TWO PHASE 1 CLINICAL STUDIES EVALUATING THE CUMULATIVE IRRITATION AND CONTACT SENSITIZATION ON INTACT AND ABRADED SKIN OF MBN-101, A NOVEL ANTIMICROBIAL PRODUCT IN DEVELOPMENT FOR DIABETIC FOOT ULCER INFECTION

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ABSTRACT

MBN-101, a novel product in a new class of antimicrobial compounds with unique, broad-spectrum activity against bacteria and biofilm, is in clinical development for the topical treatment of chronic diabetic foot ulcer infections and local/intrasurgical treatment of orthopedic infections. Two standardized IRB-approved (Gallatin Institutional Review Board) Phase 1 clinical studies were performed according to FDA/CDER guidance to investigate whether repeated daily application with MBN-101 to the intact and abraded skin of healthy volunteers caused local irritation or allergic contact sensitization. The 30-subject skin irritation study demonstrated that repeated (daily) application, resulting in continuous topical exposure to MBN-101 at five concentrations (25 to 2500 µg/mL) for 21 days, produced significantly ($p<0.05$) less skin irritation than the positive control (0.1% sodium lauryl sulfate, SLS) and was not significantly ($p<0.05$) different from vehicle control or negative control (0.9% NaCl). Exposed sites were visually evaluated daily, based on a standardized scoring scale of skin condition (erythema, edema, papules). The sum of daily scores yielded a total cumulative score (TCS) for each subject. The mean of TCSs from all 30 subjects resulted in scores for intact/abraded skin of 17.5/23.6 for 0.9% NaCl; 32.3/43.7 for SLS; 18.1/22.9 for vehicle control; and 14.7-17.5/18.2-20.4 for all MBN-101 concentrations. MBN-101 (2500 µg/mL) was subsequently evaluated in a 209-subject skin sensitization study comprised of 9 sequential applications for 48-72 hours each for 21 days of continuous exposure (induction phase), a 2-week rest phase with no MBN-101 exposure, and a final 48-hour re-exposure (challenge phase). MBN-101 was non-irritating and no sensitization was observed on intact and abraded skin over a 72-hour period following the single re-exposure. These data demonstrate very low potential for irritation and sensitization, supporting the safety and further development of MBN-101 for treatment of chronic wounds including diabetic foot ulcer infection and other topical/local infectious conditions.

MBN-101

- MBN-101 is BisEDT formulated as topical aqueous suspension.
- Bismuth-1,2-ethanedithiol (BisEDT) is a member of the bismuth-thiols, a novel antibiotic class.
- BisEDT is a broad-spectrum antimicrobial, antibiofilm agent with activity against many antibiotic-resistant organisms (e.g., MRSA, vancomycin-resistant Enterococci, and MDR-*P. aeruginosa*) which led to Qualified Infectious Disease Product (QIDP) designation from FDA for 3 clinical indications.
- BisEDT has low propensity for development of resistance.

BisEDT has potent broad-spectrum activity against pathogenic bacteria

Gram-positive Aerobes			Gram-Negative Aerobes			Anaerobes		
Organism (N)	MIC Range	$MIC_{50/90}$	Organism (N)	MIC Range	$MIC_{50/90}$	Organism (N)	MIC Range	$MIC_{50/90}$
S. aureus (155)	≤0.03-1	0.25/0.5	*E. coli* (55)	0.5-2	2/2	Gram-positive (33)	≤0.015-4	1/4
S. epidermidis (100)	≤0.03-0.25	0.06/0.12	*K. pneumoniae* (58)	1-8	4/8	Clostridium spp. (10)	0.25-4	2/4
S. pyogenes (53)	0.03-0.5	0.25/0.5	*P. aeruginosa* (56)	0.5-8	1/4	*P. acnes* (9)	≤0.03-4	1/-
S. agalactiae (55)	0.25->16	8/16	*A. baumannii* (29)	0.5-4	2/2	Peptostreptococcus spp. (4)	0.25-4	-/-
S. pneumoniae (7)	0.25-1	1/-						
E. faecalis (104)	0.12-2	1/2				Gram-negative (19)	≤0.015-4	0.25/2
E. faecium (102)	0.5-2	1/2				Bacteroides spp. (9)	0.03-4	0.5/-

