Vical

Therapeutic DNA Vaccine for Genital Herpes

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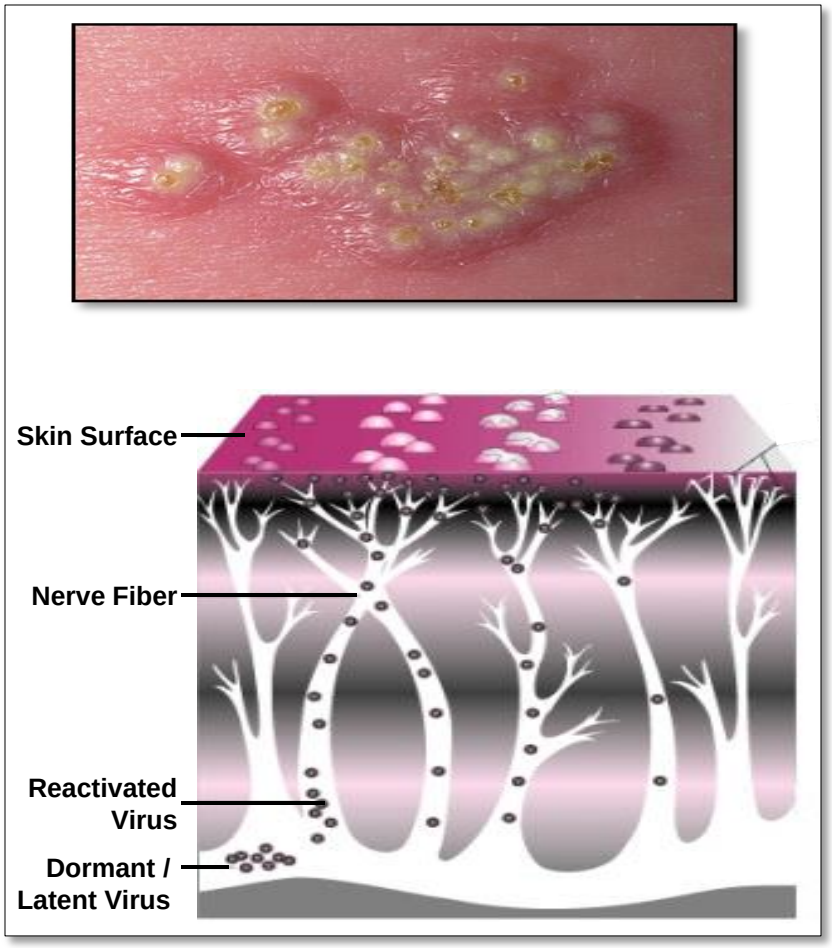
Disclosures

- Trial funded by Vical, Inc.
- MPM employed by Vical, Inc.

Genital Herpes

- Recurrent sexually-transmitted infection; mainly due to HSV-2
- 16% of U.S. population 14 to 49 years of age are infected
- 417 million infected worldwide, (Looker, et al, PLoS One, 2015)
- Initial outbreak followed by intermittent viral shedding with or without genital lesion recurrences in “boxer shorts” distribution



Sources: Centers for Disease Control and Prevention, Nov2015 http://www.cdc.gov/std/Herpes/STDFact-herpes-detailed.htm. Image 1: http://hardinmd.lib.uiowa.edu/dermnet/herpessimplex34.html
Image 2: http://www.happy-with-herpes.com/stages-of-herpes.html

Vical's Therapeutic HSV-2 DNA Vaccine

- **T-cell responses are the strength of DNA technology**
  - Simulates live attenuated approach without safety issues
  - CMV DNA vaccine showed reduced viremia in transplant patients in Phase 2 trial*
- **Collaboration with Fred Hutchinson Cancer Research Center and University of Washington (UW)**
  - Antigen discovery by Corey and Koelle
  - Top candidates: glycoprotein D (gD) and tegument proteins UL46, UL47

Preclinical studies show immunogenicity and efficacy against HSV-2

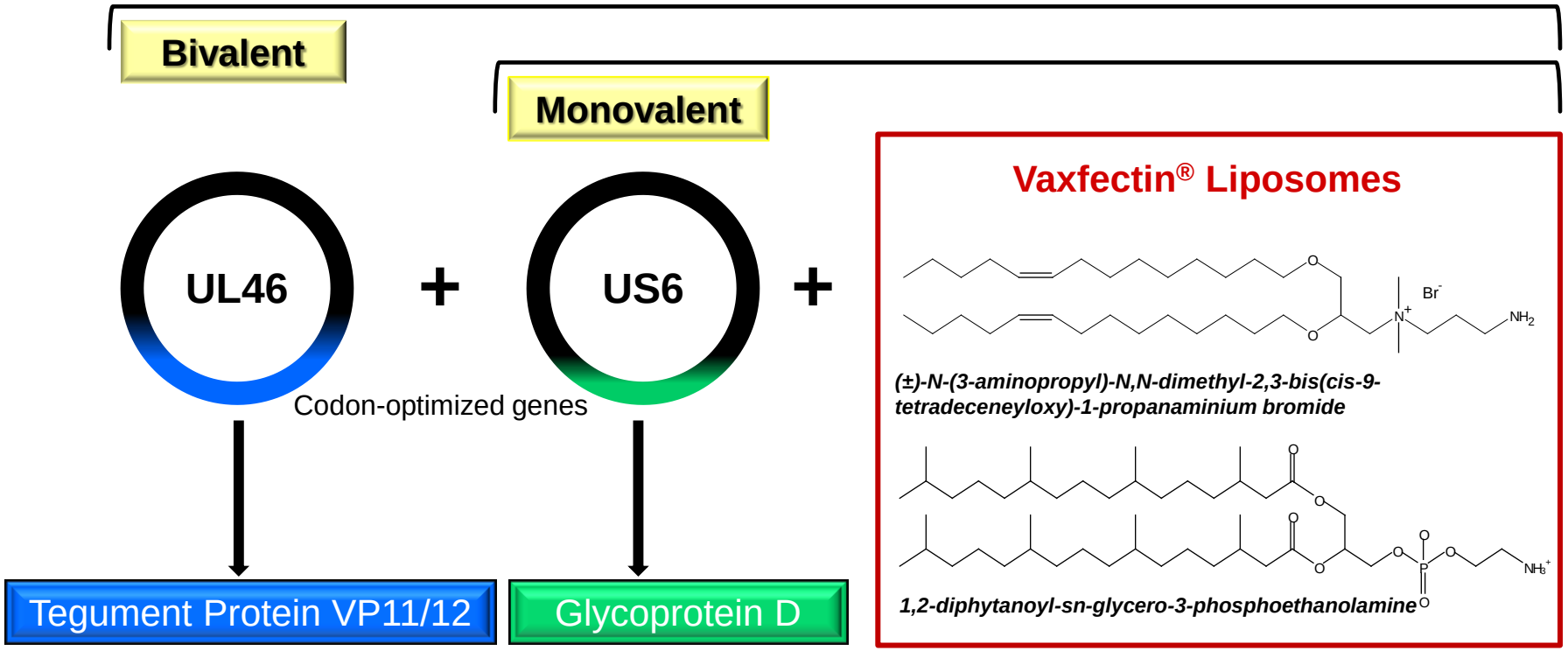
✓Mice – Immunogenicity (*Muller et al, JGV 2009*)

