GR-10

Safety, Tolerability and Efficacy of Adjunctive Treatment with Topically Applied MBN-101 in Subjects with Moderate or Severe Diabetic Foot Infection (DFI): A Phase 1 Randomized, Double-blind, Placebo-controlled Study

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ABSTRACT

Healing of diabetic foot ulcers is often compromised by microbial infections that are resistant to available antibiotics. New broad-spectrum topical antimicrobials may have potential to improve clinical outcomes for these infections.

We conducted a phase 1 randomized, double-blind, placebo-controlled, multicenter study evaluating MBN-101, a topical formulation of the novel broad-spectrum, anti-biofilm/anti-microbial BisEDT, for treating infected diabetic foot ulcers. We enrolled subjects into escalating dose cohorts of MBN-101 (150, 375, 750 µg/mL BisEDT; 3, 7.5, 15 µg/cm^2 wound area), at a ratio of 3:1 MBN-101 to placebo. Investigators topically applied MBN-101 or placebo to the ulcers 3x/week, for 2-3 weeks as an adjunct to debridement and systemic antibiotic therapy. We evaluated subjects at end of treatment (EOT), then at test of cure (TOC) and end of study (EOS) visits 2 and 4 weeks after EOT, respectively. Assessments included adverse events, systemic exposure to BisEDT, wound area (by 3D digital photography), and clinical resolution of infection signs/symptoms.

Among 52 subjects treated, 12 received 3 µg/cm^2, 12 7.5 µg/cm^2 , 15 15 µg/cm^2 and 13 were in the placebo group. MBN-101 was well tolerated. There was no evidence of BisEDT systemic exposure and no differences in resolution of infection signs/symptoms across treatment groups. At EOT, 42% of all MBN-101 subjects had a >50% reduction in wound size vs 23% of placebo subjects (p = 0.32). A >50% wound size reduction occurred in a greater proportion of MBN-101 subjects than placebo at TOC (59% vs 39%, p = 0.33) and EOS (61% vs 42%, p = 0.33). Target ulcer-related amputation in the pooled MBN-101 treatment groups were 2.6% vs 15.4% for placebo (p = 0.15).

These data suggest, that topical MBN-101 may be beneficial in reducing wound size in diabetic persons with an infected foot ulcer.

INTRODUCTION

Systemic antibiotics administered alone are frequently ineffective for the treatment of chronic DFIs, in part because altered perfusion hinders effective and timely delivery of antibiotics to the ulcer site, as well as the presence of biofilm. Topical administration of MBN-101, in adjunct to standard of care, is expected to more effectively address bacterial presence DFIs and provide an improved environment for wound size reduction and DFI resolution.

ABOUT MBN-101

- **MBN-101 is BisEDT (Bismuth-1,2-ethanedithiol) formulated as topical aqueous suspension**
- **BisEDT is a broad-spectrum antimicrobial, antibiofilm agent with activity against many antibiotic-resistant organisms (e.g., MRSA, VRE, and MDR-*P. aeruginosa*)**
- **BisEDT has a unique mechanism of action (MOA)**
- **There are no known instances of cross-resistance and BisEDT has very low propensity for development of resistance**
- **The WHO recommended INN for BisEDT is *pravibismane,* the first member of a novel antibiotic class**

STUDY OBJECTIVES AND DESIGN

Primary objective: Evaluate the safety and tolerability of MBN-101 as adjunct to standard of care in subjects with a moderate to severe DFI.

Secondary objectives: Evaluate the effect of adjunctive MBN-101 on: wound healing; prevention of lower extremity amputation; and resolution of infection. Assessments were conducted at End of Treatment (EOT), Test of Cure (TOC, 2 weeks after EOT), and End of Study (EOS, 4 weeks after EOT).

- The study was not powered to demonstrate statistical efficacy.

Dosing and Treatment Regimen:

MBN-101: 3 dose cohorts of 150, 375, and 750 µg/mL BisEDT (pravibismane) in drug vehicle resulting in target doses of 3, 7.5, and 15 µg/cm^2, respectively; **Placebo:** drug vehicle

- Subjects received topical MBN-101 or placebo, 3 times per week, for 2 to 3 weeks (i.e., 6 to 9 doses) at the discretion of the investigator and based on the resolution of infection.
- All subjects received: systemic antibiotic treatment until the resolution of infection; sharp debridement at baseline and weekly thereafter; off-loading through EOS.

