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ORIGINAL ARTICLE

# Real-World Effectiveness and Dose-Response of ON101 Therapy for Healing of Diabetic Foot Ulcers

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## Abstract

**Objective:** To evaluate the real-world effectiveness and dose-response of ON101 , especially for high-risk patients with poor healing outcomes.

**Patients and Methods:** ON101 cream, a novel treatment for diabetic foot ulcers (DFUs), modulates the function of macrophages and accelerates the emergence and expansion of anti-inflammatory properties. In this study, 80 and 98 patients with DFU who were treated using ON101 and standard care with adjuvant therapy (denoted as nonuse), respectively, from January 1, 2020, to December 31, 2022, were identified from Taipei Medical University-Shuang Ho Hospital, Taiwan. The primary outcome was a complete healing event within 120 days following treatment initiation. Secondary outcomes included ulcer recurrence, amputation, and all-cause mortality within 1 year of follow-up. Cox proportional hazard model analysis was applied to determine the treatment effect on study outcomes. The dose-response of ON101 on healing outcomes was modeled using a regression analysis.

**Results:** Compared with nonuse, ON101 use significantly increased the complete healing outcome by 79% (HR, 1.79; 95% CI, 1.24 to 2.58), with an average of 1.85 ON101 tubes used per person with healed ulcers. Favorable healing outcomes were consistently shown in the analyses of high-risk patients. The dose-response analysis results suggest 25%, 107%, 33%, and 19% decreases in the ulcer size per additional ON101 tube use for all study patients and those with Wagner grade 1, 2, and 3 ulcers, respectively (all $P<.01$).

**Conclusion:** Promising healing outcomes following ON101 therapy at lower doses among real-world patients with DFU are corroborated, with a potential therapeutic benefit for clinically disadvantaged patients and practical feasibility for use in routine practice.

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Diabetic foot ulcers (DFUs) are a common and debilitating diabetes-related complication, affecting approximately 18.6 million individuals worldwide and posing significant challenges to health care systems.[1] Despite advances in medical care, the estimated lifetime incidence of foot ulceration related to diabetes is 19% to 34%, with recurrence rates of 40% to 65% within 1 to 5 years after successful healing and a pooled 5-year mortality of 30.5% to 50%.[2-4] Complications related to DFU, such as infection and amputation, contribute to poor health outcomes, substantial economic burden, work productivity loss, and even emotional suffering.[5] Several clinical characteristics have been identified as predisposing factors for DFU development, poor healing outcomes, and increased in-hospital mortality and sepsis

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risk, including peripheral arterial disease, neuropathy, foot deformities, impaired immune function, and end-stage renal disease.[6-8]

Surgical debridement, reducing pressure placed on the ulcer, and treating lower extremity ischemia and foot infection are first-line DFU treatments. Culture-directed oral antibiotics should also be considered for localized osteomyelitis.[1] Current topical treatment options for DFUs encompass a wide range of modalities, including wound dressings, offloading devices, and advanced modalities such as hyperbaric oxygen therapy and negative pressure wound therapy.[9] Unfortunately, these interventions have limitations, including inconsistent efficacy, high costs, and accessibility problems, highlighting a great unmet need for DFU patients.

ON101 cream has recently been introduced as a novel treatment for DFUs.[10] It is specifically designed to modulate the diabetic wound microenvironment to downregulate M1 proinflammatory macrophages and foster the emergence and expansion of anti-inflammatory properties.[11,12] Topical use of ON101 cream showed superior healing efficacy than that of an absorbent dressing alone in a phase III clinical trial and is highly cost-effective compared with existing therapies.[13,14] However, the extent to which the benefits observed in trial settings translate into clinically meaningful outcomes in diverse real-world populations with DFUs, including high-risk subgroups, is unclear. Hence, robust real-world evidence to support clinical decisions for the rational use of ON101 is urgently needed.

Therefore, this study sought to determine the clinical effectiveness of ON101 in real-world populations with DFUs, focusing on clinically meaningful outcomes (ie, complete wound healing, ulcer recurrence, and amputation) and further analyzing disadvantaged patients who have risk factors (ie, dialysis-dependent end-stage renal disease, poor glycemic control, and severe ulcers) for poor healing outcomes. The results of this study can inform evidence-based treatment decisions to improve clinical outcomes for DFU patients in routine practice.