✓Mice – Vaxfectin® adjuvant effect and full-length gD (*Shlapobersky et al, JGV 2012*)

✓Guinea pigs –Therapeutic proof of concept (*Veselenak et al, Vaccine 2012*)

* Kharfan-Dabaja, et al, Lancet ID 2012

HSV-2 Vaccine Candidates



Full-length HSV-2 proteins

Phase 1/2 Trial Design

- Randomized, double-blind, placebo-controlled trial
- Bivalent and monovalent vaccines
  - for safety and efficacy
- Placebo*
  - primarily for blinded safety comparisons

Dose escalation: Cohorts A, B, C

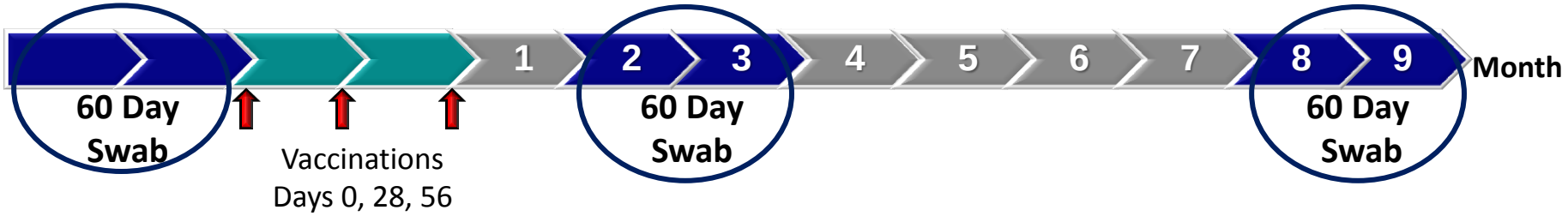
Efficacy: Cohort C only

Cohort (N)	Treatment (N)
A (7)	1 mg Bivalent or Placebo (5:2)
B (7)	2 mg Bivalent or Placebo (5:2)
C1 (14)	4 mg Bivalent or 4 mg Monovalent or Placebo (5:5:2)
C2 (137)	4 mg Bivalent or 4 mg Monovalent or Placebo (5:5:2)

* Phosphate buffered saline

Cohort C Design and Endpoints

Comparing swabbing periods – participant serves as own control



- **Primary endpoints**
  - Safety and tolerability
  - Change in shedding rate by UW PCR assay
- **Secondary endpoints**
  - Change in viral load (shedding)
  - Change in lesion rate
  - Recurrence rate post-vaccination
  - Immunogenicity

Key Eligibility Criteria

- Healthy men and women 18-50 years of age
- HSV-2 positive by Western blot
- ≥ 1-year duration of HSV-2
- 2-9 recurrences per year (self-reported)
- Willing to refrain from
  - Suppressive antivirals throughout the trial
  - Episodic antivirals during swabbing periods
- Body Mass Index (BMI) < 35
- Antinuclear antibody (ANA) ≤ 1:80

Demographics Per Protocol Efficacy Analysis

Characteristic	Bivalent (56)	Monovalent (54)	Placebo (21)
Age – median year (range)	37.2 (20-50)	34.7 (21-50)	37.5 (23-50)
Female (%)	36 (64.3%)	34 (63.0%)	12 (57.1%)
White race (%)	36 (64.3%)	37 (68.5%)	18 (85.7%)
Median years from 1st HSV episode (range)	8 (1-27)	10 (1-31)	10 (1-32)
Median # of prior HSV episodes/year (range)	4.8 (2-12)	5.1 (2-10)	4.5 (2-8)
HSV-1 seropositivity (%)	46.4%	42.6%	71.4%
Previously used suppressive antivirals (%)	14 (25.0%)	14 (25.9%)	4 (19.0%)
Mean # prevaccine swabs/ Mean # 1st postvaccine swabs	62/58	61/57	63/61

