

# Berdazimer 10.3% Gel, a Nitric Oxide-Releasing Topical Medication for Molluscum Contagiosum, Triggers BOTE (Beginning Of The End) Inflammation and Accelerates Resolution

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## Introduction

- Molluscum contagiosum (MC) is a highly contagious, persistent viral skin infection that results in small, round, firm, umbilicated, often painless bumps that may last months to years
  - MC primarily affects children<sup>1,4</sup>
- MC virus produces proteins that facilitate its ability to evade the immune system, resulting in persistence of the lesions<sup>5,6</sup>
- Nitric oxide (NO) is an endogenous small molecule that has shown therapeutic promise for the treatment of molluscum because it has both cytotoxic (antiviral, antimicrobial) and immunomodulatory properties<sup>7,8</sup>
- SB206, berdazimer 10.3% gel, is in Phase 3 development and poised to be a first-in-class, topical, controlled-NO-release medication for the treatment of MC<sup>9</sup>
- In patients with MC, it is hypothesized that berdazimer 10.3% fosters clearance of molluscum lesions (resolution) and beginning-of-the-end (BOTE) sign by triggering the immune surveillance system via localized inflammation<sup>9</sup>
- BOTE, often predicts resolution of MC, describes a set of clinical signs of localized inflammation, including erythema, edema, and crusting<sup>9,10</sup> (**Figure 1**)
- BOTE, although hypothesized to be a potential valuable clinical indicator in the resolution of MC, has never been prospectively studied

Figure 1: Patient with BOTE sign



Figure 2: Representative Patient With BOTE Sign Associated With Berdazimer Gel 10.3% Treatment (treatment week and lesion count)



## Objective

- The primary objective was to conduct a pre-defined analysis of the association between presence of baseline BOTE+ lesion and MC lesion reduction including complete clearance in patients enrolled in B-SIMPLE4.
- Exploratory objective was to understand berdazimer's effect on BOTE and MC lesion resolution

## Methods

- BOTE sign was evaluated in subjects with MC aged ≥6 months who participated in B-SIMPLE 4, a 12-week, randomized, double-blind, vehicle-controlled clinical study investigating topical NO-releasing berdazimer gel 10.3% versus vehicle<sup>11</sup> (**Figures 2,3, 4**)
  - BOTE sign was determined using prespecified criteria (**Table 1**) through 12 weeks
  - Patients were prospectively stratified based on baseline (BL) BOTE status (BOTE+ = 1, 2, 3, 4 vs BOTE- = 0) (**Table 1**)
  - A pre-defined analysis of the association between presence of BL BOTE+ lesion and MC lesion reduction including complete clearance

Table 1: BOTE Inflammation Score

Score	Global Assessment	Description
0	No inflammation	No evidence of local inflammation
1	Mild	Minimal erythema and/or edema
2	Moderate	Definite erythema and/or edema with or without hemorrhagic crusting
3	Severe	Erythema and edema with definite hemorrhagic crusting
4	Very severe	Strong reaction spreading beyond the treated area, bullous reaction, erosions

Figure 3: Berdazimer Sodium and SB206 (berdazimer 10.3% gel) Application Using Dosing Guide