## PATIENTS AND METHODS

### Data Source

This retrospective cohort study used the electronic health records for the period from January 1, 2020, to December 31, 2024, from Taipei Medical University—Shuang Ho Hospital (TMU-SHH), supervised by Taiwan's Ministry of Health Welfare. TMU-SHH is a medical center in north Taiwan with 1500 inpatient beds. It achieved a joint commission international certification in 2009. The electronic health records contain the individual-level medical records of outpatient, hospitalization, emergency, and pharmaceutical services from 36 departments and specialties. This study was approved by the Taipei Medical University Joint Institutional Review Board (TMU-JIRB N202311055).

### Cohort Identification

Patients 18 years of age and older who had been diagnosed with a DFU between 2020 and 2022 were identified from the electronic health records of TMU-SHH. The date of study enrollment (denoted as time A, Figure 1) refers to the first visit to TMU-SHH during the study period. The patient baseline characteristics were measured on this date. Patients with insufficient records of the study variables, any major amputations, bilateral DFUs, early withdrawal from the study, or life-threatening illnesses at study enrollment were excluded.

At the beginning of study enrollment, all study patients were required to have hospitalized standard of care (eg, pressure relief, Figure 1) with adjuvant therapies (eg, negative pressure wound therapy) to downgrade their ulcer severity and size. The process of downgrading the target ulcers generally took 2 to 3 months. Afterward, patients receiving ON101 were denoted as ON101 users, and those not receiving ON101 (but having a nonhospitalized standard of care with adjuvant therapies) were denoted as



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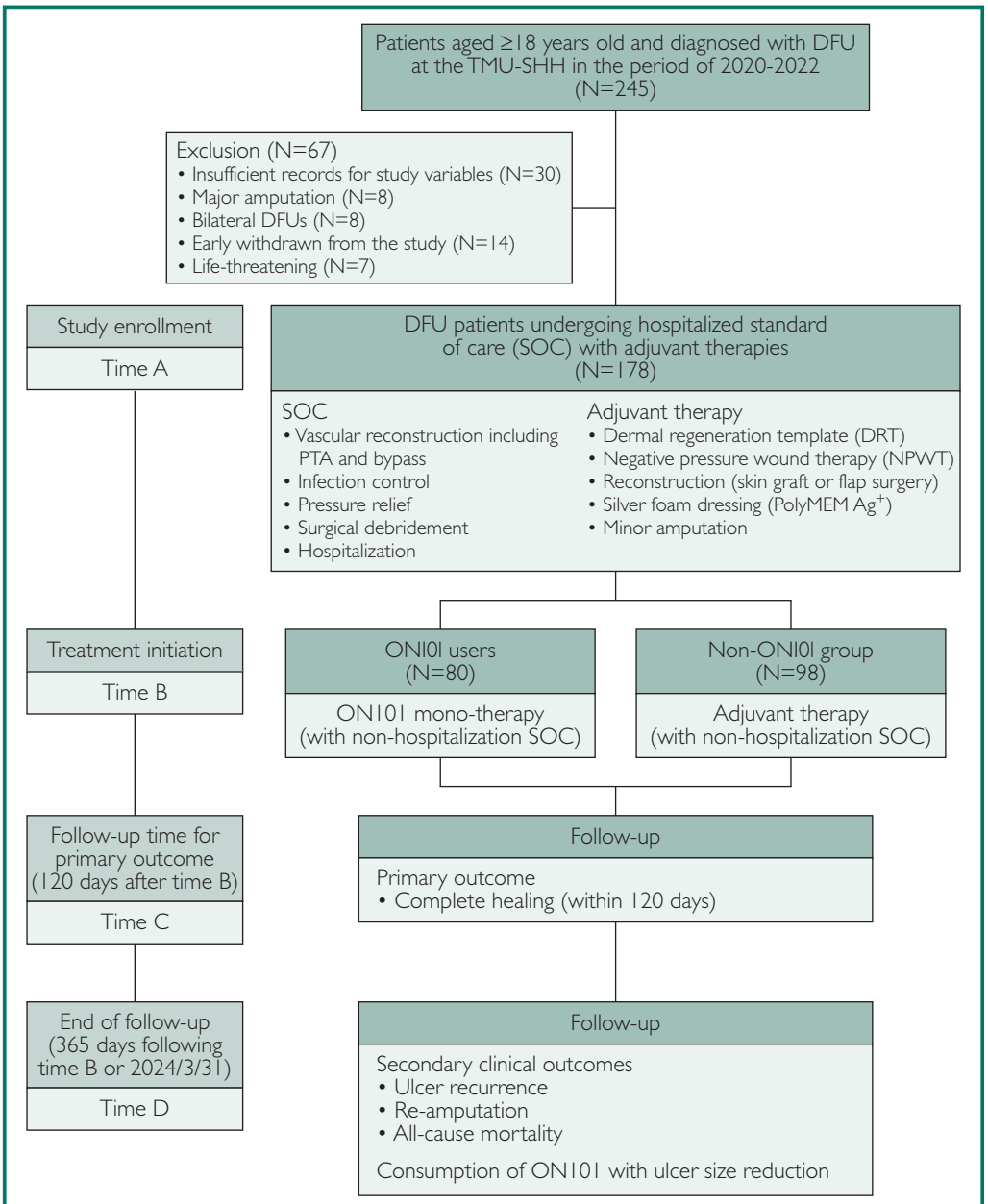



