Clinical Development Program of Novel Topical Nitric Oxide Releasing Medication Berdazimer Gel 10.3% for the Once-Daily Treatment of Molluscum Contagiosum

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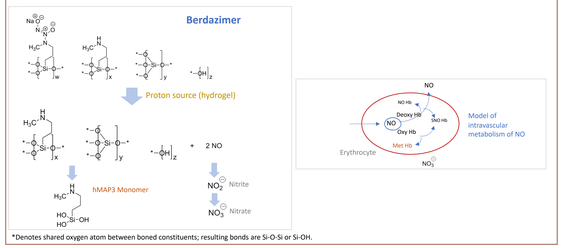
Synopsis

Topical Berdazimer Sodium Gel

- Nitric oxide (NO), an endogenous small molecule, provides localized immunity against foreign organisms by acting both as a short-lived immune modulator and a direct broad-spectrum antimicrobial agent[1]
- Until recently, the development of topical NO treatments was limited by the inability to store and safely deliver NO to the site of infection or inflammation[1]
- Berdazimer gel 10.3% (equivalent to berdazimer sodium 12%) is an investigational product that consists of 2 components: a gel containing berdazimer sodium coadministered with a hydrogel[2]
- Berdazimer sodium is a macromolecule composed of a polysiloxane backbone with covalently bound *N*-diazeniumdiolate NO donors[1]
- Coadministration with a hydrogel promotes NO release from the macromolecule at the time and site of application[1]

Figure 1: Berdazimer Sodium



*Denotes shared oxygen atom between boned constituents; resulting bonds are Si-O-Si or Si-OH.

Molluscum Contagiosum

- Molluscum contagiosum (MC) is a common poxvirus skin infection that primarily affects young children[3,4]
- Current treatment options used to resolve MC lesions include physical ablation of lesions by curettage, cryotherapy, or laser, or chemical destruction of involved skin via topically applied medications[5]
- As of April 2022, there are no FDA-approved topical treatments indicated for MC

Objective

- To review the clinical development program for berdazimer gel 10.3% as a potential therapy for MC

Table 1: Description of Key Studies

Study Design	Patients and Treatments	Primary and Secondary Objectives	Key Outcomes
Phase 1, open-label study assessing the safety, tolerability, and pharmacokinetics (PK) of once-daily berdazimer gel 10.3% under maximal use conditions in the treatment of MC (MC101)[6]	34 patients ≥6 months of age with >20 MC lesions All patients received berdazimer gel 10.3% QD	To evaluate the PK profile of hMAP3 monomer and nitrate during a 2-week PK period of once-daily berdazimer gel 10.3% application To evaluate safety and tolerability during a 12-week treatment including extension period	Minimal systemic absorption indicated by hMAP3 and nitrate Most frequent TEAEs were mild-moderate application-site pain (13/34, 47.1%) and erythema (13/34, 38.2%) Effectiveness: mean decrease from baseline in MC lesion counts, 68.4%
Phase 2, multicenter, randomized, double-blind, vehicle-controlled, ascending-dose study of berdazimer gel in patients with MC (MC201)[7] NCT03436615	256 patients ≥2 years of age with 3 to 70 MC lesions Randomized 3:1 (berdazimer:vehicle) to ascending, sequential berdazimer gel dose cohorts: 3.3% BID, 6.7% BID, 10.3% BID, 10.3% QD	To evaluate berdazimer gel efficacy vs vehicle for up to 12 weeks To evaluate safety/tolerability of berdazimer gel for up to 12 weeks To determine a safe and efficacious dosing regimen for future studies	Berdazimer gel 10.3% resulted in highest rate of complete lesion clearance (18/43, 41.9%), low rates of AEs (application-site erythema: 5/47, 10.6%), and no AEs leading to treatment discontinuation Berdazimer gel 10.3% QD selected for further evaluation in Phase 3
Phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study comparing the efficacy and safety of berdazimer gel 10.3% and vehicle once daily in the treatment of MC (NI-MC304; B-SIMPLE4)[8] NCT04535531	891 patients ≥6 months of age with 3 to 70 MC lesions Randomized 1:1 to berdazimer gel 10.3% or vehicle QD	To confirm the efficacy and safety of berdazimer gel 10.3% compared with vehicle applied once daily for up to 12 weeks	Statistically + clinically significant efficacy: complete clearance in 32.4% (144/444) of berdazimer 10.3% vs 19.7% (88/447) of vehicle patients ($P < 0.0001$) at week 12 Well tolerated: ≥1 TEAE in 43% (191/444) of berdazimer 10.3% vs 23% (103/447) of vehicle patients; most commonly mild application-site pain (last less than 30 min for most cases) and mild-moderate erythema

