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Cost-effectiveness of ON101 with general wound care for diabetic foot ulcers among patients with type 2 diabetes in Singapore: Analysis of a multi-ethnic country in Asia

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Abstract

Aims: Diabetic foot ulcers (DFUs) impose a vast health and economic burden on individuals and healthcare systems globally. We assessed the cost-effectiveness of adding ON101, a novel treatment for accelerating wound healing, to general wound care (GWC) versus GWC alone for DFUs in Singapore, a multi-ethnic country with increasing DFU prevalence in a growing type 2 diabetes population.

Materials and Methods: A Markov model was utilized to estimate the healthcare costs and quality-adjusted life years (QALYs) over 5 years from a healthcare sector perspective. Model inputs were mainly derived from the Singapore Wound Registry and published literature. The primary outcome was the incremental cost-effectiveness ratio (ICER). Subgroup analyses stratified by clinically important DFU conditions and scenario analyses were conducted to confirm the study's robustness.

Results: Compared to GWC alone, adding ON101 yielded greater QALY gained (i.e., 0.15) and lower healthcare costs (i.e., −US$16237) for patients with DFUs. Remarkable cost-savings from the use of ON101 with GWC were observed for patients with complex DFUs, namely ICERs of −US$161 963, −US$181 726 and −US$199 130 per QALY gained for cases with HbA1c ≥ 9%, ulcer duration >6 months and ulcer size >5 cm^2, respectively. Scenario analysis comparing ON101 with GWC to negative pressure wound therapy with GWC yielded an ICER of −US$677 243 per QALY gained.

Conclusions: Combining ON101 with GWC versus GWC alone was highly cost-effective for DFUs in Singapore. Also, the economic results for complex DFU cases underscore the value of ON101 in addressing DFU treatment challenges for managing complex cases, offering cost-savings alongside clinical benefits.

KEYWORDS
diabetic foot ulcer, economic evaluation, incremental cost-effectiveness ratio, negative pressure wound therapy, wound healing

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1 | INTRODUCTION

The global prevalence of diabetic foot ulcers (DFUs) is increasing with the rapid growth in diabetes and extended longevity and diabetes duration.[1] DFUs in the Asia-Pacific region are especially of concern, as diabetes in this area is projected to most rapidly increase.[2] DFUs could lead to lower extremity amputation and subsequent disability, high mortality and compromised quality of life.[3] Singapore, a multi-ethnic country comprising primarily Chinese (East Asians), Malay (Southeast Asians) and Indian (South Asians) populations, is viewed as a microcosm of Asia. Between 2017 and 2020, the incidence of diabetic foot in Singapore increased,[4] with the event rate of associated lower extremity amputation three times higher than that observed in other countries.[5] Among the ethnic subgroups, Malay demonstrated the highest incidence rate of diabetes-related lower extremity complications and amputation.[5] Accordingly, the rise in healthcare utilization and expenditures attributable to DFUs (i.e., an extra 50%–200% of the baseline diabetes-related cost[1]) has imposed a great financial burden on individual patients and the health system, highlighting the urgent need for appropriate and timely intervention.[2]

ON101 modulates the balance between M1 and M2 macrophages by suppressing inflammatory M1 macrophage activity and promoting M2 macrophage polarization via granulocyte colony-stimulating factor, thereby shifting the ulcers from the inflammatory phase to the proliferation and remodelling stages.[6] Moreover, the efficacy of topical ON101 cream in accelerating wound healing and increasing healing events when combined with general wound care (GWC) has been demonstrated for patients with DFUs,[6] even those with complex baseline characteristics (e.g., larger ulcer size and longer ulcer duration).[7] Despite the promising healing efficacy of ON101, its high acquisition cost might affect its wide use in clinical practice, especially in budget-constrained countries. A cost-effectiveness analysis (CEA) determines the value of an intervention, optimizes resource allocation and facilitates reimbursement policy; it thus plays an essential role in health decision-making.[8] A previous study of Taiwanese populations demonstrated the cost-effectiveness of ON101 in conjunction with GWC versus GWC alone for DFUs, even for patients with complex DFU conditions.[9]