**FIGURE 1.** Flow chart for patient selection. DFU, diabetic foot ulcer; TMU-SHH, Taiwan Medical University—Shang Ho Hospital.

nonusers. Generally, ON101, as a topical cream, was applied on the wound surface twice daily with a thicker layer. The gauze can be covered on the wound surface. Each patient was asked to visit the clinic every 2 weeks. In addition, the therapy, including , including negative pressure wound therapy, collagen matrix, and skin graft and flap, can be applied if needed during the same therapeutic course. However, during the course administered with ON101 in this study, only a single therapy (ie, one tube of ON101) was prescribed for ON101 users to avoid the bias of the clinical study. The date of ON101 initiation was denoted as the index date (ie, time B). The index date for nonusers refers to the time when the ulcer was downgraded.



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### Study Outcomes

The primary outcome was the complete healing of DFUs within a 120-day period following treatment initiation, which aligns with the study period in the efficacy trial of ON101 for healing outcomes.[13] Time C (Figure 1) refers to the end of 120 days of observation for healing events. The secondary outcomes of interest were several clinically meaningful outcomes for patients with DFUs, including ulcer recurrence after a healed event, re-amputation, and all-cause mortality, which were assessed in the year following the index date (ie, treatment initiation, time B). The end of 356 days following time B was denoted as time D.

### Statistical Analyses

Descriptive analyses for patient characteristics were conducted. Continuous variables (eg, age, diabetes duration, and laboratory measurements) are presented as means and standard deviations and categorical variables (eg, comorbidities and complications) are presented as frequencies and proportions. Survival analyses were performed to assess the association between treatment exposure (ie, ON101 use and nonuse) and complete healing outcome following treatment initiation (ie, time B in Figure 1). Specifically, Kaplan-Meier survival curves were first plotted to show the difference in time-to-event (ie, complete healing) between ON101 users and nonusers, with a log-rank test applied to detect a significant between-group difference ($P<.05$). The Cox proportional hazard model was then used to examine the clinical effectiveness of ON101 therapy for the complete healing outcome. The results are presented as HRs with associated 95% CIs.

Subgroup analyses focusing on the complete healing outcome were also performed for subsets of study patients stratified by several clinically meaningful characteristics related to DFUs: (1) Wagner classification (ie, grades 1, 2, and 3); (2) hemoglobin $A_{1c}$ (ie, $Hb_{A1c}$ $\geq$75 mmol/mol and <75 mmol/mol); (3) Infectious Diseases Society of America (IDSA) classification (ie, 1, 2, and 3); (4) ulcer size (ie, $\geq$5 $cm^2$ and <5 $cm^2$); (5) joint characteristics (ie, dialysis status with Wagner grade 1, 2, and 3 ulcers, respectively); and (6) vascular reconstruction (including percutaneous transluminal angioplasty and bypass) (ie, yes and no), which were determined according to the patient characteristics measured at treatment initiation (ie, time B). Moreover, to quantify the dose response relationship between ON101 use and complete healing outcomes, a linear regression analysis was conducted for ON101 users to model the proportion of healed ulcer size (%) (as the dependent variable in the analysis) as a function of total consumption of ON101 therapy (in number of tubes) (as an independent variable). The healed ulcer size (%) was defined as the percentage change of ulcer size from times B to C and calculated as the difference in ulcer size between times B and C divided by the ulcer size at time B. All data analyses were performed using SAS software version 9.4.