Methods

Figure 2: Phase 2 Berdazimer Gel Dose-finding Study Design[7]

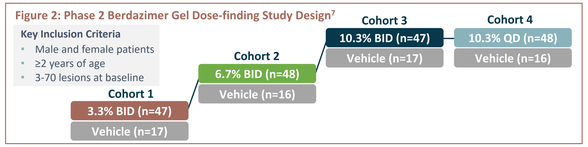
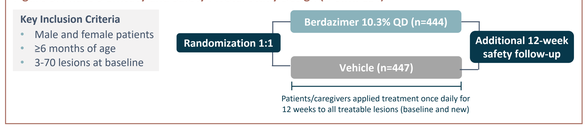


Figure 3: Phase 3 Efficacy and Safety Pivotal Study Design (B-SIMPLE4)[8]



Results

Table 2: Patient Disposition, Demographics, and Baseline Characteristics*

	Phase 1 PK[6]	Phase 2 Dose Finding[7]		Phase 3 Pivotal (B-SIMPLE4)[8]	
	Berdazimer 10.3% QD	Vehicle	Berdazimer 10.3% QD	Vehicle	Berdazimer 10.3% QD
ITT population, n	34	66	48	447	444
Safety population, n	34	66	47	447	444
Prematurely discontinued study, n (%)	5 (14.7)	5 (7.6)	4 (8.5)	70 (15.9)	67 (15.1)
Adverse event	0	0	0	3 (0.7)	5 (1.1)
Withdrawal by patient/caregiver	4 (11.8)	2 (3.0)	0	21 (4.7)	19 (4.3)
Lost to follow-up	1 (2.9)	3 (4.5)	4 (8.5)	46 (10.3)	43 (9.7)
Completed study, n (%)	29 (85.3)	61 (92.4)	43 (91.5)	377 (84.3)	377 (84.9)
Age, y, mean (range)	5.3 (2-12)	7.0 (2-16)	5.7 (2-11)	6.5 (1-49)	6.6 (1-48)
Female, n (%)	17 (50.0)	27 (40.9)	25 (52.1)	234 (52.3)	216 (48.6)
White, n (%)	33 (97.1)	58 (87.9)	44 (91.7)	382 (85.5)	387 (87.2)
Baseline lesion count, mean (range)	50.2 (21-212)	18.3 (3-70)	17.6 (3-69)	20.5 (3-69)	23.1 (3-70)

*Percentages for disposition data are based on safety populations; demographic and baseline characteristics are for ITT populations.

PK Analyses

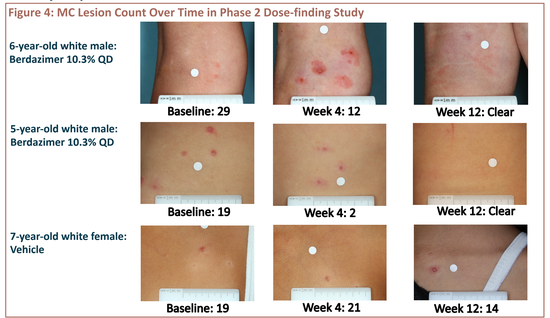
- Phase 1 maximal-use PK study in patients with MC[6]
  - No patients had quantifiable plasma hMAP3 concentrations at any timepoint on day 1 (Table 3)
  - 2 patients had quantifiable concentrations on day 15 (1 was borderline)
  - Nitrate levels remained flat throughout the 2-week PK period

