 infection at Weeks 62 and 88, were summarized by number and percentage of subjects with no evidence of HPV-16 and/or HPV-18 by treatment group at each visit. Specifically, the virology results at Week 62 were those between Day 420 and Day 448 and the virology results at Week 88 were those between Day 602 and Day 630. Assessment of markers including but not limited to cluster of differentiation (CD)8+ and FoxP3+ infiltrating cells and visualization of granulysin, perforin, CD137, CD103 and PD-L1 in cervical tissue were to be performed. These tissue response magnitudes were compared between treatment groups using a difference in means and associated t-distribution based 95% CIs for changes from baseline at each postbaseline timepoint. Subjects enrolled in the United States, Canada, Mexico, Germany, and the United Kingdom were to complete patient-reported outcome (PRO) questionnaires (36-Item Short Form Survey [SF-36], EuroQol 5-Dimensions 5-Level [EQ-5D-5L], and two [2] additional global PRO questions assessing quality of life [QoL] after excision or biopsy). For the SF-36, section scores at each of the eight (8) domains (physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health) and score changes from baseline were summarized at each visit by treatment group. Scoring of the eight (8) SF-36 subscales was done by Quality Metric Health Outcomes(tm) Scoring Software 5.0. For the EQ-5D-5L, each of the five (5) domains (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) and global health status score were summarized at each visit and relative to baseline by treatment

group. For the two (2) additional global PRO questions assessing QoL after excision or biopsy, the time outcome (median number of days that a worsened QoL was experienced) and the binary outcomes to yes/no questions were summarized by treatment group. SF-36 scores were compared between treatment groups using exact nonparametric 95% CIs for the differences in median changes from baseline. The EQ-5D-5L scores were analyzed in the same fashion. Days of worsened QoL for the Week 40 QoL questionnaire were analyzed using an exact nonparametric 95% CI for the difference in the median number of days. The yes/no worsened QoL responses for the Week 40 QoL questionnaire were analyzed using a 95% Miettinen and Nurminen CI for the difference in proportions between treatment groups. In addition, PRO endpoints at each visit that occurred after Week 36 were summarized according to those with excision (excluding biopsy) versus those without. The subjects in the mITT set with at least one (1) postbaseline corresponding measurement were used for PRO analyses.

Safety Analyses

All safety analyses were conducted on the safety set.

Adverse Events

Adverse event verbatim reported terms were coded by system organ class (SOC) and preferred term (PT) using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event summary tables included numbers and percentages of subjects experiencing at least one (1) event by treatment group. The following AE summary tables were generated:

- Overview of AEs overall, and with onset within 28 days/7 days after clinical trial treatment
- Treatment-emergent AEs (TEAEs) overall, and with onset within 28 days/7 days after clinical trial treatment by SOC and PT
- Treatment-emergent AEs overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, SOC, and PT
- Treatment-emergent AEs overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, Common Toxicity Criteria for Adverse Events (CTCAE) grade, SOC, and PT
- Serious TEAEs overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, SOC, and PT

- Treatment-emergent AEs overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, relationship to investigational product (IP) and EP, SOC, and PT
- Serious TEAEs overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, relationship to IP and EP, SOC, and PT
- Grade ≥3 TEAEs overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, SOC, and PT
- Grade ≥3 TEAEs overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, relationship to IP and EP, SOC, and PT
- Treatment-emergent AEs with action of clinical trial treatment held overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, SOC, and PT
- Treatment-emergent AEs with action of clinical trial treatment permanently discontinued overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, SOC, and PT
- Adverse events of special interest overall, and with onset within 28 days/7 days after clinical trial treatment by dose number, SOC, and PT

A subject with two (2) or more different AEs within the same level of the MedDRA term and regimen was counted only once in that level using the most extreme incident (most severe for the intensity analyses and related for the relationship to clinical trial treatment analyses).