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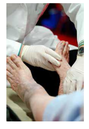
Clinical Indications for BisEDT



Topical/Local Administration

- Diabetic foot ulcer infections
- Orthopedic device-related infections
- These conditions are typically polymicrobial biofilm infections, caused by aerobic Gram-positive cocci (*S. aureus*, MRSA), Gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), and anaerobes

Inhaled BisEDT

- Chronic respiratory infections

STUDY DESIGN

In pre-IND discussions, FDA-CDER required two safety studies for Phase 2 topical and/or local/intrasurgical orthopedic use:

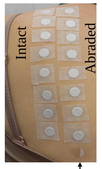
- Skin irritation potential evaluation[1, 2], using ≥ 30 human subjects (intact & abraded skin); and
- Skin sensitization potential evaluation[1, 2], using ≥ 200 human subjects (intact & abraded skin)

SKIN IRRITATION - MBN-101-101

- 21-day continuous treatment on intact & abraded (tape stripping) skin
  - MBN-101 drug product formulated with 5 concentrations of BisEDT (25, 75, 250, 750, & 2500 µg/mL)
  - MBN-101 Vehicle Control
  - Negative Control (0.9% Saline)
  - Positive Control (0.1% sodium lauryl sulfate)
- Test products applied daily via patches
- Skin condition scored daily by an evaluator blinded to randomized product assignments on skin

SCORE	DESCRIPTION
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3*	Erythema and papules
4*	Definite edema
5*	Erythema, edema, and papules
6†	Vesicular eruption
7†	Strong reaction spreading beyond test site

* Product application on a site discontinued
† Adverse Event; subject discontinued from testing



Abraded Skin sites produced by tape stripping with D-Squame Sampling Discs

SKIN SENSITIZATION - MBN-101-102

Induction Phase

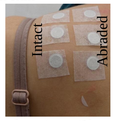
- 21-day continuous treatment on intact & abraded (tape stripping) skin
  - MBN-101 drug product formulated with 2500 µg/mL BisEDT (highest non-irritating concentration)
  - MBN-101 Vehicle Control
  - Negative Control (0.9% Saline)
- Test products applied 3 times/week via patches
- Skin condition scored at each application by an evaluator blinded to randomized product assignments on skin

Rest Phase

- No treatment for 2 weeks to allow for adaptive immune response (sensitization)

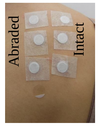
Challenge Phase

- 48-hour re-exposure to test products from Induction Phase
- Test products applied via patches (to opposite side of back) and removed after 48 hours
- Skin condition scored at 30 minutes, 24 hours, 48 hours, & 72 hours after patch removal, by an evaluator blinded to randomized product assignments on skin



Induction Phase

Rest Phase

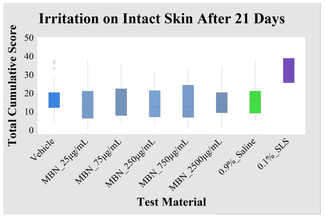


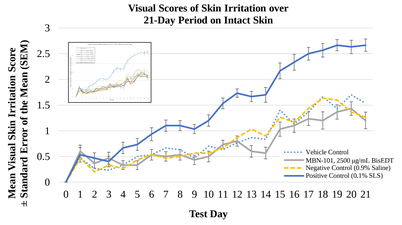
Challenge Phase

RESULTS: SKIN IRRITATION - MBN-101-101

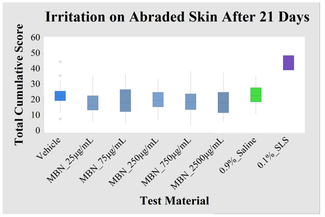
- Sample Size = 30 subjects; 5 male (17%) / 25 female (83%). There were no adverse events related to MBN-101 or other test products.