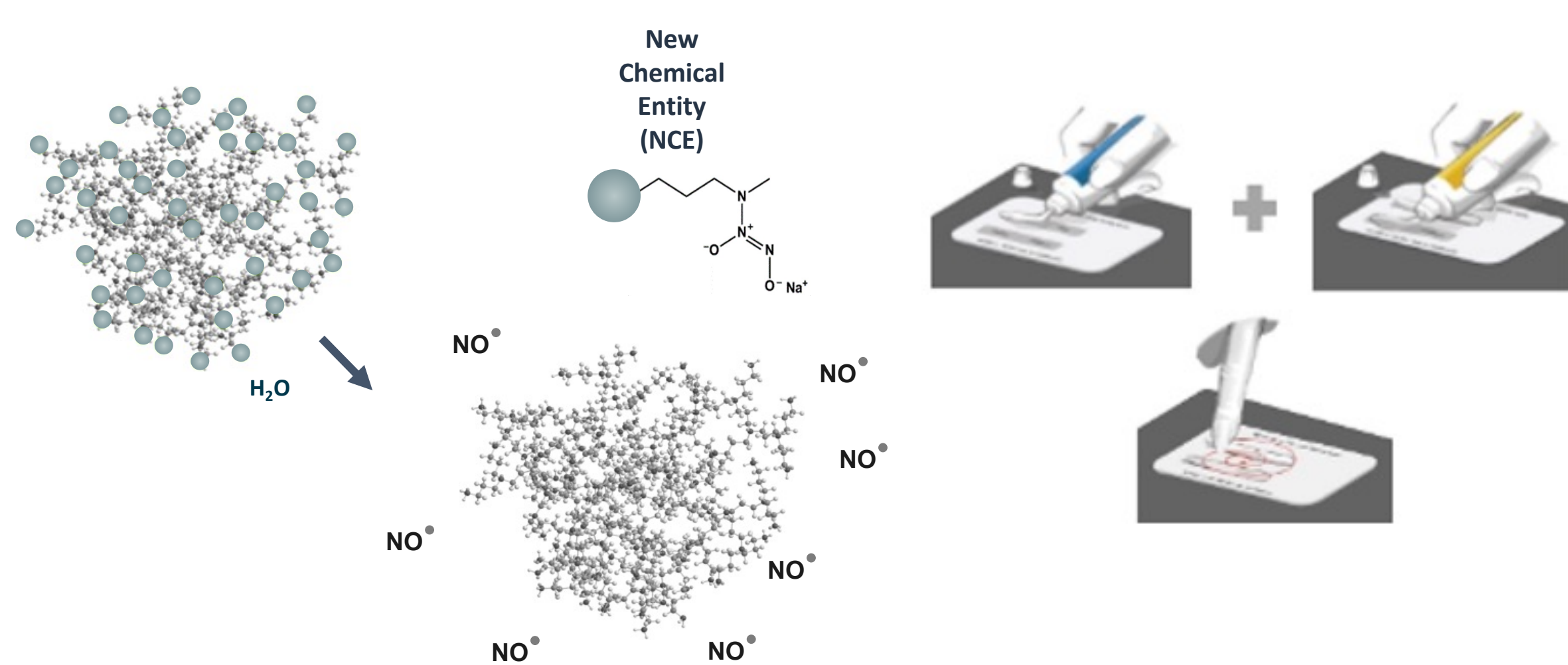
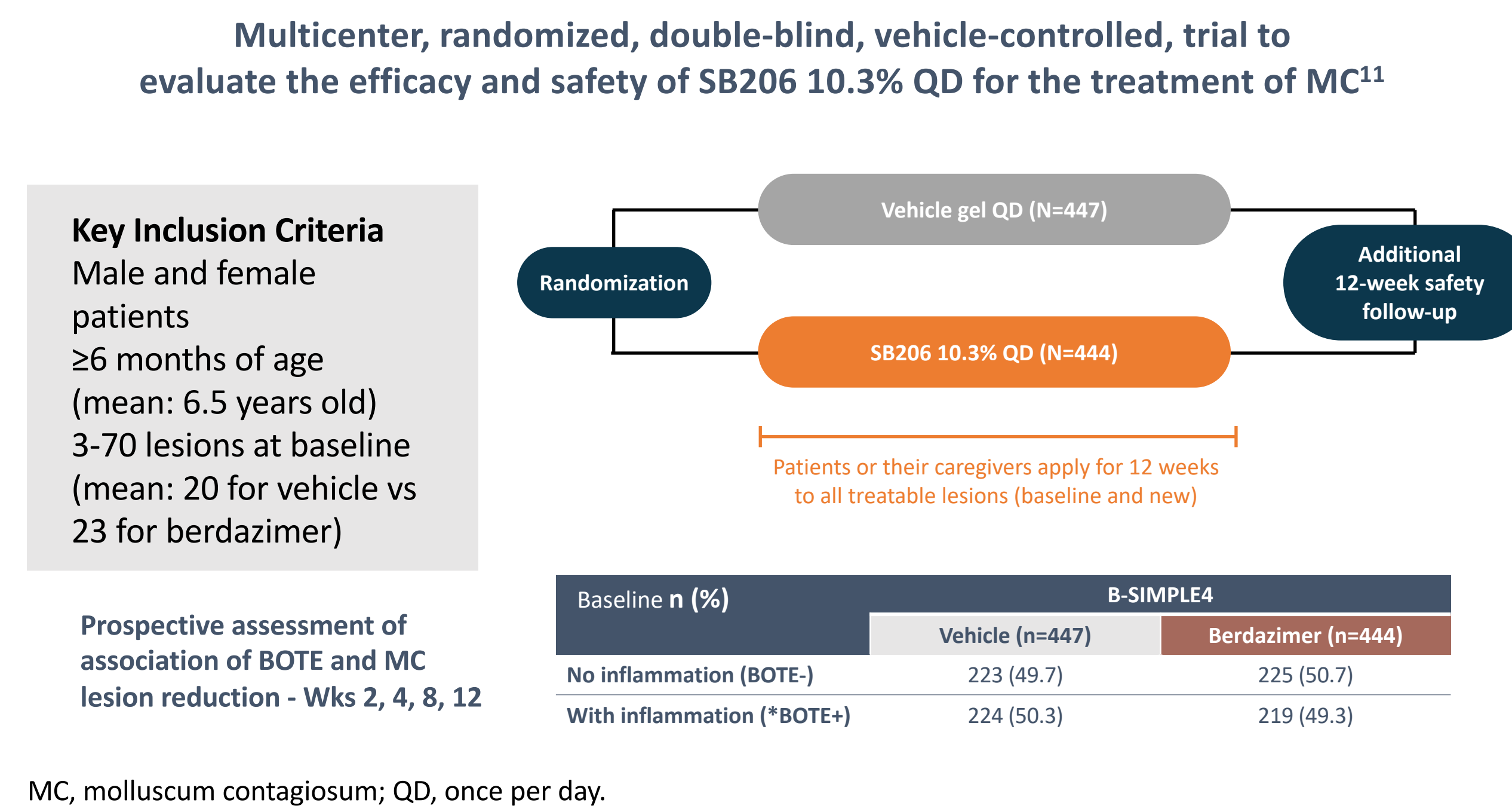