Data listings were provided for AE, SAE, AEs leading to treatment discontinuation, AEs with CTCAE grade ≥3, AEs with onset within 28 days/7 days after clinical trial treatment, and AEs resulting in death separately.

Incidence of Adverse Events

For the AEs with onset date within 28 days after any dose, the frequency of SOC and PT events were compared between treatment groups with risk differences and 95% CIs using the method of Miettinen and Nurminen. As this analysis used many event categories and produced many CIs, caution was to be exercised when interpreting these CIs.

A similar analysis was provided for AEs within 7 days after any dose and for AEs during the clinical trial after any dose.

Clinical Laboratory Evaluations

Safety laboratory tests (including hematology, serum chemistry, and urinalysis) were performed at screening (within 30 days prior to Day 0) and a summary of screening information was provided by treatment group and by total.

Vital Signs, Physical Examination, and Other Observations Related to Safety

Vital sign data was summarized at each visit by treatment group. Changes from baseline to each scheduled postbaseline visit were presented.

During physical examination, body systems were assessed as normal, abnormal, or not examined at each scheduled visit, and the percentage of subjects with abnormal physical examination findings at each timepoint were summarized by body system and by treatment group.

Electrocardiogram results were summarized by treatment group and by total, for interpretation results including normal, abnormal not clinically significant, abnormal clinically significant, and not done.

Summary of Results:

Subject Disposition: Subject disposition is summarized in Table S2.

Table S2: Subject Disposition (ITT Population)

	VGX-3100 + EP (N=138) n (%)	**Placebo + EP (N=63) n (%)**	**Total (N=201) n (%)**
Total number of subjects randomized	138	63	201
Completed all electroporation/trial treatment	129 (93.5)	61 (96.8)	190 (94.5)
Discontinued electroporation/trial treatment	7 (5.1)	2 (3.2)	9 (4.5)
Completed trial	117 (84.8)	56 (88.9)	173 (86.1)
Discontinued trial	21 (15.2)	7 (11.1)	28 (13.9)
Primary reason for discontinuation from trial treatment			

	VGX-3100 + EP (N=138) n (%)	**Placebo + EP (N=63) n (%)**	**Total (N=201) n (%)**
Withdrawal by subject	1 (0.7)	1 (1.6)	2 (1.0)
Unrelated to trial procedures	0	0	0
Subject refused further EP	1 (0.7)	1 (1.6)	2 (1.0)
Adverse event	0	0	0
Progressive disease	2 (1.4)	0	2 (1.0)
Lost to follow-up	1 (0.7)	0	1 (0.5)
Physician decision	0	0	0
Trial terminated by sponsor	0	0	0
Protocol deviation	1 (0.7)	0	1 (0.5)
Pregnancy	2 (1.4)	0	2 (1.0)
Other	0	1 (1.6)	1 (0.5)
Primary reason for discontinuation from trial			
Withdrawal by subject	5 (3.6)	3 (4.8)	8 (4.0)
Unrelated to trial procedures	4 (2.9)	3 (4.8)	7 (3.5)
Subject refused further EP	1 (0.7)	0	1 (0.5)
Adverse event	1 (0.7)	0	1 (0.5)
Progressive disease	1 (0.7)	0	1 (0.5)
Lost to follow-up	8 (5.8)	2 (3.2)	10 (5.0)
Physician decision	1 (0.7)	0	1 (0.5)
Trial terminated by sponsor	0	0	0
Protocol deviation	2 (1.4)	0	2 (1.0)
Pregnancy	0	0	0
Other	3 (2.2)	2 (3.2)	5 (2.5)

Note: There were two (2) subjects who were randomized to VGX-3100 + EP group but not treated.

Note: Denominator used in the percentage calculations was randomized subjects in each treatment.

Abbreviations: EP: Electroporation; ITT: Intent-to-Treat; N: Sample Size for the Group; n: Number of Subjects.