## RESULTS

There were 80 ON101 users and 98 nonusers identified for the period between 2020 and 2022. Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) shows the patient characteristics and wound-related information at study enrollment. Generally, compared with nonusers, ON101 users were younger (ie, 68.7±13.2 years of age vs 62.5±15.1 years of age), had a higher proportion who had been treated with a combination of oral hypoglycemic agents and insulin (ie, 25.5% vs 45.0%), and had a more severe infection status (eg, IDSA classification 4: 5.1% vs 23.8%) at baseline. Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org) shows the clinical characteristics of the target ulcers for ON101 users and nonusers from study enrollment (ie, time A) to the index date (time B). Briefly, the size of the target ulcer was reduced by 12.6 $cm^2$ (ie, from 18.2 $cm^2$ at time A to 5.6 $cm^2$ at time B) and 15.4 $cm^2$ (ie, from 19.9 to 4.5 $cm^2$) for ON101 users and nonusers, respectively, with significant improvement in ulcer severity following the downgrading (supported by no Wagner grade 4 ulcer cases at time B). Supplemental Table 3 (available



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online at http://www.mayoclinicproceedings.org) details the therapies for the target ulcers during the downgrading period. During approximately 2 weeks (ie, 14.9±6.8 days for ON101 users vs 15.8±7.0 days for nonusers) of inpatient stay for the ulcer downgrading, all patients were treated by antibiotics and surgical debridement. Compared with nonusers, ON101 users had a lower rate of infectious cases (ie, 100.0% vs 91.3%) and a higher rate of pressure relief (ie, 39.8% vs 68.8%).

As shown in Figure 2, the Kaplan-Meier analysis suggests a statistically superior complete healing rate of ON101 users compared with that of nonusers (*P* value of log-rank = 0.0016). Figure 3 shows the results of Cox model analyses for complete healing outcomes for the overall study population and subgroups. Overall, the use of ON101 increased the chance of achieving complete healing of the target ulcer by 79% compared with nonuse (ie, HR, 1.79; 95% CI, 1.24 to 2.58). Consistently, the subgroup analysis results indicate significantly increased probabilities of complete healing of the target ulcers associated with the use of ON101 vs nonuse for patients with Wagner grade 2 ulcers (ie, HR, 1.78; 95% CI, 1.20 to 2.66), $Hb_{A1c}$ less than 75 mmol/mol (ie, HR, 1.80; 95% CI, 1.20 to 2.71), IDSA classification 1 (ie, HR, 2.28; 95% CI, 1.30 to 4.02) or 2 (ie, HR, 6.21; 95% CI, 2.63 to 14.66), ulcer size greater than or equal to 5 $cm^2$ (ie, HR, 2.56; 95% CI, 1.10 to 5.96) or less than 5 $cm^2$ (ie, HR, 1.83; 95% CI, 1.21 to 2.75), and without vascular reconstruction (ie, HR, 2.25; 95% CI, 1.27 to 3.98). Supplemental Table 4 (available online at http://www.mayoclinicproceedings.org) shows the adjuvant therapies prescribed from study enrollment (time A) to the end of study follow-up (time D). Supplemental Table 5 (available online at http://www.mayoclinicproceedings.org) indicates no ulcer recurrence or re-amputation events after healing among ON101 users, and no mortality cases in either group.

Figure 4 shows that, among all ON101 users, there was a statistically significant decrease in ulcer size of 25% per additional tube of ON101 applied ($P<.0001$). Figure 5 shows 107%, 33%, and 19% reductions in the target ulcer size for one additional tube of ON101 used among patients with Wagner grade 1, 2, and 3 ulcers, respectively (all $P<.05$). For example, for patients with Wagner grade 3, the ulcer can be reduced in size by 19% with the use of one tube of ON101. Also, for those with Wagner grade 1, the ulcer can be healed completely using less than one tube of ON101. In other words, for such less severe ulcers (ie, Wanger grade 1), a healed event can be achieved using ~0.93 tubes of ON101 (ie, 100%/107%). Supplemental Table 6 (available online at http://www.mayoclinicproceedings.org) summarizes the clinically meaningful factors and patient characteristics at study enrollment among the patients without complete healing in the study period. A high proportion of these patients had a severe condition of the target ulcer (eg, Wagner grade 3 ulcer, infected ulcer, or undergoing dialysis).