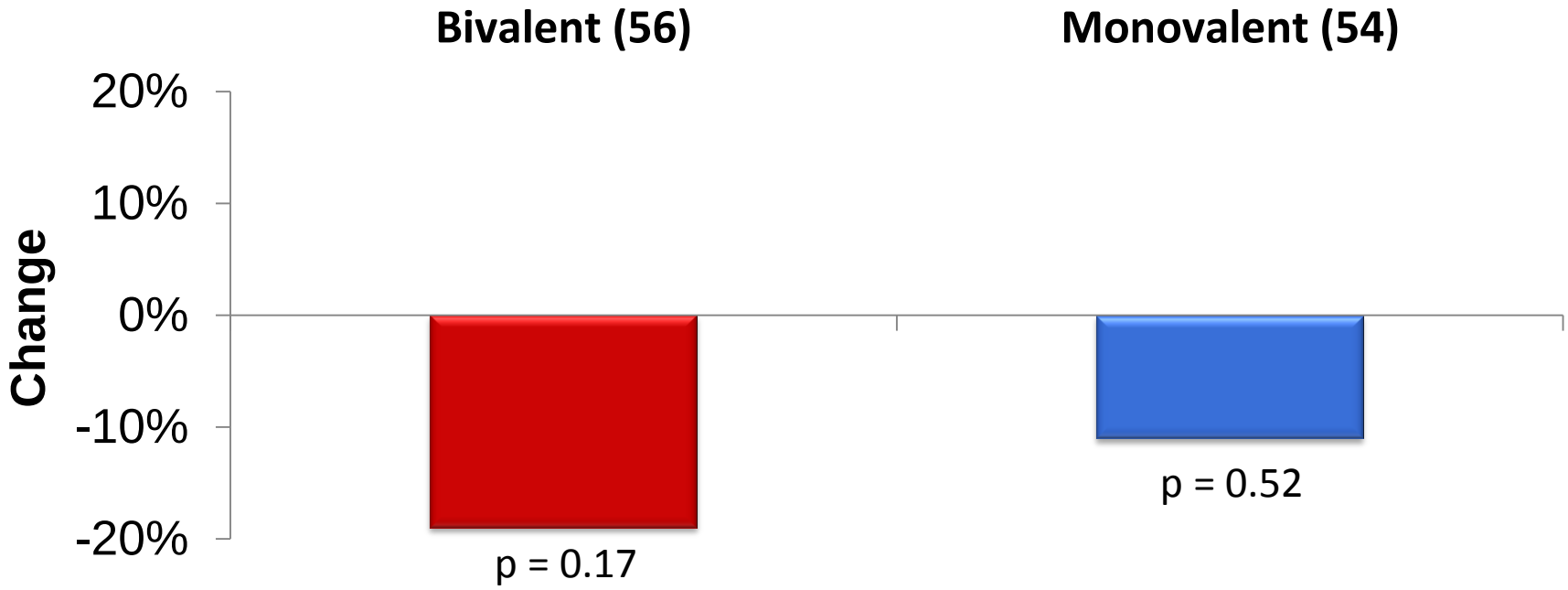
Significant Adverse Events (AEs) Related to Study Product in All Cohorts

Grade 3 AEs	Fatigue	Headache	Myalgia	Nausea	Vomiting	Injection Site Pain or Tenderness	Fever
# of AEs	12	4	8	1	1	11	3
# of Participants	11	4	7	1	1	7	2

- Summary
  - No serious adverse events / No AEs of special interest
  - No Grade 4 AEs
  - Grade 3 AEs: 21 (13%) of participants (20 in Cohort C)
    - 10 bivalent, 11 monovalent
- Independent Safety Monitoring Board reviewed all AEs
  - Deemed vaccines to be safe and tolerable in this trial

Primary Endpoint: Shedding Rate at 3mo Compared to Baseline*

(150 copies/mL assay cut-off)



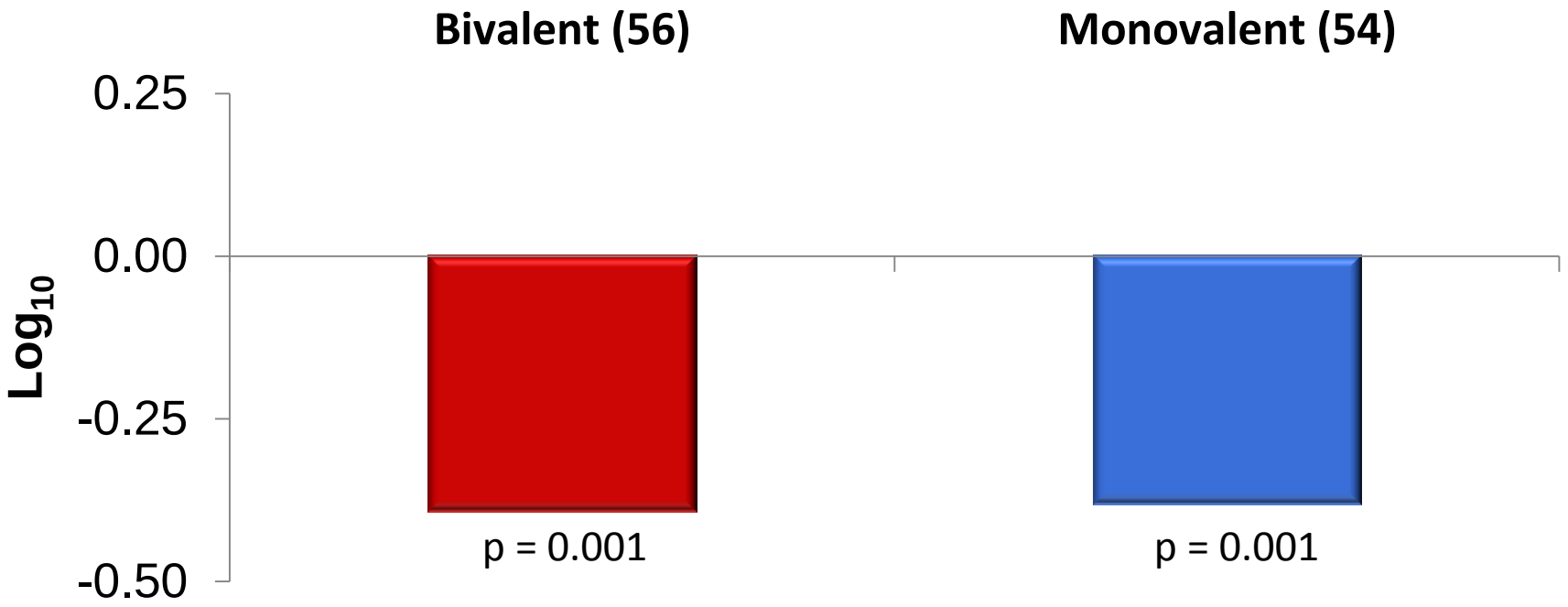
Placebo (21): -45%, p = 0.002

Shedding rate: HSV DNA PCR+ swab per total # swabs per participant

Baseline shedding rates: Bivalent 14.7%, Monovalent 15.0%, Placebo 18.4%

*Based on University of Washington's revised methodology http://biostats.bepress.com/uwbiostat/paper410/