However, the economic analysis results are sensitive to the target population, clinical practice and healthcare system.[10] Given the wide variation in DFU prevalence and ethnicity across the Asia-Pacific region,[11] CEA results may not be generalizable to contexts beyond the original study setting. In addition, there is a lack of economic evaluations of ON101 in the Southeast Asia region, one of the regions with the largest increase in diabetes populations and associated lower extremity complications. Against this background, we conducted a CEA using a Markov state-transition model to evaluate the cost-effectiveness of ON101 with GWC versus GWC alone among patients with DFUs from a healthcare sector perspective in Singapore.

2 | MATERIALS AND METHODS

2.1 | Model structure overview

A Markov state-transition model, which simulates the disease progression of patients with DFUs,[9] was adopted to evaluate the health and economic results of ON101 therapy added on to GWC versus GWC alone. The model comprises six mutually exclusive health states: uninfected DFU, infected DFU, gangrene, post-amputation, healing and death. Patients with DFUs were simulated using the model with a monthly cycle length, starting from the health state of uninfected DFU until death or the end of the 5-year time horizon. Per recommendations, healthcare costs and quality-adjusted life years (QALYs) were assigned in each cycle and discounted at an annual rate of 3% over the simulation horizon.[12] Details of the model and input parameters are available in Figure 1 and Table S1, respectively.

This model-based economic analysis was performed using TreeAge Pro 2020 (TreeAge Software, LLC, Williamstown, MA). The results are reported in compliance with the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) checklist[13] (Table S2).

2.2 | Simulation cohort and treatment intervention

A hypothetical cohort, aligned with the patient's characteristics in the ON101 trial[6] was adopted for this economic analysis. The ON101 trial was a randomized, evaluator-blinded phase 3 study that included patients with type 1 or type 2 diabetes and baseline HbA1c < 12%, followed up for up to 16 weeks.[6] Additional inclusion criteria, which were also applied to the hypothetical cohort, specified patients aged 20–80 years with a DFU that had a severity of Wagner grade 1 or 2, a size ranging from 1 to 25 cm^2 and a duration of at least four weeks.[6] Patients in both treatment groups underwent GWC, which comprised wound examinations and treatments such as cleansing, debridement and antibiotics, comorbidity control, patient education and care from multidisciplinary healthcare experts[14]; those in the ON101 group received additional ON101 cream according to their wound size.

2.3 | Transition probabilities, health utilities and healthcare costs

Most of the input parameters were obtained from the Singapore Wound Registry, a major wound care registry based on Asian data in a tropical climate, involving three healthcare clusters in Singapore.[15] Patients with neuro-ischaemic ulcers (i.e., DFUs and ischaemic ulcers related to peripheral arterial disease) from November 2019 to November 2021 were included for analysis. The electronic medical records contain encrypted, individual-level data on patients' baseline characteristics and clinical outcomes (e.g., wound healing and amputation) and wound management and associated healthcare utilization

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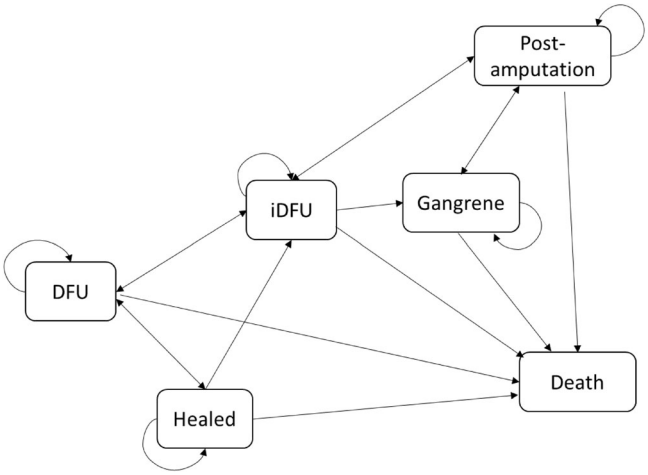


FIGURE 1 Overview of Markov state-transition model structure. A single arrow indicates an irreversible transition between health states; a double arrow indicates a reversible transition between health states. DFU, diabetic foot ulcer; iDFU, infected diabetic foot ulcer.