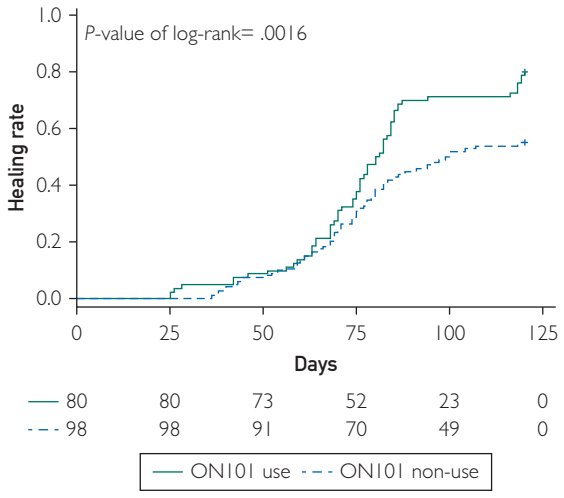



**FIGURE 2.** Kaplan-Meier survival curves for time-to-event (complete healing) between ON101 users and nonusers.

## DISCUSSION

This study is the first to determine the real-world effectiveness and dose response of ON101 therapy for complete healing and other clinically meaningful outcomes (eg, recurrence, amputation) and analyze



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clinically disadvantaged patients (ie, dialysis-dependent, $Hb_{A1c}$ ≥75 mmol/mol, and Wagner grade 3 ulcers), who are usually excluded from trials. Individual-level data, which consisted of detailed laboratory and image records, were used to ensure study robustness. We found consistent healing effects of ON101 across real-world and trial settings, with favorable outcomes observed in severe ulcer cases. Importantly, real-world patients required a lower dosage or shorter length of treatment compared with that of trial participants. Hence, these results support the rational use of ON101 cream as a valuable treatment strategy for DFUs in routine practice, particularly in high-risk populations.

## DISCUSSION

### Promising Healing Outcomes of ON101 Across Trial and Real-World Settings: Early Intervention for Better Management and Possibly Cost Savings

The consistent healing effect of ON101 cream for Wagner grade 1 and 2 ulcers in real-world settings mirrors the efficacy observed in a pivotal trial.[13] Compared with trial participants, the complete healing rate was even more remarkable in real-world patients (ie, 60.7% vs 80.0%), with shorter treatment duration and lower dosage of ON101 (ie, average of 1.85 tubes used per person with healed ulcers in this study) required for complete healing events, and no apparent adverse clinical outcomes (ie, no ulcer recurrence, re-amputation, or mortality following healing) (Supplemental Table 5) were observed in real-world ON101 users. Although caution should be made while comparing the trial and real-world study results given the differences in the patient composition (eg, real-world patients having more diverse and severe clinical characteristics), the discrepancy in treatment outcomes between trial and real-world settings also implies that the provision of multidisciplinary care in routine practice to ensure the therapeutic effect of ON101 is crucial.[15] A previous economic study using ON101 trial data found that ON101 therapy is an economically rational alternative to existing treatments for DFU patients.[14] The results of the present study suggest potential cost savings attributable to a reduced treatment burden (ie, lower dosage and shorter duration) with ON101 use in addition to standardized care for DFUs. Taken together, the results highlight the importance of timely intervention in the early stage of DFUs (eg, Wagner grade 1 or 2) to increase the chance of complete healing and mitigate the need for prolonged treatment duration in high-risk individuals. We found that ON101 use in less severe DFU cases (ie, Wagner grade 1 or 2 ulcer) compared with more severe DFU cases (ie, Wagner grade 3 ulcer) yielded higher healing rates with lower dosage and shorter treatment duration (Figure 5). This suggests that the inclusion of ON101 in early intervention measures, such as optimized glycemic control, regular wound cleansing, and patient education, would help prevent the aggravation of DFUs or reduce their severity, thereby potentially reducing the complications and cost burden associated with long-term treatments.