Figure 4: Study Design



## Results

- B-SIMPLE4 enrolled 447 patients in the vehicle group and 444 in the berdazimer (**Table 2**)
  - BOTE sign was evaluated in all individuals participating in B-SIMPLE4 (**Figure 2**)
- Treatment assignment was well balanced within BL BOTE status:
  - Of 447 patients randomized to vehicle, 50.3% were BOTE+ and 49.7% were BOTE-;
  - Of 444 patients randomized to berdazimer (active), 49.3% were BOTE+ and 50.7% were BOTE-.
- Of all patients that were BOTE- at BL, a higher proportion of patients in the active arm became BOTE+ by Week 2 vs the vehicle arm: 141/225 (66.7%) vs 75/223 (33.6%) (**Figure 5**)
- MC lesion counts at Week 12 decreased from BL in both treatment groups at a higher level for BOTE+ vs BOTE- patients (mean±SE); (**Figure 6**)
  - vehicle arm: 44.4±4.5% BOTE+ vs 21.2±4.6% BOTE- (p<0.0001)
  - active arm: 65.6±4.2% BOTE+ vs 59.9±4.2% BOTE- (p=0.233)
- At Week 12, a similar pattern was observed for patients achieving complete clearance:
  - vehicle arm: 56 (25.0%) BOTE+ vs 32 (14.3%) BOTE- (p=0.0043)
  - active arm: 85 (38.8%) BOTE+ vs 59 (26.2%) BOTE- (p=0.0043) (**Table 3**)
- A higher proportion of patients failed to initiate BOTE during the study in the vehicle arm vs the active arm; 73 (16.3%) vs 33 (7.4%), indicating over 80% of patients would present BOTE during the disease course. Patients who never developed BOTE in the vehicle group did not show lesion reduction at Week 12 (**Figure 7**).
- Berdazimer's effect on BOTE may start as early as Week 2 (**Figure 5**). An exploratory analysis using week 2 BOTE status (BOTE-wk2 vs BOTE-wk2) produced results consistent with Baseline BOTE, and demonstrated berdazimer decreased MC lesions regardless BOTE status. BOTE positivity at week 2 in the vehicle group resulted in a greater reduction of percent lesion count vs. BOTE - wk 2 vehicle (**Figure 8**).

Table 2: Study Populations and Study Discontinuation

	B-SIMPLE4	
	Vehicle	Berdazimer 10.3%
ITT population,* n	447	444
BOTE+ at BL	224	219
BOTE+ at Week 2	240	316
BOTE+ at anytime during the study	374	411
<b>Disposition</b>		
Completed 12 weeks	400 (89.5)	394 (88.7)
Discontinued Study (by week 24) <sup>a</sup>	70 (15.7)	67 (15.1)
Adverse Events	3 (0.7)	5 (1.1)
Lost to follow-up	46 (10.3)	43 (9.7)
Physician decision	0	0
Withdrawal by patient/caregiver	21 (4.7)	19 (4.3)
Completed Study (24 weeks)	377 (84.3)	377 (84.9)

\*All randomized patients.