(i.e., medical visits, costs and patient-reported health-related quality of life) from the period November 2019 to November 2021.[15]

All patients in the GWC-alone and ON101 groups had a health state of uninfected DFU at the first cycle. Patients could move to a different health state or stay in their current state, depending on the monthly transition probabilities. Since the efficacy data of ON101 therapy are unavailable for the Singapore setting, the transition probabilities for the GWC-alone and ON101 groups were conservatively assumed to be the same, except for that from the health state of uninfected DFU to healing. Specifically, the transition probability from uninfected DFU to healing for the ON101 group was that of GWC multiplied by a statistically significant relative risk extracted from the ON101 trial to reflect its optimal efficacy in wound healing.[6] The relative risk was calculated based on the number of patients with/without complete healing within individual treatment groups (i.e., 74/48 patients with/without complete healing for the ON101 group; 40/74 for the GWC group). It is assumed that all transition probabilities are time-invariant and independent of sex and age.

The health utility scores, ranging from 0 to 1, for individuals' health states were also analysed using data from the Singapore Wound Registry. Patients with neuro-ischaemic-related ulcers were eligible for analysis, and their quality of life was assessed using the standardized EuroQoL 5-Dimensional (EQ-5D) questionnaire.[15] Given the lack of utility data collected from the ON101 trial,[6] the utility parameters of modelled health states were conservatively assumed to be the same for both treatment groups.

The healthcare costs associated with different health states were mainly obtained from the Singapore Wound Registry and estimated as total medical costs of healthcare utilization, including inpatient visits, outpatient visits, operational visits and costs, diagnosis fees, polyclinic visits, home nursing care, dressings and infection treatments for local and systemic ulcers.[15] In cases where cost parameters were unavailable from the registry, local expert consultations were employed. To account for uncertainty regarding these estimates, a series of sensitivity analyses were conducted. These costs were classified into two categories, namely the one-time event/hospitalization costs incurred while patients moved from any health state to that of infection, amputation or gangrene, and monthly state costs incurred per cycle for each health state excluding death. ON101 cream was specifically indicated for patients with uninfected and infected ulcers and was thus discontinued once patients progressed to the health state of healing, gangrene or post-amputation. All cost values were standardized into year 2023 costs using healthcare inflation rates in Singapore[16] and are presented in United States dollars with an exchange rate of the Singapore dollar to the United States dollar of 0.75. The impact inventory for this CEA is given in Table S3.

2.4 | Base-case CEA

In the base-case analysis, for each treatment group, a patient's total healthcare costs and effectiveness data were simulated over a 5-year time horizon from a healthcare sector perspective. The total healthcare costs of each patient following the model simulation was the sum of the healthcare costs associated with modelled health states and the treatment cost of ON101. QALYs, the primary effectiveness outcome, were estimated as the sum of the life years (adjusted by the utility scores) spent in each health state over 5 years. The cost-effectiveness of ON101 with GWC versus GWC alone over a 5-year projection was measured in terms of the incremental cost-effectiveness ratio (ICER), which is the incremental total healthcare costs divided by the incremental total QALYs. Given the lack of an explicit willingness-to-pay (WTP) threshold, implicit WTP thresholds of $34 000 and $56 600 per QALY gained, commonly adopted by Singapore's health technology assessment agency and based on earlier economic studies in Singapore,[17] were adopted to assess whether ON101 added to GWC versus GWC alone is highly cost-effective (i.e., ICER ≤ $34 000) or cost-effective (i.e., ICER ≤ $56 600). In fact, most new technologies with the ICERs within these thresholds would receive positive recommendations from the agency for health insurance reimbursement.[17]