### Promising Healing Effect of ON101 in High-Risk Patients: Potential for Clinically Challenging Cases

This study found significantly increased complete healing outcomes following ON101 therapy in the patient subgroups with ulcer size greater than or equal to 5 $cm^2$ (ie, HR, 2.56; 95% CI, 1.10 to 5.96) (Figure 3) and IDSA classification 2 (HR, 6.21; 95% CI, 2.63 to 14.66), and favorable but insignificant healing outcomes in those with Wagner grade 3 ulcers (HR, 4.70; 95% CI, 0.95 to 23.30), those with $Hb_{A1c}$ greater than or equal to 75 mmol/mol (HR, 1.85; 95% CI, 0.81 to 4.23), certain dialysis cases (ie, with Wagner grade 2 ulcers) (HR, 1.97; 95% CI, 0.68 to 5.69), and individuals requiring vascular reconstruction (HR, 1.43; 95% CI, 0.87 to 2.36). These findings are clinically significant considering that these high-risk patients often exhibit poor glycemic control and multiple comorbidities, thereby complicating the clinical management of wound



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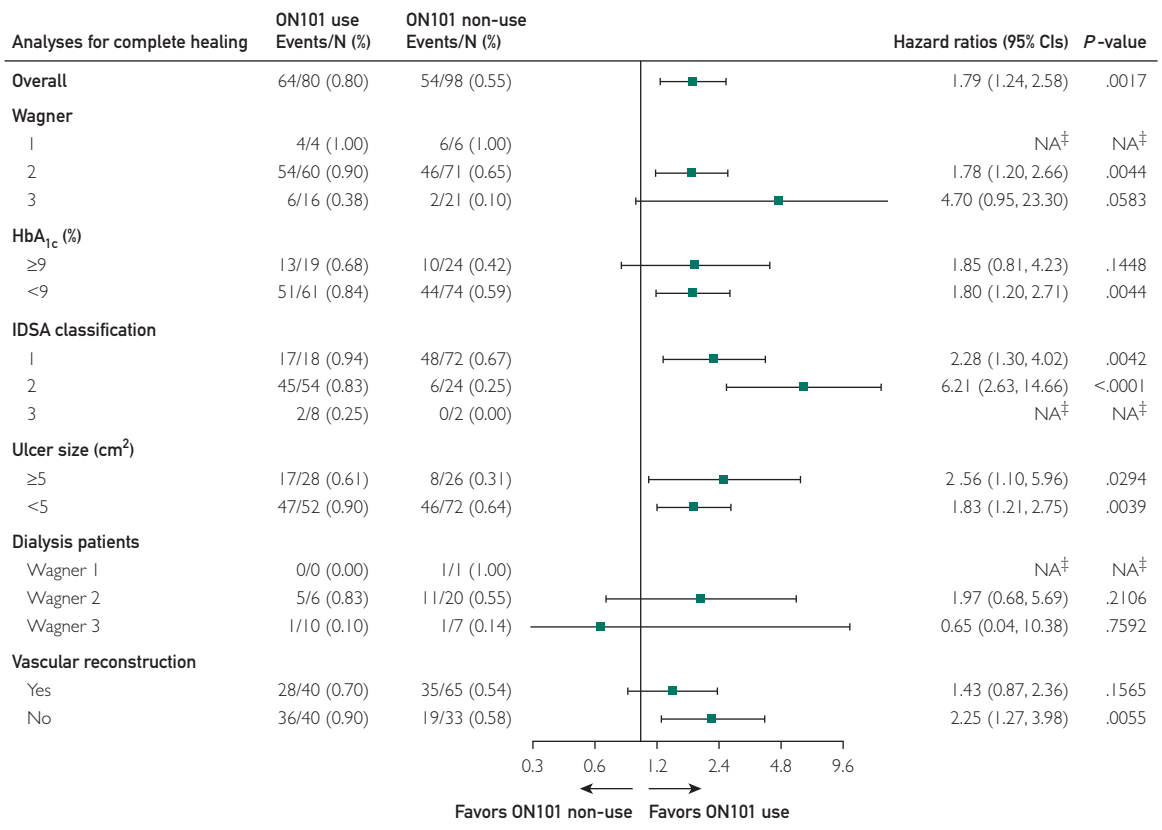



**FIGURE 3.** Event rates and HRs of complete healing event with ON101 use vs nonuse in overall study population and patient subgroups stratified by clinically significant characteristics. Given complete healing rates of 100% and 0% for the ON101 use and ON101 nonuse groups, respectively, the HR was not estimated. An $\alpha$ level of 0.05 (ie, significance level) was set to reduce the chance of type I error, with $P<.05$ for the HRs (statistically significant) suggesting a minimal concern of type I error in this study. $HbA_{1c}$, hemoglobin $A_{1c}$; IDSA, Infectious Diseases Society of America; NA, not available.