Key Inclusion Criteria:

- Diabetes mellitus and a moderately or severely infected skin ulcer located on or distal to the malleolus that was >4 weeks old
- Received no more than 36 hours of antibiotic therapy prior to enrollment unless there was evidence of failure
- Adequate arterial perfusion in the affected limb

Table 1: Selected demographic and baseline characteristics for all randomized subjects

Demographics/Characteristics Category/Statistic	Total (N=53)
Age (years) (mean [SD])	52.8 (9.01)
Age group (n [%])	
<65	49 (92.5)
≥65	4 (7.5)
Gender (n [%])	
Male	45 (84.9)
Female	8 (15.1)
BMI (kg/m^2) (mean [SD])	32.64 (6.794)
Documented DFU duration (days) (mean [SD])	186.4 (244.92)
8-Item Wound Score (mean [SD])	14.3 (3.58)

Key Exclusion Criteria:

- Involvement of bone (i.e., osteomyelitis)
- More than 1 concurrent, infected, DFU
- The area of the DFU was >200 cm^2

SAFETY RESULTS

- No TEAEs and SAEs occurring in the study were considered related to study drug [Table 2] and no subjects died in this study.

Table 2: Overview of Adverse Events – Safety Population

	3 µg/cm^2 (N=12) n (%)	7.5 µg/cm^2 (N=12) n (%)	15 µg/cm^2 (N=15) n (%)	Placebo (N=13) n (%)
All TEAEs	7 (58.3)	4 (33.3)	11 (73.3)	5 (38.5)
Drug-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All SAEs	2 (16.7)	1 (8.3)	1 (6.7)	2 (15.4)
Drug-related SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation of study drug due to TEAEs	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)

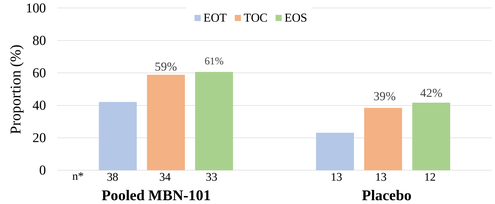
- Most commonly reported TEAEs were DFI, diabetic foot, cellulitis, and osteomyelitis; and the majority of TEAEs and SAEs were considered to be mild or moderate in severity.
- No evidence of BisEDT (pravibismane) systemic exposure or clinically meaningful changes from baseline for chemistry and hematology lab parameters were found, and the majority of vital signs and physical examination findings were within normal limits.
- There were no clinically significant abnormalities in 12-lead ECG findings.

EFFICACY RESULTS

Ulcer Size

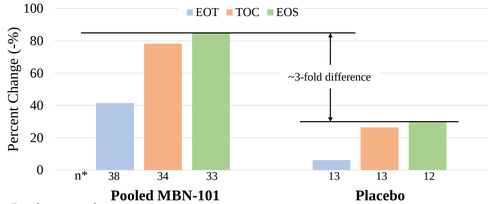
- Although the study was not powered to demonstrated statistical efficacy, a numerical trend indicating >50% wound size reduction occurred in a greater proportion of pooled MBN-101 treated subjects than placebo at TOC (59% vs 39%) and EOS (61% vs 42%) [Figure 1].
- The median percent reduction in ulcer wound size from baseline was approximately 3-fold higher in the pooled MBN-101 group compared to placebo [Figure 2].

Figure 1: Proportion of Subjects with a >50% Reduction in Wound Size by Visit – MITT Population



*n was the number of subjects with both baseline and postbaseline measurements.

Figure 2: Median Percent Change from Baseline of Ulcer Wound Size by Visit – MITT Population



*n was the number of subjects with both baseline and postbaseline measurements.

Lower Extremity Amputations

- 2 of 13 (15.4%) placebo subjects underwent an amputation related to the target infected ulcer compared to 1 of 39 (2.6%) of all MBN-101 treated subjects, an approximately 6-fold reduction [Table 3].

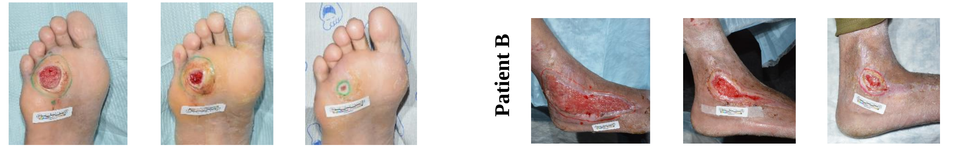
Table 3: Proportion of Subjects That Underwent Target Ulcer-Related Lower Extremity Amputations

	Pooled MBN-101 (N=39)	Placebo (N=13)
Amputations Involving Target Ulcer (n [%])	1 (2.6%)	2 (15.4%)

Resolution of Infection

- There were no differences in resolution of infection signs/symptoms across treatment groups at EOT.

MBN-101 DFI WOUND SIZE REDUCTION: BASELINE AND AFTER TREATMENT



CONCLUSIONS

- **MBN-101 (BisEDT [pravibismane] topical suspension formulation) was safe and well tolerated at all doses**
- **Although the study was not designed to demonstrate statistical efficacy, a trend of greater median wound size reduction and reduced amputation rate with MBN-101 treatment was observed compared to placebo**
- **There was no evidence of BisEDT (pravibismane) systemic exposure**
- **Based on results of this Phase 1 study, wound closure and amputation rate will be assessed in future MBN-101 DFI clinical studies**