2.5 | Sensitivity analyses

Deterministic sensitivity analyses (DSAs) and probabilistic sensitivity analyses (PSAs) were performed to quantify the impact of parameter uncertainty on the ICER estimates. In the DSAs, each input parameter's lower and upper bounds were applied. The most dominant drivers of ICER were defined as the parameters with a variation in ICER estimates of ≥20% and are illustrated in a tornado diagram. The PSAs, which allow all modelled inputs to vary simultaneously in given plausible ranges with predefined distributions (Table S1), were performed using a Monte Carlo simulation with 10 000 iterations.

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2.6 | Subgroup and scenario analyses

The above analyses stratified by baseline HbA1c level (i.e., ≥9% or <9%), ulcer size (i.e., 1–5 or >5 cm^2) and ulcer duration (i.e., ≥6 or <6 months), which are clinically meaningful DFU features, were also conducted to assess the possible heterogeneity in the ICER results. Furthermore, several scenario analyses were performed to confirm the study's robustness. First, the simulation time horizon was restricted to 1 year and extended to 10 years to assess the uncertainty due to the length of the simulation period. Second, the annual discount rate was set to 0% and 5%. Third, considering that negative pressure wound therapy (NPWT), which promotes the complete healing of ulcers and shortens healing time compared to conventional dressing, has been recently reimbursed for Singapore and patients with DFUs,[18] a scenario analysis was conducted where NPWT was added on to GWC for patients with uninfected DFUs in the GWC-alone group. The treatment cost of NPWT was incurred as a one-time event/hospitalization cost during the transition from any health state to that of uninfected DFUs, as well as monthly treatment costs. In addition, the transition probability from uninfected DFU to healing for patients using NPWT-added GWC was multiplied by the relative risk of NPWT versus standard wound dressing to achieve complete healing, which was obtained from systematic reviews.[19] Of note, the DSAs and PSAs were re-run for this scenario. Lastly, a break-even cost analysis was conducted to determine the marginal monthly drug cost of ON101 for a range of WTP thresholds.

3 | RESULTS

3.1 | Base-case analysis

Over the 5-year simulation, 25% and 18% of the patients achieved complete healing in the ON101 and GWC-alone groups, respectively (Figure 2A). The cumulated probabilities of adverse DFU complications, namely uninfected/infected DFU (i.e., 11.4%/7.2% vs. 13.4%/7.6%), gangrene (i.e., 9.4% vs. 10.3%), post-amputation (i.e., 4.8% vs. 5.2%) and death (i.e., 41.9% vs. 46.0%), were generally lower in the ON101 group and consequently decreased healthcare costs were found for ON101 users compared to the GWC-alone group (e.g., total healthcare costs in 5 years for uninfected/infected DFU: $104 060/$61 802 vs. $110 465/$62 102) (Figure 2B). In the base-case analysis, compared with GWC alone, adding ON101 onto GWC yielded an additional 0.15 QALYs while reducing total healthcare costs by $16 237 per type 2 diabetes patient with DFUs over a 5-year simulation, resulting in an ICER of −$109 677 per QALY gained (Table 1).