healing and increasing the risk of numerous adverse outcomes.[16,17] Hence, such favorable results suggest that ON101 may offer benefits beyond those of traditional wound care approaches, even in patients with significant medical comorbidities. This highlights the potential of ON101 to address the underlying pathophysiologic mechanisms of DFUs, such as inflammation and impaired wound healing, irrespective of the severity of the ulcer or the patient's glycemic control.[11]

### Role of ON101 in DFU Treatment: Implications for Clinical Guidelines for Better Wound Care

Careful assessment of patients with DFU is crucial to determine suitability for ON101 therapy. For severe cases or those with poor wound characteristics (eg, extensive tissue necrosis or uncontrolled infection), initial surgical interventions, such as debridement, and antibiotic therapy are necessary to optimize wound conditions before initiating ON101.[18] Vascular problems should also be addressed before the use of ON101 if DFUs are complicated with peripheral arterial disease and/or venous insufficiency.[10] The results of this study support the importance of initial interventions/management, including vascular reconstruction, infection control, pressure relief, and debridement (Supplemental Table 3), to ensure the effectiveness of subsequent ON101 therapy. During ON101 therapy, close monitoring of wound healing prognosis, infection status,



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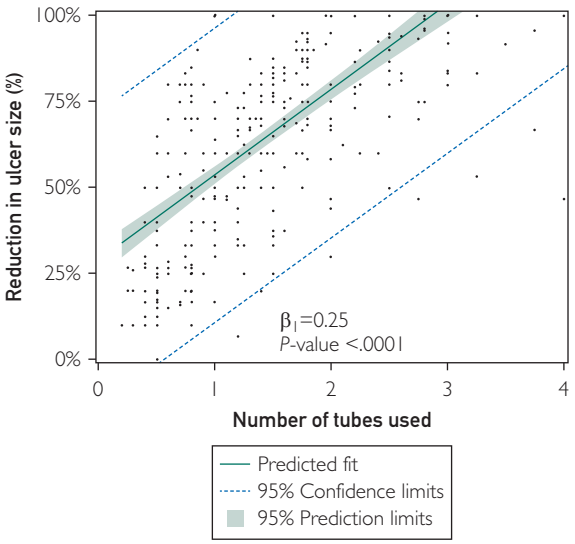



**FIGURE 4.** Association Between ON101 Dosage (in number of tubes) and proportion of reduction in target ulcer size (%) in overall study population. $\beta_1$ is the coefficient for the number of ON101 tubes used, which was estimated using a linear regression model analysis where the dependent variable was the proportion of the healed target ulcer size (%) and the independent variable was the number of ON101 tubes used. The results suggest a 25% decrease in the target ulcer size per additional tube of ON101 applied. Patients with complete healing events were treated with an average of 1.85 tubes of ON101.The average of ON101 consumption for all patients was 2.05 tubes (1 tube = 15 mg) per person during the study follow-up period.

and any adverse reactions is essential to ensure the treatment effect. In addition, patient education on proper wound care, glycemic control, and offloading techniques should be provided as part of comprehensive DFU management.[19] Regular follow-up appointments, wound assessments, and laboratory tests may be required to evaluate treatment response as needed. Clinicians should monitor for infection signs, noncompliance, or inadequate wound healing, which may necessitate treatment modifications or additional interventions.

This real-world study also observed that ON101 offers unique advantages as a topical cream for DFU treatment, providing convenience and flexibility for both patients and clinical care teams. Its ease of application allows for self-administration at home, reducing the need for frequent clinic visits or hospital stays. This not only enhances patient autonomy and comfort but also promotes treatment adherence and continuity of care. Moreover, the topical formulation minimizes the systemic side effects associated with oral medications, making it a safe option for long-term use. Ideal candidates for ON101 therapy include patients with Wagner grade 1 and 2 ulcers, as these typically represent less severe wounds with better healing potential. The present study showed that certain Wagner grade 3 ulcers may also benefit from ON101, particularly if they exhibit favorable wound characteristics and are amenable to topical treatment and under aggressive infection control, debridement, or other local treatments along with ON101 therapy. Clinical guidelines for vascular wound care include ON101 as a recommended treatment option for eligible patients with DFU.[10] Guidelines also emphasize the importance of comprehensive wound assessment, patient education, and regular monitoring throughout DFU treatment.[19-21] In addition, pre-treatment optimization and post-treatment follow-up should be emphasized to ensure safe and effective DFU management.