Figure 5: Proportion of Patients Who Developed BOTE Over Time was Higher with Berdazimer Gel 10.3% vs Vehicle

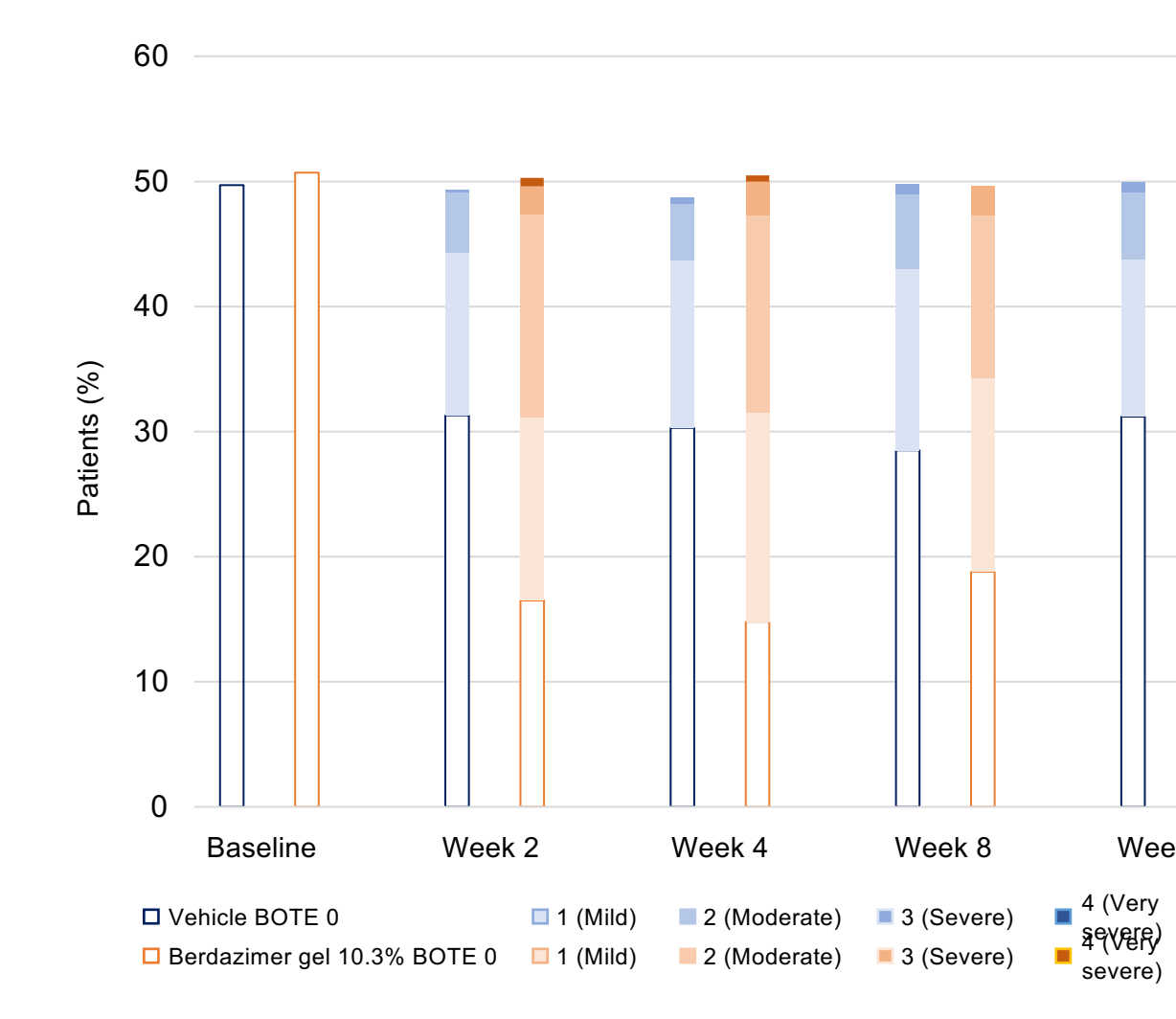


Figure 6: Rapid Reduction of Lesion Counts in Patients Who Were BOTE+ at Baseline—Time Course