Table 3: hMAP3 Concentrations in Phase 1 PK Study

PK Period Timepoint	hMAP3 Concentration (ng/mL)	Predose	Time Postdose (h)		
		0	1	3	6
Day 1	N	35	34	13	12
	N > LLOQ	0	0	0	0
	Mean	0	0	0	0
	Median (min, max)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Day 15	N	30	31	27	13
	N > LLOQ	1	1	2	1
	Mean	0.347	0.671	1.45	1.73
	Median (min, max)	0 (0, 10.4)	0 (0, 20.8)	0 (0, 33.9)	0 (0, 22.5)

Efficacy: Representative Patient Outcomes

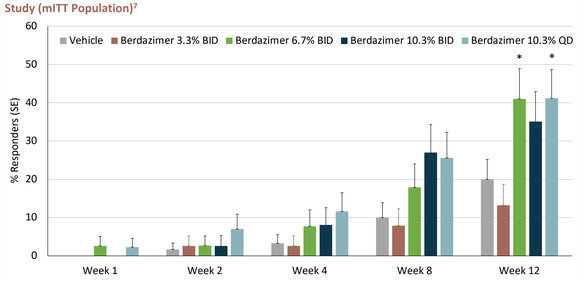
Figure 4: MC Lesion Count Over Time in Phase 2 Dose-finding Study



Efficacy: Primary Endpoint Analyses

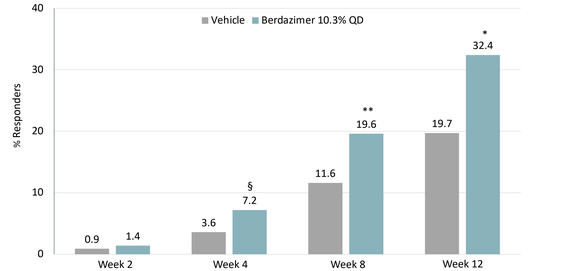
In both the phase 2 and 3 studies, complete MC clearance was defined as a patient having a lesion count of 0 at a visit.

Figure 5: Complete Clearance of All Molluscum Lesions at Each Treatment Visit in the Phase 2 Dose-finding Study (mITT Population)[7]



*P<0.05 vs vehicle.

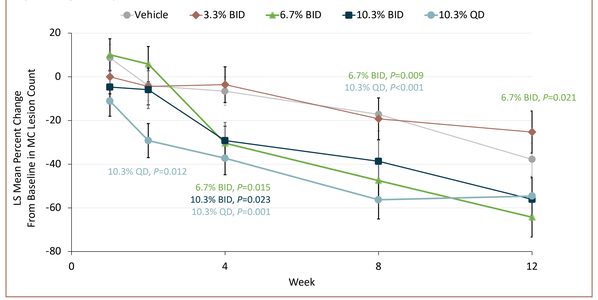
Figure 6: Complete Clearance of All Molluscum Lesions at at Each Treatment Visit in the Phase 3 Pivotal Study (B-SIMPLE4, ITT Population)[8]



*P<0.0001; **P=0.001; §P=0.01 vs vehicle.

Efficacy: Secondary Endpoint Analyses

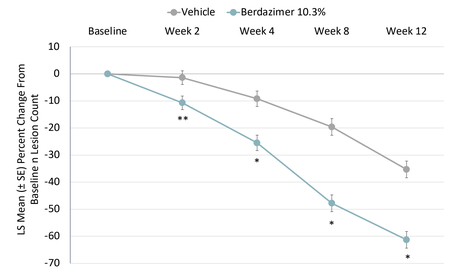
Figure 7: Molluscum Lesion Count Mean Percent Change From Baseline in the Phase 2 Dose-Finding Study (mITT Population)[7]



Abbreviations

AEs, adverse events; AUC, area under the concentration–time curve; BID, twice daily; C_{max}, maximum plasma concentration; ECG, electrocardiogram; hMAP3, hydrolyzed N-methylaminopropyl-trimethoxysilane; ITT, intention to treat; LC/MS-MS, liquid chromatography tandem mass spectrometry; LLOQ, lower limit of quantitation; mITT, modified ITT; LS, least squares; QD, once daily; SE, standard error; TEAEs, treatment-emergent AEs; T_{max}, time to C_{max}.

