CLINICAL TRIAL REPORT ERRATA

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
REVEAL 1 Trial
(Randomized Evaluation of VGX-3100 and Electroporation for the Treatment of Cervical HSIL)

PROTOCOL NUMBER
HPV-301

ERRATA DATE: 31 MAR 2023

CONFIDENTIAL

1. Reason for the Errata

This errata describes a correction to the VGX-3100 HPV-301 Clinical trial report (dated 03 Mar 2022). An error was identified that impacts two summaries (Table 14.2.9.1 and Table 14.2.9.2) that were provided to Inovio and used to develop the Clinical Trial Report for HPV-301 study. Many of the estimates and confidence intervals on these tables were updated, the interpretation of the results does not change with the exception of one parameter at one timepoint. The impacted value was included in the Clinical Trial Report and the interpretation of the result was incorrect as a result of the error in the tables of TLFs.

2. Impact to the Clinical Trial Report and Synopsis

The impact to the Clinical Trial Report and Synopsis is minor and impacts interpretation of 1 exploratory efficacy endpoint.

Impact of prior micro ribonucleic acid (miRNA) result on histopathological regression of cervical high-grade squamous intraepithelial lesion (HSIL) lesions and virologic clearance of human papilloma virus-16 (HPV-16) and/or HPV-18 at Week 36 intent-to-treat (ITT) Population. (Table 14.2.9.1).

Impact of prior deoxyribonucleic acid (DNA) methylation result on histopathological regression of cervical HSIL lesions and virologic clearance of HPV-16 and/or HPV-18 at Week 36 ITT Population (Table 14.2.9.2).

One of the parameters in these two categories have 95% confidence interval (CI) including 1.00, indicating no significant influence of the parameter on the response outcome. For the NKAIN2 DNA methylation, the 95% CI does not include 1.00. In the original version this was interpreted as odds of response significantly decreased as Day 0 NKAIN2 increased (presumably since the Screening timepoint). Since modeling response = 0 (i.e., no response) was mistakenly included instead of modeling response = 1, this Clinical Trial Report sentence would need to be updated to include, “odds of response increased as Day 0 NKAIN2 increased.”

3. Changes to the Appendices and the Clinical Trial Report Table of Contents

In Section 14.2 of the Clinical Trial Report, Table 14.2.9.1 and Table 14.2.9.2 have been updated and same Tables have been updated in the Table of Content.

4. Changes to the Clinical Trial Report Body and Synopsis

4.1 Changes to the Clinical Trial Report Synopsis

Changes from the original text are noted below - ~~strike-through text~~ indicates deleted text and ***bold italics*** text indicates newly added text.

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 ~~decreased~~ ***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 (36-item short form survey [SF-36], EuroQol 5-dimensions 5-level [EQ-5D-5L], Week 40 quality of life [QoL] responses) were overall similar in the VGX-3100 + electroporation [EP] and placebo + EP groups.

4.2 Changes to the Clinical Trial Report Body

Changes from the original text are noted below - ~~strike-through text~~ indicates deleted text and ***bold italics*** text indicates newly added text.

6.4 Exploratory Efficacy Results

6.4.1 Impact of Prior miRNA and DNA Methylation Profile on Histopathologic Regression of Cervical HSIL and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36

Impact of prior miRNA and DNA methylation result on histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36 is summarized for the ITT Population in Table 14.2.9.1 and Table 14.2.9.2, respectively. MicroRNA and DNA methylation results for individual subjects are given in Listing 16.2.3.6.

The 95% CI of the odds ratio of response (i.e., histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 at Week 36) given miRNA and DNA methylation values at screening, Day 0, Week 8 (miRNA only), and Week 15 (DNA methylation only) included 1.0 for all five (5) types of miRNA and at least ten (10) of 11 types of methylated DNA, indicating that such parameters did not significantly influence the odds of the response at an individual subject level. For Day 0 methylated NKAIN2, the odds ratio (95% CI) was 0.93 (0.86, 0.99), indicating that the odds of response significantly ~~decreased~~ ***increased*** as Day 0 NKAIN2 increased.

6.8 Efficacy Results

6.8.4 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 ~~decreased~~ ***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.

12 Discussion and Conclusion

12.1 Discussion

Up to 13,000 women in the US alone are diagnosed with cervical cancer each year, with an estimated 4,120 deaths [4]. HPV-16 is the most common high-risk genotype and combined with HPV-18 these two (2) genotypes are estimated to cause about 70% of all cervical cancers [5, 6]. 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. VGX-3100 is delivered *in vivo* using the CELLECTRA™ 5PSP EP device.