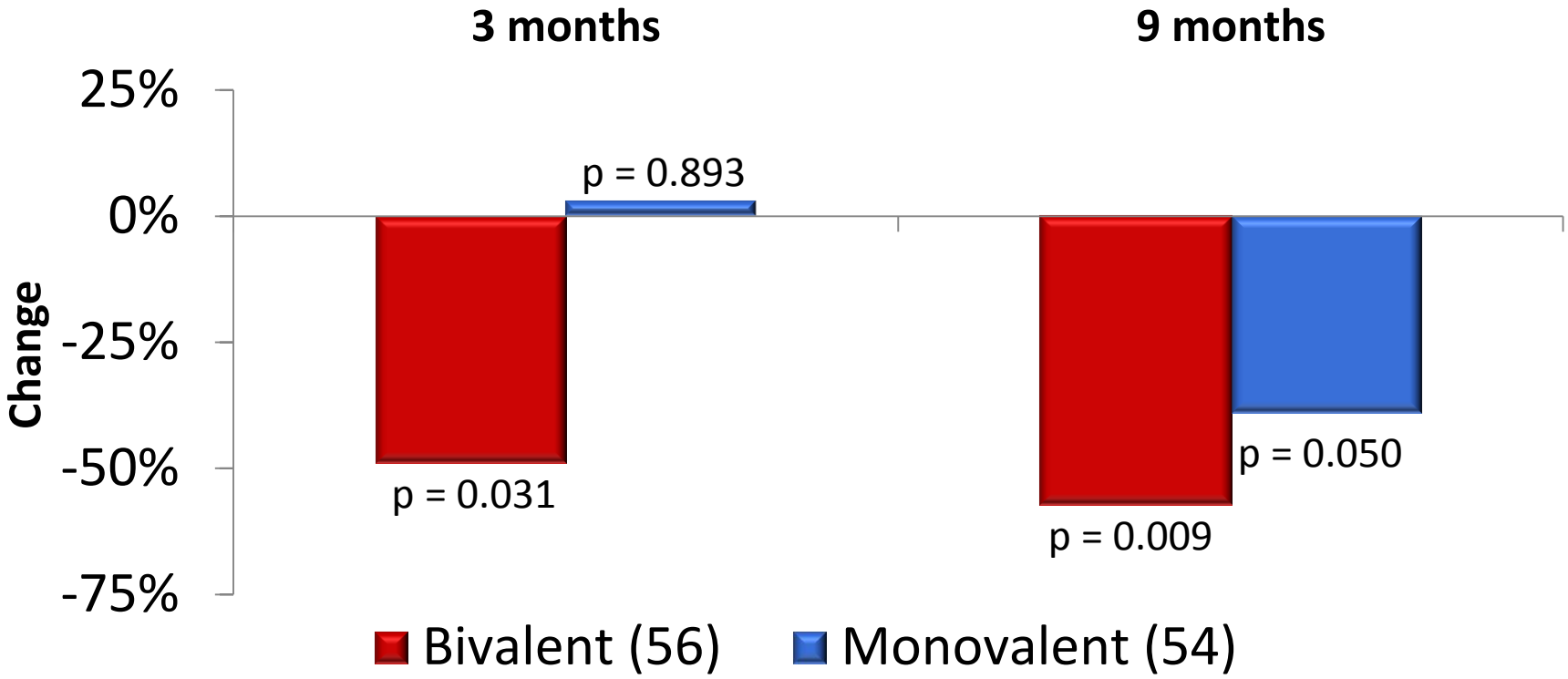
Secondary Endpoint: Viral Load in Positive Swabs at 3mo Compared to Baseline



Viral load: HSV DNA copies, Log_{10}

Placebo (21): Change of +0.28, p = 0.127

Secondary Endpoint: Lesion Rate Compared to Baseline*



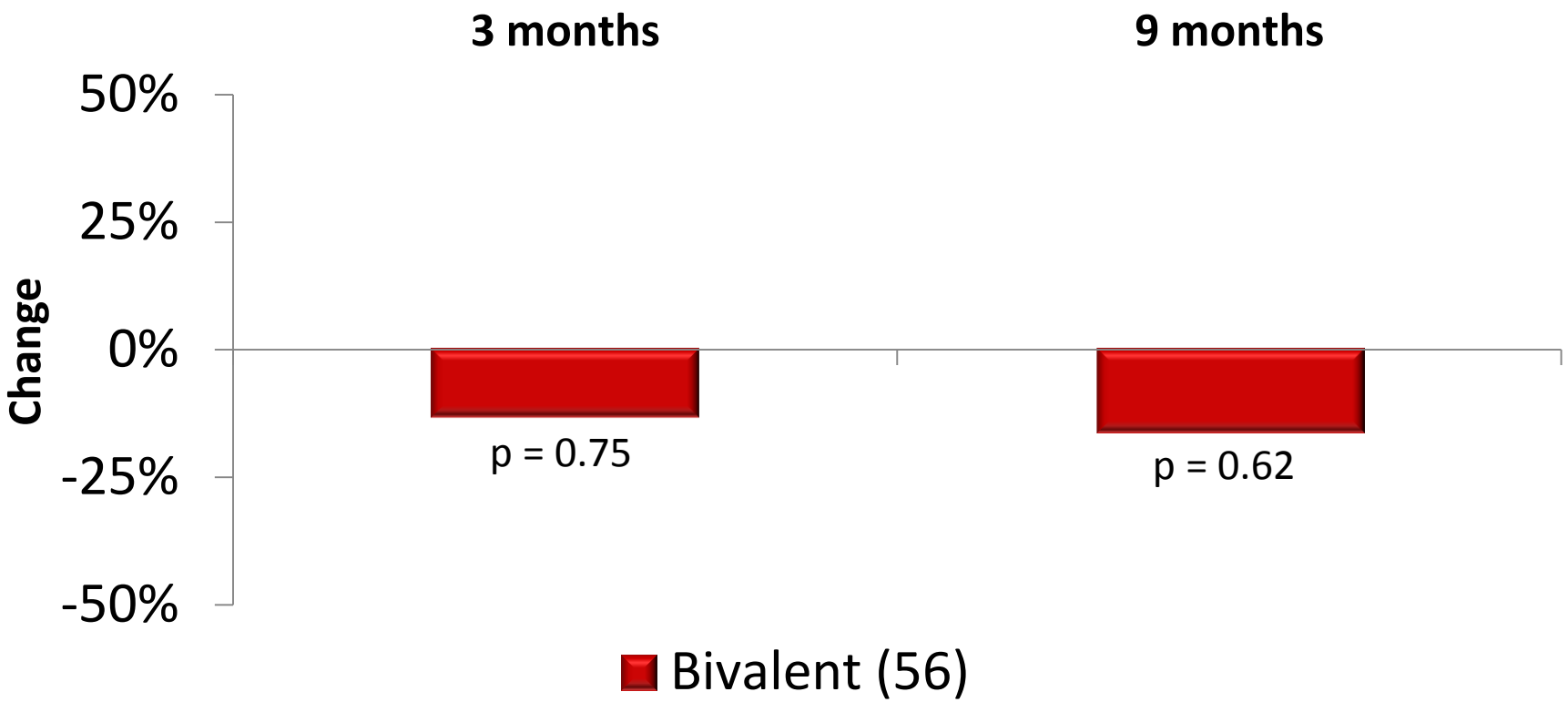
Placebo (21): 3mo: -47%, p = 0.135 and 9mo: -62%, p = 0.062