Demography and Baseline Characteristics:

The mean age of the subjects was 31.5 years and ranged from 20 to 55 years. Majority of the subjects (77.1%) were White, and not Hispanic or Latino (82.6%). The mean BMI was 25.07 kg/m^2 and ranged from 16.5 to 56.5 kg/m^2. The demographic characteristics were similar across both the treatment groups.

Randomization was stratified at baseline based on age, BMI, and the CIN stage. In each individual strata and combinations of strata, the proportions of subjects were similar between the treatment groups.

Sixteen subjects (8.0%) were exposed to prophylactic HPV vaccine before clinical trial participation: 14 subjects (10.1%) in the VGX-3100 + EP group and 2 subjects (3.2%) in the placebo + EP group. The most recent Pap smear result was abnormal in majority (76.6%) of subjects. The most recent Pap smears were obtained between 21 and 735 days prior to baseline. Most subjects had either CIN2 (43.9%) or CIN3 (39.8%) diagnosis. The median time from initial CIN diagnosis was 86.5 days and ranged from 21 to 4695 days. Fourteen subjects (7.0%) had received prior treatment for CIN, most commonly LEEP (11 subjects [78.6%]). The median time from last CIN treatment was 489.0 days and ranged from 250 to 4771 days.

Efficacy Results:

Overall, the percentage of responders was higher in the VGX-3100 + EP group as compared with placebo + EP group for the primary endpoint of histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 for ITT, mITT, and PP Populations. The percentage of primary endpoint responders was significantly higher (p-value <0.025) in the VGX-3100 + EP group as compared with placebo + EP group in the mITT and PP Populations. Results were similar for the secondary endpoint of histopathological regression of cervical HSIL at Week 36. For other secondary endpoints including virologic clearance of HPV-16 and/or HPV-18 at Week 36; histopathological regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18 at Week 36; histopathological regression of cervical HSIL to normal at Week 36; and virologic clearance of HPV-16 and/or HPV-18 from noncervical anatomic locations at Week 36, the percentage of responders was higher in the VGX-3100 + EP group as compared with placebo + EP group, and the lower bound of the 95% CI generally exceeded zero (0). The efficacy results are summarized below.

Primary Efficacy Endpoint

The primary endpoint was no evidence of cervical HSIL on histology (i.e., biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in cervical samples by type-specific HPV testing at Week 36 visit.

In the ITT Population, the percentage of responders (i.e., subjects with histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36) was 22.5% in the VGX-3100 + EP group as compared with 11.1% in the placebo + EP group. The difference between the responders in the two (2) groups was not statistically significant (one-sided p-value = 0.029). In the mITT Population, the percentage of responders was 23.7% in the VGX-3100 + EP group as compared with 11.3% in the placebo + EP group. The difference between the responders in the two (2) groups was statistically significant (one-sided p-value = 0.022). Of the 4 subjects excluded from the mITT Population (VGX-3100 + EP group), two (2) subjects had not received any IP and two (2) other subjects had received only one (1) dose of the IP. The results of the PP Population and the sensitivity analysis in PP Population supported the mITT Population results.

Secondary Efficacy Endpoints

Histopathological regression of cervical HSIL at Week 36: In the ITT Population, the percentage of responders (i.e., subjects with histopathological regression of cervical HSIL at Week 36) was 31.9% in the VGX-3100 + EP group as compared with 19.0% in the placebo + EP group. For the mITT Population, the percentage of responders was 33.6% in the VGX-3100 + EP group as compared with 19.4% in the placebo + EP group and the lower bound of the 95% CI for the difference in percentage of responders exceeded zero (0), providing evidence for superior efficacy of VGX-3100 + EP in achieving histopathological regression of cervical HSIL at Week 36 in mITT Population. The results of the PP Population and the sensitivity analysis on PP Population supported the mITT Population results.