This Phase 3 clinical trial, HPV-301, employed a prospective, randomized, double-blind, placebo-controlled design to demonstrate the efficacy, safety, and tolerability of VGX-3100 followed by EP in women with cervical HSIL 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.

A total of 201 subjects were randomly assigned to receive either 6 mg (in 1 mL) VGX-3100 (138 subjects) or placebo (63 subjects), IM followed by EP. Subjects were randomly assigned in a stratified manner according to: 1) CIN severity observed in the biopsy specimens at screening (CIN2 vs. CIN3), 2) 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. The first clinical trial treatment was administered on Day 0, the second at Week 4, and the third (final) at Week 12.

The mean age of the subjects was 31.5 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. The demographic and baseline characteristics were similar across both the treatment groups.

Most subjects in both treatment groups received all 3 doses of clinical trial treatment with EP: 93.5% subjects in the VGX-3100 + EP group and 96.8% subjects in the placebo + EP group.

The primary efficacy 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 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 the PP Population supported the mITT Population results.

Results for the secondary endpoint of histopathological regression of cervical HSIL at Week 36 were similar to those of the primary endpoint. For other secondary efficacy 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 of the difference between responder percentages in the two (2) groups generally exceeded zero (0). For the secondary endpoint of nonprogression of cervical HSIL to cervical carcinoma at Week 36, both treatment groups showed similar response rates.

In subgroup of subjects with no history of exposure to prophylactic HPV vaccine, the response rate in VGX-3100 + EP was higher as compared with placebo + EP for the efficacy endpoints of 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; and 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.

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 ~~decreased~~ ***increased*** as the Day 0 NKAIN2 increased. Baseline immunoscore also did not significantly influence the odds of the response. The odds of achieving a response at Week 36 were higher if the prior colposcopy and cytology result showed an improvement as compared with no change or possible progression. The odds of achieving a response at Week 36 were also higher if HPV had cleared from the cervical lesions at Weeks 8, 15, and 28. VGX-3100 + EP demonstrated superior efficacy for 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 percentages of subjects with no evidence of cervical HPV-16 and/or HPV-18 at Week 62 and Week 88 were higher in the VGX-3100 + EP group as compared with the placebo + EP group; however, the difference between the groups decreased over time.

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.

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. A notable increase from baseline was seen in the SFU/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). 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.

Device performance was evaluated using the number of successful and unsuccessful EP

attempts. Most (>95%) EP attempts, in both VGX-3100 + EP and placebo + EP groups, were successful. The small number of unsuccessful attempts (4.1% and 3.1% in VGX-3100 + EP and placebo + EP groups, respectively) were most commonly due to Array problems or an error message received from the device.

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 findings were in-line with those seen with VGX-3100 and closely related DNA plasmid products. The TEAEs of injection-site pain, headache, fatigue, injection-site erythema, injection-site pruritus, myalgia, and injection-site swelling were most commonly reported during the clinical trial. Most TEAEs were CTCAE grade 1 or 2 in intensity. Most common TEAEs of grade ≥3 included injection-site pain and headache. One (1) subject died during the clinical trial on Day 450, 365 days after Dose 3 of VGX 3100 + EP due to the unrelated TEAE of pulmonary embolism. 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.

4.3 Changes to the Appendices

In Section 14.2 of the Clinical Trial Report, Table 14.2.9.1 and Table 14.2.9.2 have been updated and are included here.

14.2 Efficacy Data

Number	Title
Table 14.2.9.1	Impact of Prior miRNA Result on Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 ITT Population
Table 14.2.9.2	Impact of Prior DNA methylation result on Histopathological Regression of Cervical HSIL Lesions and Virologic Clearance of HPV-16 and/or HPV-18 at Week 36 ITT Population

5. Signature Page

STUDY TITLE: 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

STUDY NUMBER: HPV-301

I have read this report and confirm that to the best of my knowledge it accurately describes the results of the study.

Sponsor's Responsible Medical Officer:

SIGNATURE:  03 April 2023

Jeffrey Skolnik
Senior Vice President of Clinical Development

Date

Inovio Pharmaceuticals, Inc.
660 W. Germantown Pike, Suite 110
Plymouth Meeting, PA 19462
United States
Telephone: 267-434-4052
Email: jeffrey.skolnik@inovio.com

Responsible Biostatistician:

SIGNATURE: Elizabeth Kumm 03April2023

Elizabeth Kumm
Principal Biostatistician

Date

PPD
929 N. Front Street
Wilmington, NC 28401
United States
Telephone: + +910-558-3236
Email: elizabeth.kumm@ppd.com