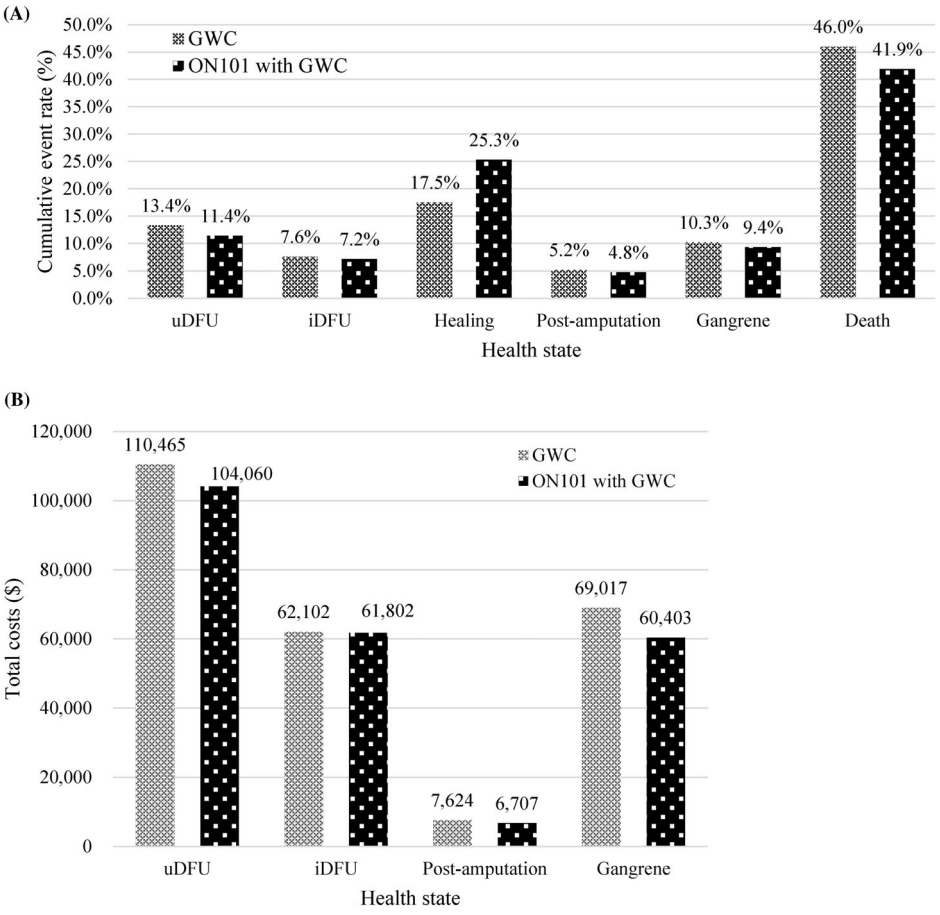


FIGURE 2 (A) Cumulative event rates and (B) healthcare costs for individual health states after 5-year simulation for general wound care (GWC) alone and ON101 with GWC in the base-case analysis. The total costs include one-time event costs, monthly state costs, and monthly drug cost of ON101. All costs are presented in 2023 United States dollars. iDFU, infected diabetic foot ulcer; uDFU, uninfected diabetic foot ulcer.

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TABLE 1 Results of cost-effectiveness of ON101 with GWC versus GWC alone in base-case, subgroup, and scenario analyses.

	Total costs, $			Total LYs		Total QALYs				
	GWC	ON101[a]	ΔCost, $	GWC	ON101[a]	GWC	ON101[a]	ΔQALYs	ICER, $/QALY	Probability of highly CE at defined WTP[b]
Base-case analysis										
	249 208	232 971	−16 237	3.556	3.662	2.043	2.191	0.148	−109 677	87.7%
Subgroup analyses										
HbA1c < 9%	249 208	237 904	−11 305	3.556	3.650	2.043	2.174	0.131	−86 403	87.7%
HbA1c ≥ 9%	249 208	215 152	−34 057	3.556	3.707	2.043	2.253	0.210	−161 963	97.9%
Ulcer size 1–5 cm^2	249 208	241 839	−7369	3.556	3.640	2.043	2.160	0.117	−62 923	75.6%
Ulcer size >5 cm^2	249 208	203 752	−45 456	3.556	3.736	2.043	2.293	0.250	−181 726	99.0%
Ulcer duration <6 months	249 208	240 287	−8921	3.556	3.644	2.043	2.165	0.123	−72 811	85.8%
Ulcer duration ≥6 months	249 208	189 385	−59 824	3.556	3.772	2.043	2.343	0.300	−199 130	99.7%
Scenario analyses										
(1) Time horizon										
10 years	364 187	348 743	−15 444	5.130	5.415	2.905	3.197	0.292	−52 896	87.4%
1 year	67 006	64 200	−2806	0.937	0.940	0.561	0.582	0.020	−136 890	69.3%
(2) Discount rate										
0%	265 988	348 791	−17 197	3.797	3.913	2.178	2.339	0.160	−107 154	87.8%
5%	239 093	223 444	−15 649	3.411	3.511	1.961	2.102	0.141	−111 307	87.5%
(3) NPWT added on GWC	262 950	232 971	−29 978	3.630	3.662	2.147	2.191	0.044	−677 243	92.4%