## Study Limitations

First, this study was conducted at a single medical center, which may limit the generalizability of the obtained results to broader populations or healthcare settings. Second, the limited sample size, especially in subgroups such as patients with Wagner grade 3 ulcers, may affect the statistical power and precision of estimates for these specific cohorts. Third, unmeasured confounders (eg, impaired immune function) could potentially influence treatment outcomes but were not fully accounted for in the analysis. Furthermore, the short follow-up duration (ie, 1 year), attributed to the recent launch of ON101 in Taiwan, restricts the assessment of long-term outcomes (eg, amputation) and recurrence rates. Therefore, future research should focus on conducting well-designed clinical trials to further investigate the efficacy of ON101 in high-risk subgroups. These trials should incorporate comprehensive patient



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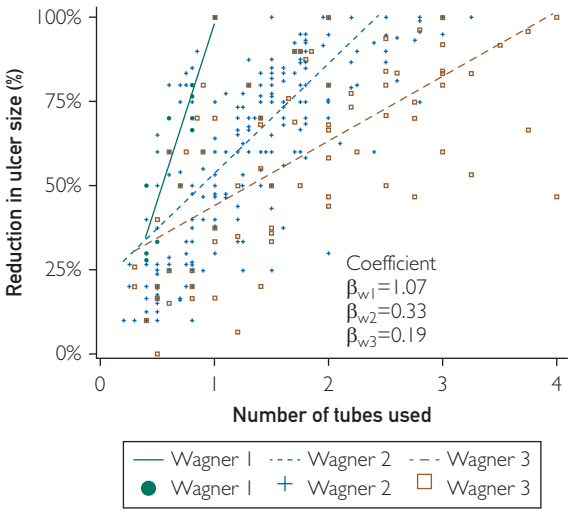



**FIGURE 5.** Association between ON101 use and proportion of reduction in target ulcer size in patient subgroups stratified by Wagner classification. $\beta_{W1}$, $\beta_{W2}$, and $\beta_{W3}$ are the coefficients for the number of ON101 tubes used in the subgroups with Wagner grade 1, 2, and 3 ulcers, respectively, which were estimated using linear regression model analyses where the dependent variable was the proportion of the healed target ulcer size (%) and the independent variable was the number of ON101 tubes used. The results suggest 107%, 33%, and 19% reductions in the target ulcer size per additional tube of ON101 applied for patients with Wagner grade 1, 2, and 3 ulcers, respectively. Among patients with complete healing, the cases with Wagner grade 1, 2, and 3 ulcers were treated by an average of 1.00, 1.92, and 1.83 ON101 tubes, respectively. The average of ON101 consumption was 1.00, 1.98, and 2.56 tubes (1 tube = 15 g) per person during the study follow-up period for patients with Wagner grade 1, 2, and 3 ulcers, respectively. *P* values for the coefficients of the number of tubes used for patients with Wagner grade 1, 2, and 3 ulcers are all less than 0.05.

stratification based on various risk factors, including glycemic control, comorbidity burden, and wound severity, to identify specific patient profiles that may benefit most from ON101 therapy.

## CONCLUSION

Promising healing outcomes following ON101 therapy with lower dosage and shorter treatment duration among real-world patients with DFUs are well supported by this study. ON101 has a potential therapeutic benefit for clinically disadvantaged patients and practical feasibility for use in routine practice. Use of ON101 offers potential in enhancing DFU management, reducing the health care burden, and improving patient outcomes in routine clinical practice. ON101 should thus be integrated into clinical guidelines as a valuable treatment option for DFUs.

## POTENTIAL COMPETING INTERESTS

All authors report no potential competing interests.

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The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing is not available in this study as data management and analyses were only allowed to be conducted in Taipei Medical University-Shuang Ho Hospital owing to considerations of data privacy and safety.

## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.



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Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** **DFUs,** diabetic foot ulcers; **$HbA_{1c}$,** hemoglobin $A_{1c}$; **IDSA,** Infectious Diseases Society of America; **TMU-SHH,** Taipei Medical University-Shuang Ho Hospital

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