Lesion rate: # days with lesions relative to number of days evaluated

Baseline lesion rates: Bivalent 6.0%, Monovalent 6.0%, Placebo 6.4%

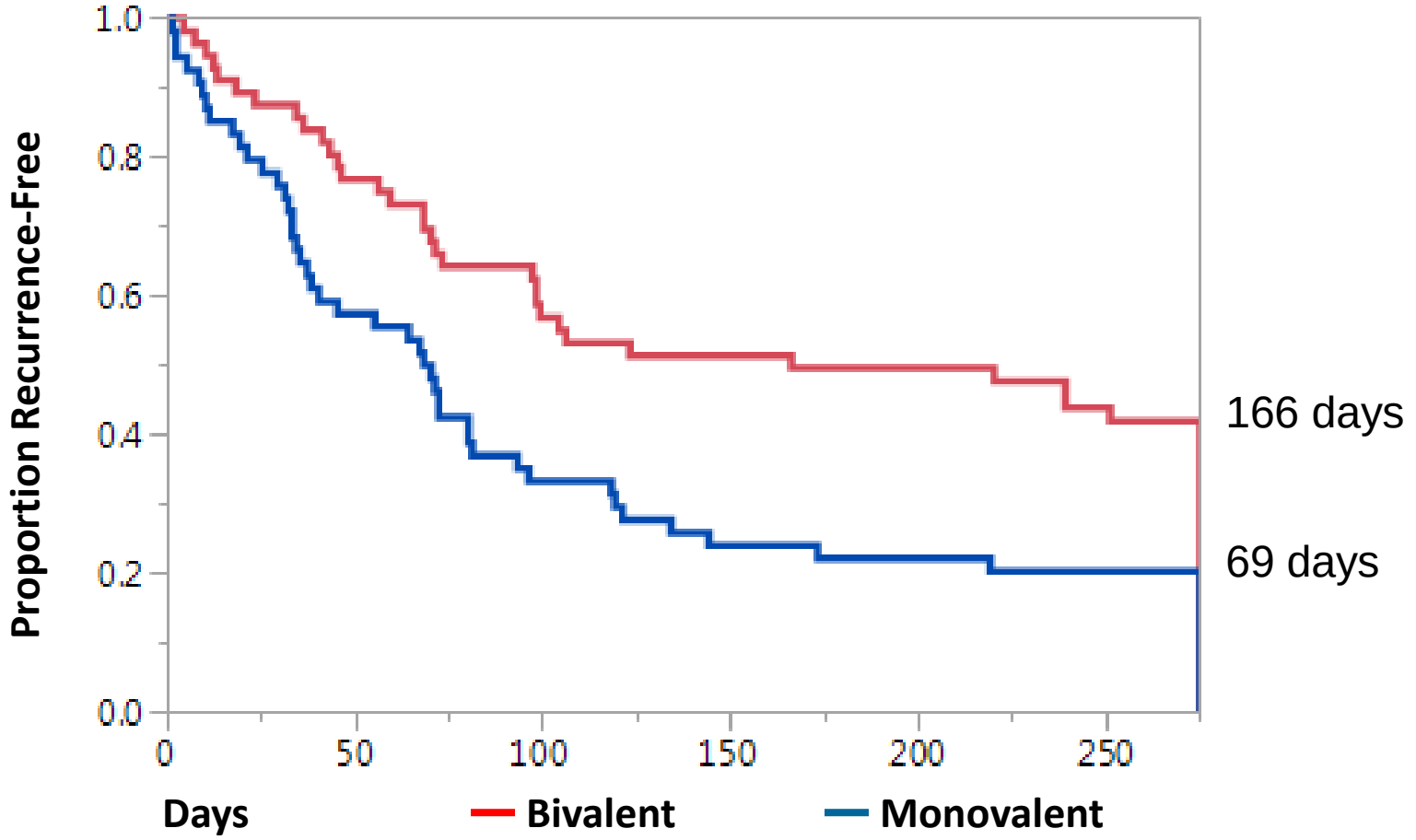
*Based on University of Washington's revised methodology http://biostats.bepress.com/uwbiostat/paper410/