Note: All costs are presented in 2023 United States dollars.
Abbreviations: CE, cost-effective; GWC, general wound care; HbA1c, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; LYs, life years; NPWT, negative pressure wound therapy; QALYs, quality-adjusted life years.
[a]ON101 here indicates ON101 with GWC.
[b]WTP threshold was $34 000 per QALY gained.

3.2 | Sensitivity analyses

Figure 3A shows the DSA results. The most influential driver of the ICER value is the relative risk of ON101 versus GWC for the healing event, followed by the drug cost of ON101 and monthly treatment cost for uninfected DFU. The PSA results obtained using 10 000 model iterations indicate that the use of ON101 with GWC was cost-effective in approximately 88% of simulations for a WTP threshold of $34 000 (Figure S1).

3.3 | Subgroup analyses

The cost-effectiveness results for subgroup populations (categorized by baseline HbA1c level, ulcer size and ulcer duration) are consistent with the base-case analysis results (Table 1). Under the predefined WTP threshold of $34 000, ON101 was highly cost-effective in 86%–100% of the simulations for all subgroups of the DFU population, except for subgroups with an ulcer size of less than 5 cm^2 (76%).

3.4 | Scenario analyses

The results of the scenario analyses (i.e., using different time horizons and discount rates and adding NPWT to the GWC-alone group) are consistent with those of the base-case analysis, showing the cost-effectiveness of ON101 as an add-on therapy to GWC. Compared with NPWT added to GWC, adding ON101 to GWC yielded an additional 0.04 QALYs while reducing total healthcare costs by $29 978 per type 2 diabetes patient with DFUs over a 5-year simulation, resulting in an ICER of −$677 243 per QALY gained. In most scenarios, the use of ON101 was considered highly cost-effective in 88%–92% of the model iterations for a WTP threshold of $34 000; the probability of being cost-effective decreased to 69% when the timeframe for the simulation was restricted to 1 year (Table 1). Figure 3B shows the DSA analysis results for the scenario that includes NPWT with GWC and ON101 with GWC. The most influential drivers of ICER results, namely the relative risk of ON101 and that of NPWT for ulcer healing, were simultaneously varied in a two-way sensitivity analysis (Figure S3). Figure 4 and Table S4 show the value-based price of ON101. Under a WTP of $34 000,