Figure 8: Molluscum Lesion Count Mean Percent Change From Baseline in the Phase 3 Pivotal Study (B-SIMPLE4, ITT Population)[7]



*P<0.0001; **P<0.001 vs vehicle.

Safety Analyses

Table 3: Adverse Events From Safety Populations

AE, n (%)	Phase 1 PK[6]	Phase 2 Dose Finding[7]		Phase 3 Pivotal (B-SIMPLE4)[8]	
	Berdazimer 10.3% QD (n=34)	Vehicle QD (n=66)	Berdazimer 10.3% QD (n=47)	Vehicle QD (n=447)	Berdazimer 10.3% QD (n=444)
Patients with ≥1 TEAE	16 (47.1)	19 (28.8)	19 (40.4)	103 (23.0)	191 (43.0)
Mild	5 (14.7)	13 (19.7)	13 (27.7)	75 (16.8)	108 (24.3)
Moderate	8 (23.5)	6 (9.1)	1 (2.1)	26 (5.8)	78 (17.6)
Severe	3 (8.8)	0	5 (10.6)	2 (0.4)	5 (1.1)
3 most common TEAEs in B-SIMPLE4					
Application-site pain	13 (38.2)	0	4 (8.5)	23 (5.1)	83 (18.7)
Application-site erythema	6 (17.6)	0	5 (10.6)	6 (1.3)	52 (11.7)
Application-site pruritus	0	0	2 (4.3)	5 (1.1)	33 (7.4)

Conclusions

- **PK:** Topical application of berdazimer gel 10.3% is associated with minimal systemic absorption as indicated by plasma hMAP3 and nitrate levels[6]
- **Phase 2 dose-finding study:** Berdazimer gel 10.3% applied once daily was selected as the best regimen for phase 3 development, balancing lesion clearance and tolerability[7]
- **Efficacy:** The phase 2 dose-finding and phase 3 B-SIMPLE4 studies both demonstrated clinically relevant and statistically significant differences between berdazimer gel 10.3% once daily and vehicle in the percentage of patients achieving complete clearance of all molluscum lesions at week 12[7,8]
  - The phase 2 study demonstrated complete clearance in 41.9% (18/43) of berdazimer gel 10.3% once daily vs 20% (12/60) of vehicle patients (P<0.05) at week 12[7]
  - B-SIMPLE4 demonstrated complete clearance in 32.4% (144/444) of berdazimer gel 10.3% once daily vs 19.7% (88/447) of vehicle patients (P<0.0001) at week 12[8]
  - In B-SIMPLE4, berdazimer gel 10.3% showed a rapid treatment response, with statistically significantly greater decreases from baseline in lesion count vs vehicle as early as week 2 and further decreases through week 12[8]
- **Safety and tolerability:** Berdazimer gel 10.3% was generally well-tolerated throughout the clinical development program[6-8]
  - The most common TEAEs in Phase 1, 2, and 3 studies were mild application-site pain and mild-moderate erythema[6-8]
  - In B-SIMPLE4, 1.1% of berdazimer 10.3% patients (5/444) and 0.7% of vehicle patients (3/447) withdrew from the study due to AEs[8]
- **Overall**: Topical berdazimer gel 10.3% applied once daily by patients or caregivers is consistently well-tolerated and significantly more effective than vehicle in reducing MC lesions with minimal systemic exposure[6-8]

References

1. Stasko N, et al. *Antimicrob Agents Chemother*. 2018;62(7):e01026-17. **2.** Maeda-Chubachi T, et al. *JID Innov*. 2021;1:100019. **3.** Olsen JR, et al. *Fam Pract*. 2014;31(2):130-136. **4.** Chen X, et al. *Lancet Infect Dis*.2013;13(10):877-888. **5.** van der Wouden JC, et al. *Cochrane Database Syst Rev*. 2017;5:CD004767. **6.** Cartwright M, et al. *J Drugs Dermatol*. 2022. Submitted. **7.** Hebert AA, et al. *J Am Acad Dermatol*. 2020;82(4):887-894; **8.** Browning JC, et al. *JAMA Dermatology*. 2022. Submitted.

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