Secondary Endpoint: Post-Vaccine Recurrence Rate - Bivalent versus Placebo



Monovalent (54): 3mo: +52%, p = 0.29 and 9mo: +30%, p = 0.39

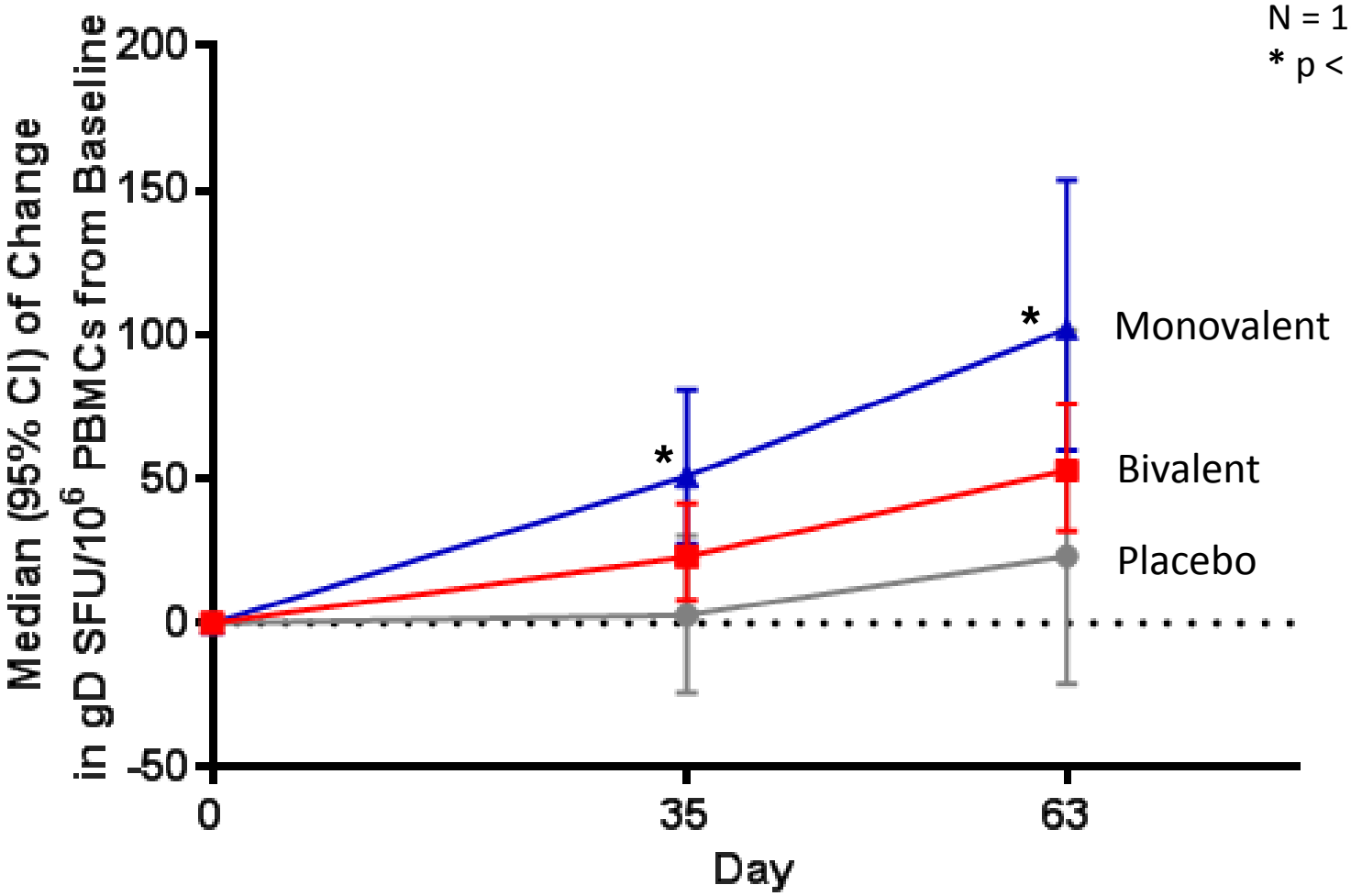
Exploratory Endpoint: Median Time to First Recurrence Until 9 Months



Placebo (21): 111 days

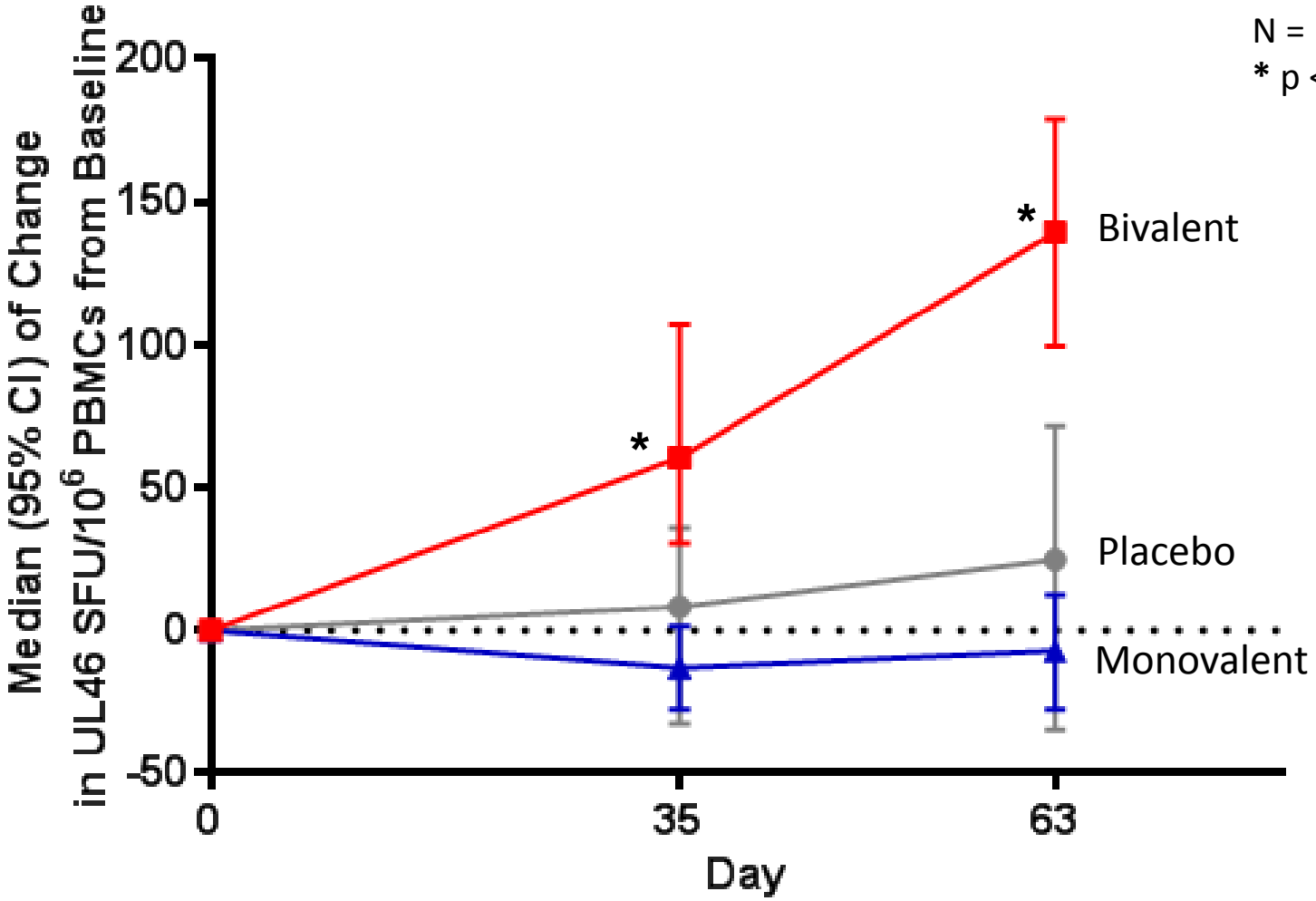
Bivalent vs monovalent p = 0.003 Bivalent vs placebo p = 0.396