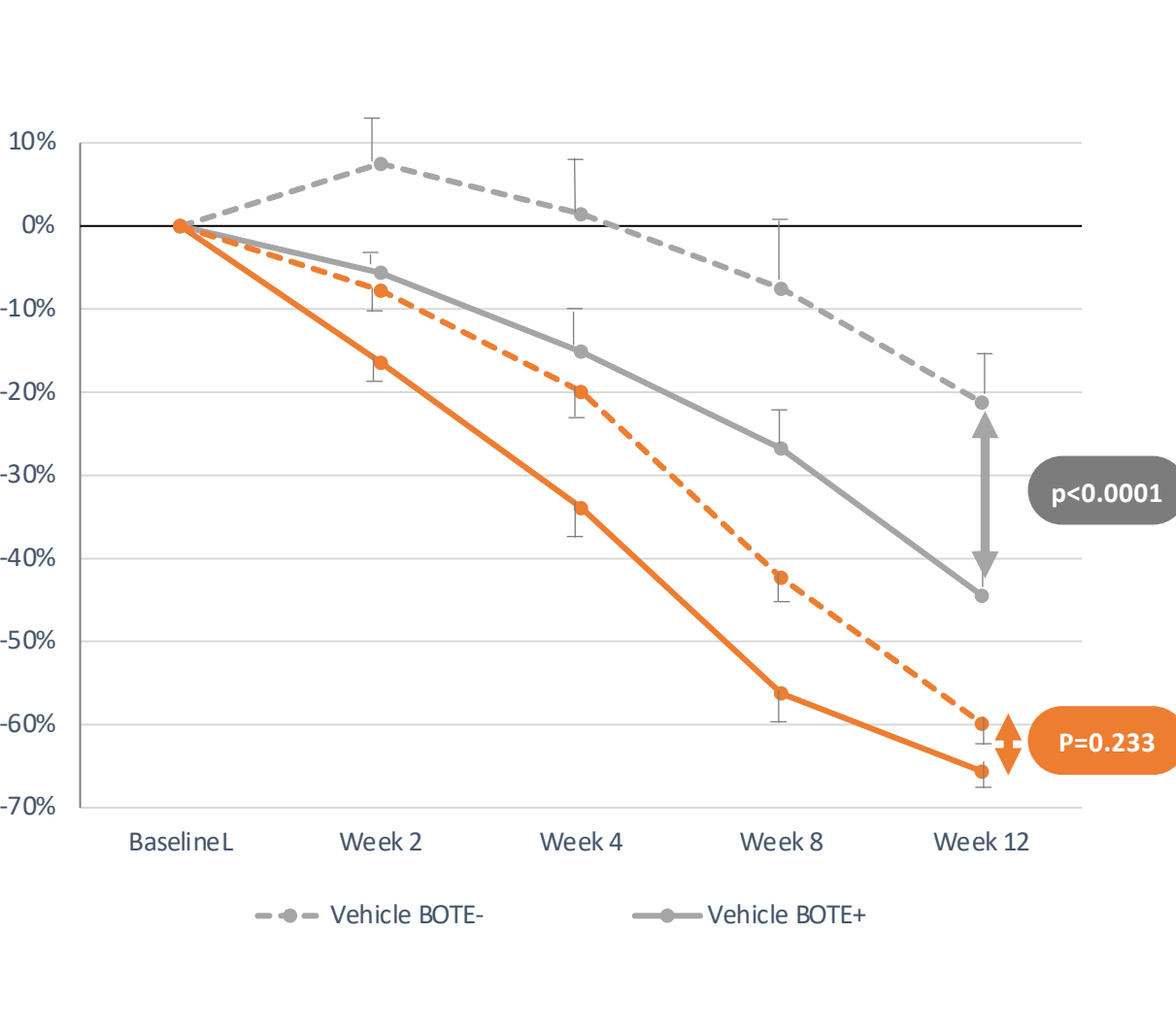


Table 3: Complete Clearance by Baseline BOTE Status

n/N (%)	B-SIMPLE4	
	Vehicle (n=447)	SB206 (n=444)
No inflammation (BOTE-)	32/223 (14.3)	59/225 (26.2)
With inflammation (BOTE+)	56/224 (25.0)	85/219 (38.8)

BOTE, beginning of the end.