Virologic clearance of HPV-16 and/or HPV-18 at Week 36**:** For the ITT Population, the percentage of responders was higher in the VGX-3100 + EP group (34.1%) as compared with the placebo + EP group (15.9%). The lower bound of the 95% CI for the difference in percentage of responders exceeded zero (0), providing evidence for superior efficacy of VGX-3100 + EP in achieving virologic clearance of HPV-16 and/or HPV-18 at Week 36. The results of the mITT and PP Populations and the sensitivity analysis on PP Population supported the ITT Population results.

Histopathological regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18 at Week 36**:** For the ITT Population, the percentage of responders was higher in the VGX-3100 + EP group (18.1%) as compared with the placebo + EP group (6.3%). The lower bound of the 95% CI for the difference in percentage of responders exceeded zero (0), providing evidence for superior efficacy of VGX-3100 + EP in achieving histopathological regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18 at Week 36. The results of the mITT and PP Populations and the sensitivity analysis on PP Population supported the ITT Population results.

Histopathological regression of cervical HSIL to normal at Week 36**:** For the ITT Population, the percentage of responders was higher in the VGX-3100 + EP group (24.6%) as compared with the placebo + EP group (11.1%). The lower bound of the 95% CI for the difference in percentage of responders exceeded zero (0), providing evidence for superior efficacy of VGX 3100 + EP in achieving histopathological regression of cervical HSIL to normal at Week 36. The results of the mITT and PP Populations and the sensitivity analysis on PP Population supported the ITT Population results.

Nonprogression of cervical HSIL to cervical carcinoma at Week 36**:** For the ITT Population, the percentage of responders in the VGX-3100 + EP group (84.1%) was similar to those in the placebo + EP group (85.7%). The 95% CI for the difference in percentage of responders did not exclude zero (0), indicating no difference in the efficacy of VGX-3100 + EP and placebo + EP in preventing progression of cervical HSIL to cervical carcinoma at Week 36. The results of the mITT and PP Populations and the sensitivity analysis on PP Population supported the ITT Population results.

Virologic clearance of HPV-16 and/or HPV-18 from noncervical anatomic locations at Week 36: In the ITT Population, the percentage of responders (i.e., subjects with virologic clearance of HPV-16 and/or HPV-18 from noncervical anatomic locations at Week 36) was 20.3% in the VGX-3100 + EP group as compared with 11.1% in the placebo + EP group. The lower bound of the 95% CI for the difference in percentage of responders in the ITT Population did not exceed zero (0), providing no evidence for superior efficacy of VGX-3100 + EP compared with placebo + EP in achieving virologic clearance of HPV-16 and/or HPV-18 from noncervical anatomic locations at Week 36 in the ITT Population. The results of the mITT and PP Population supported the ITT Population results.

Subgroup Analysis

Subgroup analyses of the primary and secondary efficacy endpoints were conducted by history of exposure to prophylactic HPV vaccines (yes, no). Histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 were also assessed by stratification factors.

Among subjects with no history of exposure to prophylactic HPV vaccine, VGX-3100 + EP showed superior efficacy as compared with placebo + EP in the following efficacy measures:

- Histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36
- Virologic clearance of HPV-16 and/or HPV-18 at Week 36
- Histopathological regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18 at Week 36
- Histopathological regression of cervical HSIL to normal at Week 36.

There was no evidence for efficacy of VGX-3100 + EP as compared with placebo + EP with respect to the following efficacy measures, irrespective of previous exposure to prophylactic HPV vaccine:

- Histopathological regression of cervical HSIL at Week 36
- Nonprogression of cervical HSIL to cervical carcinoma at Week 36
- Virologic clearance of HPV-16 and/or HPV-18 from noncervical anatomic locations at Week 36.

The percentage of subjects with histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 was higher in the VGX-3100 + EP group as compared with the placebo + EP group for all stratification combinations. The difference in percentage of responders was highest (5.8%) in subjects who were ≥25 years of age and had BMI ≤25 kg/m^2 and CIN2.