gD-Specific T-cell Responses: Vaccine Shows Biological Activity



IFN-γ *ex vivo* ELISPOT assay using 15-mer **gD** peptides overlapping by 11 amino acids

UL46-Specific T-cell Responses: Vaccine Shows Biological Activity



IFN-γ *ex vivo* ELISPOT assay using 15-mer **UL46** peptides overlapping by 11 amino acids

Trial Conclusions: Bivalent Vaccine

- **Virologic endpoints**
  - Nonsignificant reduction in shedding rate <150 copies/mL (primary endpoint)
  - Significant reduction in viral load among PCR+ swabs (secondary endpoint)
- **Lesion rate (secondary endpoint)**
  - Significant reduction of 49% (p= 0.031) at 3 months
  - Significant reduction of 57% (p = 0.009) at 9 months - suggests a durable effect
  - Nonsignificant reductions for monovalent and placebo groups
- **Additional clinical endpoints**
  - Favorable impact on recurrence rate, time to first recurrence and recurrence-free
- **Immunological endpoint**
  - Significant increase in UL46-specific IFN- producing T cells after 2nd & 3rd doses
- **Safety**
  - Independent SMB deemed trial vaccinations to be safe and tolerable

➢ **Trial results support further clinical investigation in Phase 2**

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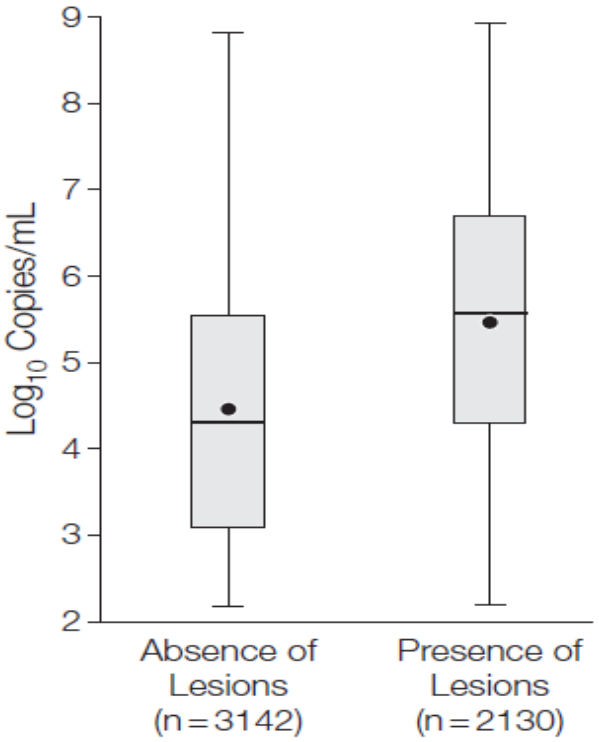
Backup Slides

Why the discordance between impact of bivalent vaccine on shedding and lesion rates?

Viral Load (copies/mL)	% of Shedding Episodes	% Associated with Lesions
Low (10^2 – 10^4)	41	9
Medium (>10^4–10^6)	24	27
High (>10^6)	35	67