Figure 7: BOTE Status and Impact of BOTE During Course of the Disease

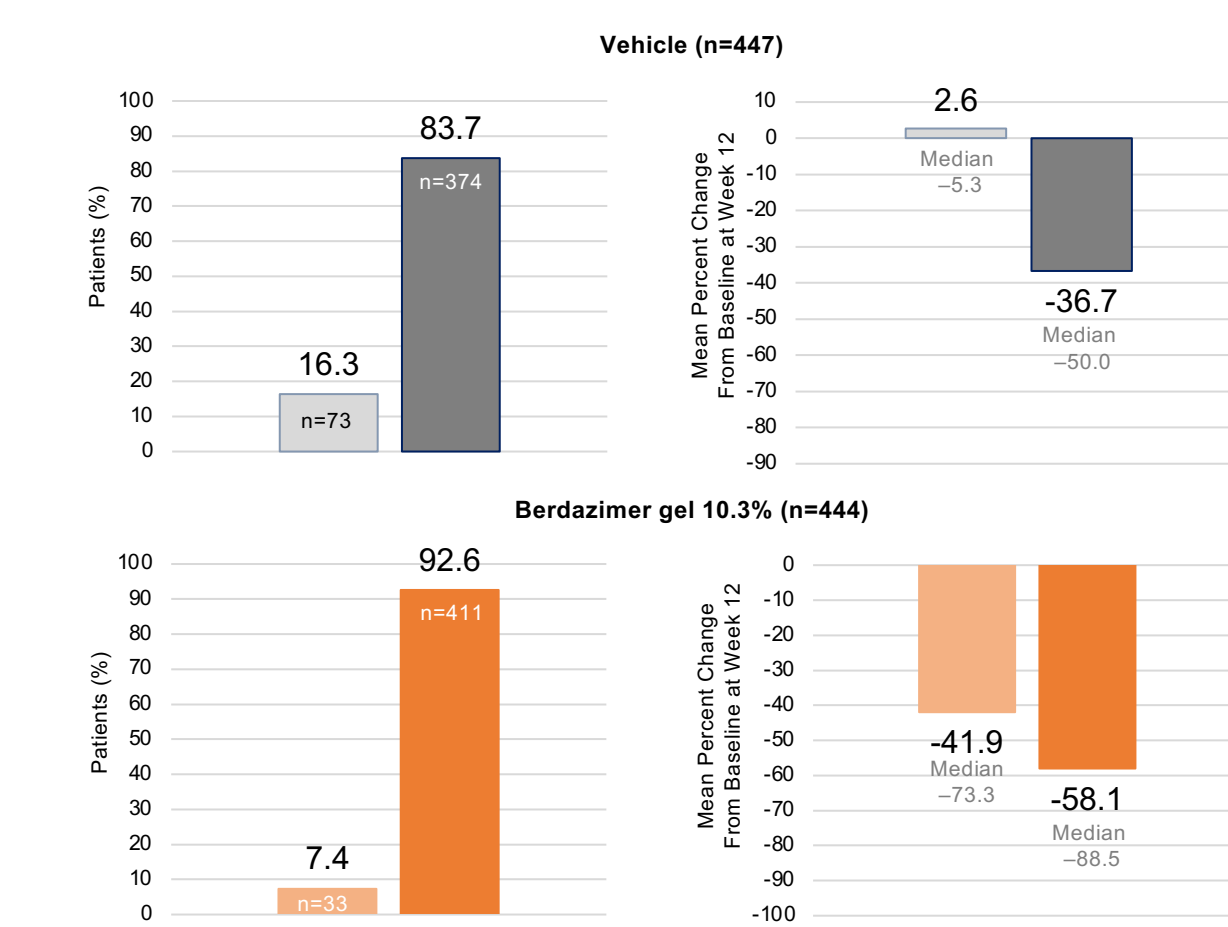
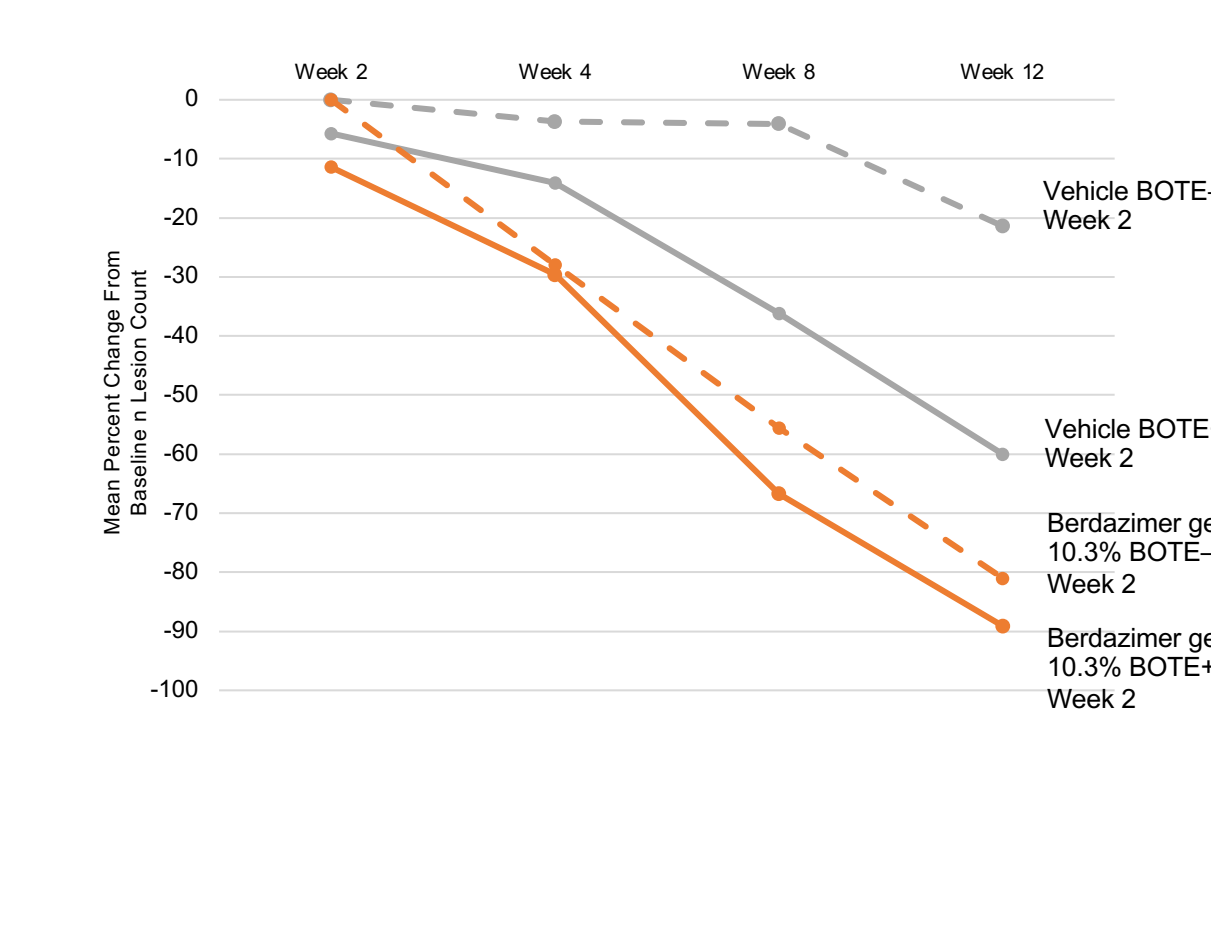


Figure 8: Reduction in Lesion Counts by BOTE Status at Week 2



## Conclusion

- The B-SIMPLE studies are the largest enrolling molluscum trial program to date where over 900 subjects received berdazimer 10.3% gel.
- First analysis to prospectively and systematically evaluate BOTE sign
- Demonstrated an over 80% incidence of the BOTE sign during the 12-week periods, regardless of active or vehicle treatment, but BOTE severity were greater and peaked at Week 4 with berdazimer
- BOTE+ patients consistently showed greater reduction than BOTE- patients
- Berdazimer showed greater reduction in lesion count than vehicle regardless of BOTE status at baseline
- BOTE sign is predictive of resolution of MC and may be a useful clinical indicator
- Patients who were both BOTE+ and treated with berdazimer had the greatest reduction in MC lesion count
- Berdazimer may trigger BOTE sign and hasten MC clearance. The mechanisms are unknown but may be due in part to immunomodulatory effect of NO as indicated by induction of BOTE, although other mechanisms may be involved including a possible direct antiviral effect.

## References

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- ClinicalTrials.gov. NCT04535531

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