This presentation contains forward-looking statements including, but not limited to, statements related to pharmaceutical development of nitric oxide-based product candidates and future prospects. Forward-looking statements are subject to a number of risks and uncertainties that could cause actual results to differ materially from our expectations. These forward-looking statements speak only as of the date of this presentation, and Novan disclaims any intent or obligation to update these forward-looking statements, except as expressly required by law.

I have financial interest as an employee and stockholder of Novan, Inc that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Most common sexually transmitted infection

Approximately 14 million people become infected each year

>500,000 people in the United States are actively infected

No currently approved HPV treatments with a direct anti-viral mechanism of action

Topical and ablative therapies are largely ineffective for long-term wart eradication.

- Average recurrence rates ranging from 30% to 70% within the first 6 months
Two Fundamental Mechanisms of Action of Nitric Oxide

- **Broad Spectrum**
- **Antimicrobial**
- **Modulator of Inflammation**
Nitricil: Lead Candidate NCEs

In vitro nitric oxide release profiles at pH 7.4

**NO-loaded Monomer A**

**Backbone Monomer**

**NO-loaded Monomer B**

**NVN1000**
“Fast Releasing”

**NVN4000**
“Slow Releasing”

C<sub>max</sub> = 240 ppb NO/ mg NVN1000

C<sub>max</sub> = 27 ppb NO/ mg NVN4428

t<sub>1/2</sub> = 2.3 min

% NO Release

Time (min)
HPV-18 Infected Organotypic Epithelial Raft Culture Model

HPV-18 L1 viral capsid (reddish brown) accumulates in the upper live cell strata and cornified layers by D16 in an organotypic raft culture.

Image adapted from Wang, 2015 Methods Mol Bio
Nitric Oxide Inhibition of DNA Replication

**BrdU Stain, mitotic index for rapidly dividing nuclei**

*Untreated Control*

Large number of BrdU stained cells indicative of pervasive viral infection throughout epithelium

*1.5 mg/mL NVN1000*

Mitotic activity present only at basal layers indicative of normal epithelium proliferation

*1.5 mg/mL NVN4000*
Nitric Oxide Inhibition of Viral Replication

qPCR analysis of HPV-18 viral copy number

HPV-18 Copy Number at Day 6

- Control
- 0.75 mg/mL NVN4000
- 1.0 mg/mL NVN4000
- 1.5 mg/mL NVN4000
- 2.0 mg/mL NVN4000

HPV-18 Copy Number at Day 6

- Control
- 0.75 mg/mL NVN1000
- 1.0 mg/mL NVN1000
- 1.5 mg/mL NVN1000

* Denotes significant difference compared to control
Cottontail Rabbit Papillomavirus Model

- Mutant virus results generates smaller, slower-growing papillomas thought to be more clinically similar to human papillomas.

- The E8 mutant papillomas are much lower in height and are less keratinized than those induced by WT CRPV.
Nitric Oxide Delivery: Fast Release is Superior

Wild-Type CRPV

- Untreated
- Placebo Gel
- Fast-Releasing
- Slow-Releasing

*Geometric Mean Diameter

Papilloma Size (mm)*

Weeks Post-DNA Inoculation

* Treatment occurs
Nitric Oxide Delivery: threshold concentration necessary for depth of penetration

A) Placebo Gel

B) Slow-Releasing: SB216 Gel 1.5% NO

C) Fast-Releasing: SB206 Gel 1.5% NO
The E8 mutant virus produces slower-growing and more clinically relevant papillomas than the Wild-Type virus.

*D vs. Placebo Control Following 5 Weeks of Treatment*

**Wild-Type**

- Placebo
- 2% SB206
- 4% SB206
- 8% SB206
- 10% SB206
- Imiquimod

**E8 Mutant**

- Placebo
- 2% SB206
- 4% SB206
- 8% SB206
- 10% SB206
- Imiquimod

* vs. Placebo Control Following 5 Weeks of Treatment
Conclusions

- Dose-dependent inhibition of HPV-18 viral replication as evidenced by both DNA copy number and BrdU immunohistochemistry.
  - Similar efficacy with NVN1000 or NVN4000 drug substance

- Dose-responsive, pharmacologic effect of SB206 Gel against papillomavirus in the Cottontail Rabbit model.

- Topical therapy with SB206 Gel is currently being studied in a Phase 2 EGW/PAW Clinical Trial with TLRs expected 2H 2016.
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