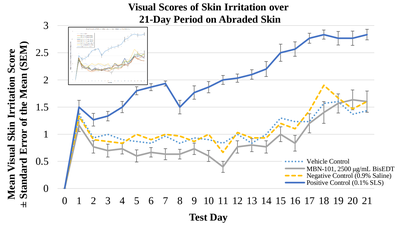
Intact Skin





Abraded Skin





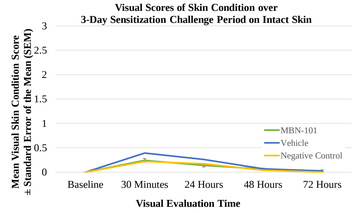
- **Even at the highest MBN-101 dosage (2500 µg/mL BisEDT), no significant irritation potential was observed on intact and abraded skin after subjects were exposed to MBN-101 for 21 days.**
- **All five concentrations of MBN-101 had similar irritation potential as the MBN-101 Vehicle Control and the Negative Control (0.9% saline).**
- **The Positive Control showed a significantly higher irritation potential on both intact and abraded skin than the MBN-101 Vehicle Control, Negative Control and all concentrations of MBN-101.**
- **The Positive and Negative Controls produced irritation scores consistent with the historical data collected at BSLI for these types of studies, providing internal validation of the study.**

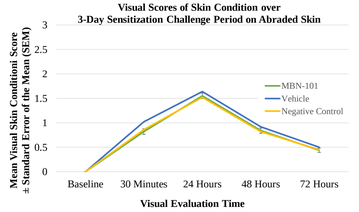
CONCLUSION

No significant irritation potential was observed for MBN-101 on intact or abraded skin.

RESULTS: SKIN SENSITIZATION - MBN-101-102

- Sample Size = 207 subjects; 90 male (43%) / 117 female (57%). There were no adverse events related to MBN-101 or other test products.





- **MBN-101 demonstrated a profile similar to the negative control (0.9% saline).**
- **A typical sensitization (allergic contact dermatitis) response is characterized by a delayed skin reaction (24-72 hours) upon re-exposure to the challenge substance and generally increases in degree of severity. This type of delayed response involves a cell–mediated reaction.**
- **The minimal to mild irritant response observed in the Challenge Phase is consistent with contact dermatitis associated with skin abrasion, rather than sensitization (allergic contact dermatitis). This skin irritation response is characterized by an immediate skin reaction and then gradually decreases in degree of severity over the 72-hour period.**

CONCLUSION

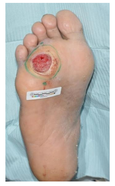
No sensitization potential was observed for MBN-101 on intact or abraded skin.

Microbion Development Pipeline

The safety and tolerability of BisEDT formulated as MBN-101 demonstrated in these Phase 1 Skin Irritation and Skin Sensitization clinical studies supported the advancement of MBN-101 into clinical studies for treatment of diabetic foot ulcer and orthopedic device-related infections.

MBN-101 Clinical Studies:

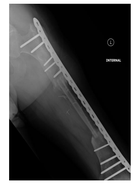
Topical Treatment of Diabetic Foot Infections (DFI)



A Phase 1b/2a Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of Adjunctive Treatment with Topically Applied MBN-101 in Subjects with Moderate to Severe Diabetic Foot Infection (DFI)

- ClinicalTrials.gov Identifier: NCT02723539
- Study was completed in 2018

Local Treatment of Post-Surgical Orthopedic Infections



A Phase 2a Randomized, Single-Blind, Placebo-Controlled, 12-week Escalating Dose Study to Assess the Safety, Tolerability and Clinical Activity of 3 Concentrations of Locally Applied MBN-101 to Infected Bone Sites

- ClinicalTrials.gov Identifier: NCT02436876
- Study was completed in 2018

References

[1] - U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry. Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products. December 1999.
[2] - Memorandum Reference Number OGD #06-0100. 2006. Guidance superseding Guidance for Industry: Skin Irritation and Sensitization Testing of Transdermal Drug Products (1999). D.P. Connor, Pharm. D. Div. Bioequiv., Off. of Generic Drugs, CDER. 9 pp.

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