Exploratory Efficacy Endpoints

The impact of prior miRNA and DNA methylation, colposcopy, cytology, and HPV result, baseline immunoscore, and baseline biomarker status on histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 was evaluated. At the individual subject level, Day 0 and Week 8 miRNA and Day 0 and Week 15 DNA methylation values did not significantly influence the odds of the response, except the Day 0 methylated NKAIN2, for which the odds of response increased as the Day 0 NKAIN2 increased. The odds of achieving a response at Week 36 were 3.55 times higher if the Week 15 colposcopy result showed an improvement as compared with no change (95% CI: 1.69, 7.48) and 2.93 times higher if the Week 28 colposcopy result showed an improvement as compared with no change (95% CI: 1.40, 6.13). The odds of achieving a response at Week 36 were 2.24 times higher if the Week 15 cytology result showed an improvement as compared with no change (95% CI: 1.01, 4.99) and 9.78 times higher if the Week 28 cytology result showed an improvement as compared with possible progression (95% CI: 1.23, 77.92). The odds (95% CI) of achieving a response at Week 36 were 7.93 (2.92, 21.54), 10.65 (4.39, 25.86), and 27.83 (10.64, 72.76) times higher if HPV had cleared at Weeks 8, 15, and 28, respectively, as compared with not cleared at these timepoints, indicating that clearance of HPV was associated with a response, and the response rate improved with time. Baseline immunoscore did not influence the odds of achieving a response (odds ratio [95% CI]: 0.99 [0.63, 1.56]). VGX-3100 + EP demonstrated superior efficacy for causing histopathological regression of cervical HSIL and virologic

clearance of HPV-16 and/or HPV-18 at Week 36 in subjects with baseline biomarker status positive when compared with placebo + EP but did not have the same impact in subjects with baseline biomarker status negative.

The percentage of subjects with no evidence of cervical HPV-16 and/or HPV-18 at Weeks 62 and 88 was higher in the VGX-3100 + EP group as compared with the placebo + EP group; however, at Week 88, the difference between the groups had reduced.

Patient-reported outcome measures (SF-36, EQ-5D-5L, Week 40 QoL responses) were overall similar in the VGX-3100 + EP and placebo + EP groups.

Immunogenicity Results:

- VGX-3100 was immunogenic as seen from the geometric means of the reciprocal endpoint titers, which were several-fold higher in the VGX-3100 + EP group as compared with the placebo + EP group at Weeks 8, 15, and 36 for both HPV-16 E7 and HPV-18 E7. Anti-HPV-16 E6 and anti-HPV-18 E6 antibodies were not assayed.
- An increase from baseline was seen in the spot forming units per 10^6 PBMCs of HPV-16 E6, HPV-16 E7, HPV-18 E6, HPV-18 E7, and related combinations in the VGX-3100 + EP group as compared with the placebo + EP group at all postbaseline timepoints (Weeks 8, 15, and 36).
- The median increases in CEF and PMA levels appeared to be similar in both treatment groups at Weeks 8, 15, and 36.
- All parameters including CD8+CD137+perforin+, CD8+CD38+perforin+, and CD8+CD69+perforin+ showed an increase in the VGX-3100 + EP group indicating greater cellular immune responses (as measured by activated CD8+ T cells with lytic potential) on flow cytometry as compared with the placebo + EP group at Week 15.
- Changes from baseline to Week 36 in CD8+, CD103+, FoxP3+, and perforin+ cells in cervical tissue normal epithelium, normal stroma, CIN2/3 epithelium, and CIN2/3 stroma were small and generally similar between the treatment groups.

Safety Results:

Overall, IM injection of VGX-3100 or placebo followed by EP was well-tolerated by subjects with HPV-16 and/or HPV-18 associated HSIL of cervix. The safety results are summarized below.