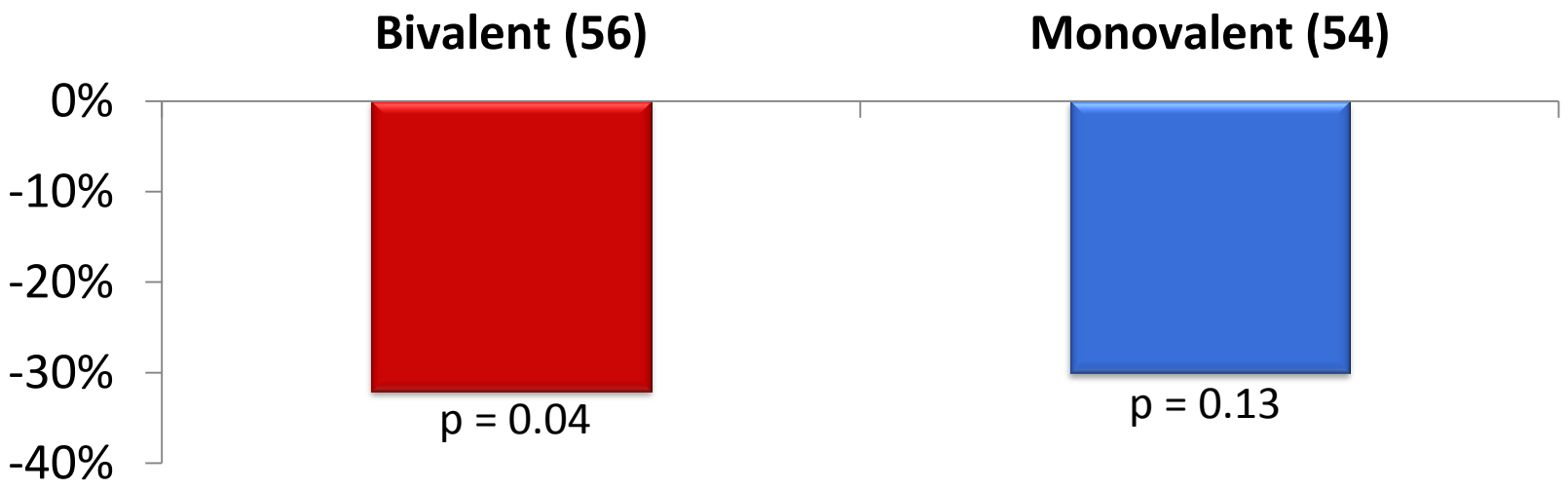


Schiffer et al, PNAS, 2010
1,000 shedding episodes among 386 participants

Tronstein et al, JAMA, 2011
Log_{10} copies/mL 5.6 in lesions vs 4.3

Exploratory Endpoint: Shedding Rate Compared to Baseline at 3mo

(10,000 copies/mL cut-off)

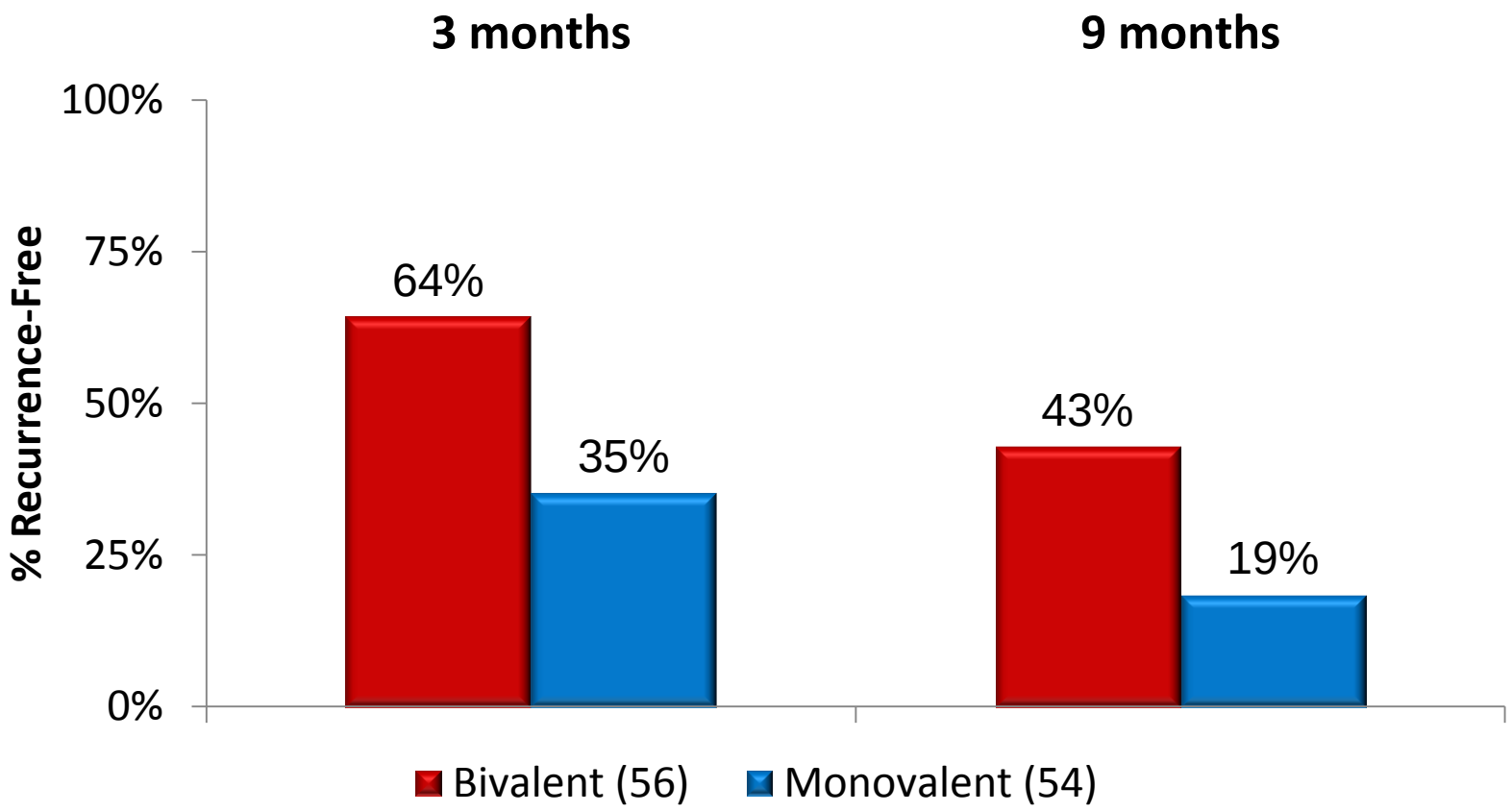


Placebo (21): -38% p = 0.08

Shedding rate: HSV DNA PCR positive swab per total # swabs collected for each participant

Baseline shedding rates: Bivalent 14.7%, Monovalent 15.0%, Placebo 18.4%

Exploratory Endpoint: Proportion of Subjects Recurrence-Free



Placebo (21): 62% at 3mo; 33% at 9mo