- Through the clinical trial completion, the incidence of TEAEs was similar among the 2 treatment groups.
- A total of 96.3% subjects in the VGX-3100 + EP group and 98.4% subjects in the placebo + EP group reported at least one (1) TEAE.
- Treatment-emergent AEs in 9.6% subjects in the VGX-3100 + EP group and 9.7% subjects in the placebo + EP group were considered to be serious. Most treatment-emergent SAEs were reported in the SOC of Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps). None of the SAEs were related to IP or EP. One (1) subject died during the clinical trial on Day 450, 365 days after Dose 3 of VGX-3100 + EP due to the TEAE of pulmonary embolism.
- Overall, injection-site pain, headache, fatigue, injection-site erythema, injection-site pruritus, myalgia, and injection-site swelling were the most commonly reported TEAEs during the clinical trial, and the incidences of these TEAEs in VGX-3100 + EP and placebo + EP groups, respectively, were as follows: Injection-site pain was reported in 78.7% and 80.6% subjects; headache was reported in 33.1% and 30.6% subjects; fatigue was reported in 28.7% and 27.4% subjects; injection-site erythema and injection-site pruritus each were reported in 25.0% and 22.6% subjects; myalgia was reported in 21.3% and 24.2% subjects; and injection-site swelling was reported in 20.6% and 24.2% subjects.
- The incidence of most TEAEs did not differ per number of doses received by the subject. Few TEAEs were reported more frequently after Dose 1 in both VGX-3100 + EP and placebo + EP groups and their incidence generally decreased after Dose 2 and Dose 3. These TEAEs included nausea, fatigue, injection-site pain, injection-site swelling, malaise, myalgia, and headache. The incidences of injection-site erythema and injection-site pruritis decreased after Dose 1 in the placebo + EP group, but slightly increased after Dose 1 in the VGX-3100 + EP group. Most of these TEAEs were reported within 28 days of clinical trial treatment.

- Most TEAEs were grade 1 or 2 in intensity, irrespective of time of onset from administration of clinical trial treatment. Treatment-emergent AEs of CTCAE grade ≥3 were reported in 14.0% subjects in the VGX-3100 + EP group and 11.3% subjects in placebo + EP group. Most common TEAEs of CTCAE grade ≥3 included injection-site pain and headache.
- Treatment-emergent AEs in 83.8% subjects in the VGX-3100 + EP group and 90.3% subjects in the placebo + EP group were related to the IP or EP. Overall, injection-site pain, fatigue, and headache were the most commonly reported IP- or EP-related TEAEs through the clinical trial completion. Treatment-emergent AEs with CTCAE grade ≥3 severity reported by the investigator to be related to the IP, EP, or both through the clinical trial completion in >1% of subjects included injection-site pain, myalgia, and headache. All of these TEAEs were reported within 7 days of clinical trial treatment.
- The TEAEs that led to withholding of clinical trial treatment included injection-site pain and upper respiratory tract infection. The TEAE of injection-site pain reported in one (1) other subject in the VGX-3100 + EP group within 7 days after Dose 1 of clinical trial treatment led to permanent discontinuation of clinical trial treatment.
- Adverse pregnancy outcomes included abortion spontaneous (1 subject) and ectopic pregnancy (1 subject), both in the placebo + EP group.

Through the clinical trial, no TEAEs related to abnormal laboratory results were reported. Vital signs and physical examination were found to be normal in most subjects and few AEs were reported due to abnormal vital signs or physical examination findings.

Device Performance Results:

Most (>95%) EP attempts, in both VGX-3100 + EP and placebo + EP groups, were successful. Seventeen of 415 (4.1%) and six (6) of 191 (3.1%) of the EP attempts in VGX-3100 + EP and placebo + EP groups, respectively, were unsuccessful. The most common reason for nonsuccess were an Array problem (47.1% and 66.7% in VGX-3100 + EP and placebo + EP groups, respectively) or an error message received from the device (41.2% and 16.7% in VGX-3100 + EP and placebo + EP groups, respectively).

Conclusions:

VGX-3100 + EP showed superior efficacy as compared with placebo + EP in achieving histopathological regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 and was safe and well-tolerated by subjects with HPV-16 and/or HPV-18 associated HSIL of cervix.

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