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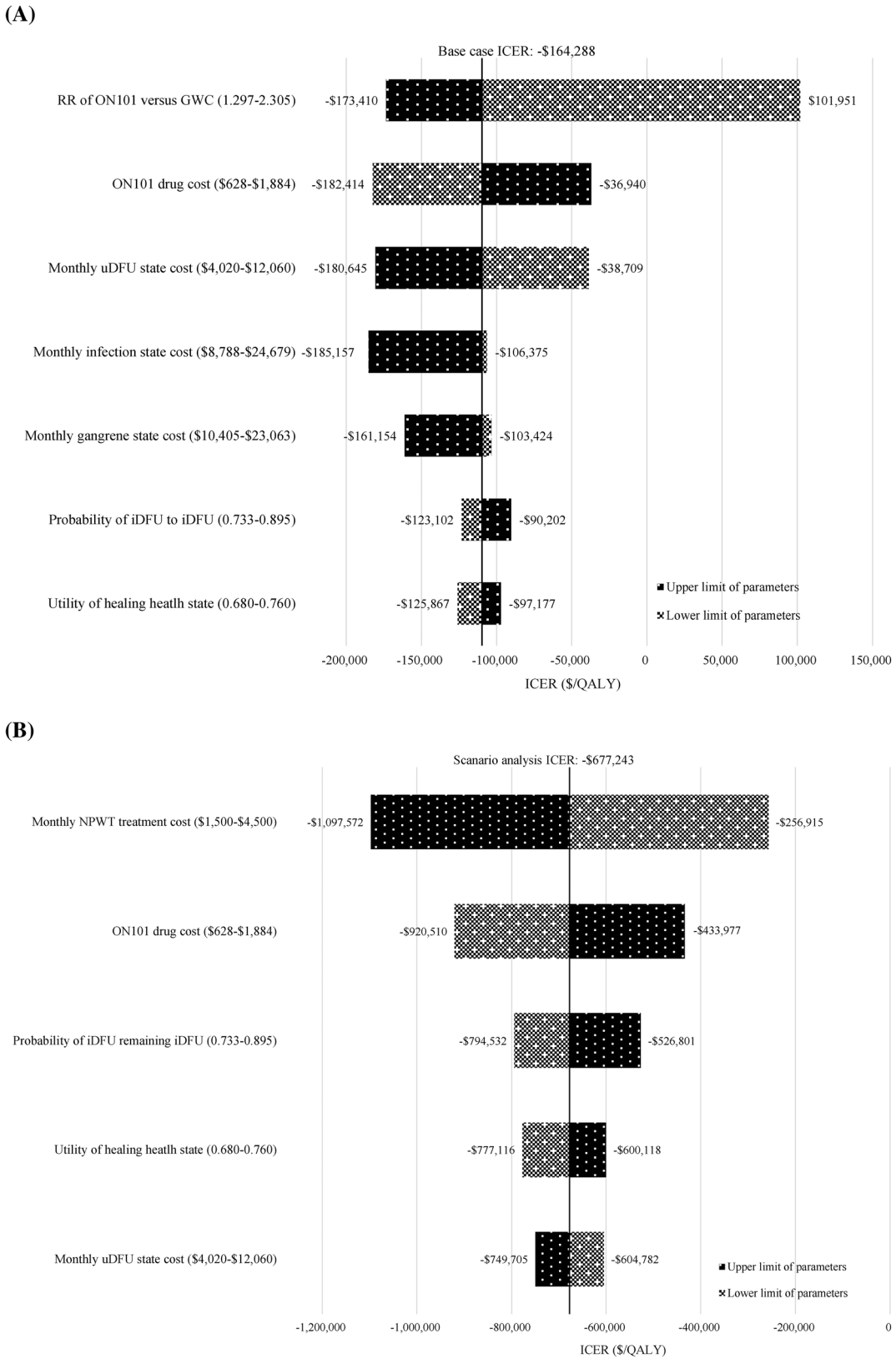


FIGURE 3 Tornado diagrams of results of deterministic sensitivity analyses of (A) ON101 with general wound care (GWC) versus GWC alone in base-case analysis and (B) ON101 with GWC versus negative pressure wound therapy (NPWT) with GWC in scenario analysis. The black solid line indicates the base-case incremental cost-effectiveness ratio (ICER) value. The end of the black (grey) bars indicates the ICER corresponding to a parameter with the input of its upper (lower) value. Only the parameters that lead to ≥20% variation of the base-case ICER are presented. All costs are presented in 2023 United States dollars. iDFU, infected diabetic foot ulcer; QALY, quality-adjusted life year; RR, relative risk; uDFU, uninfected DFU.

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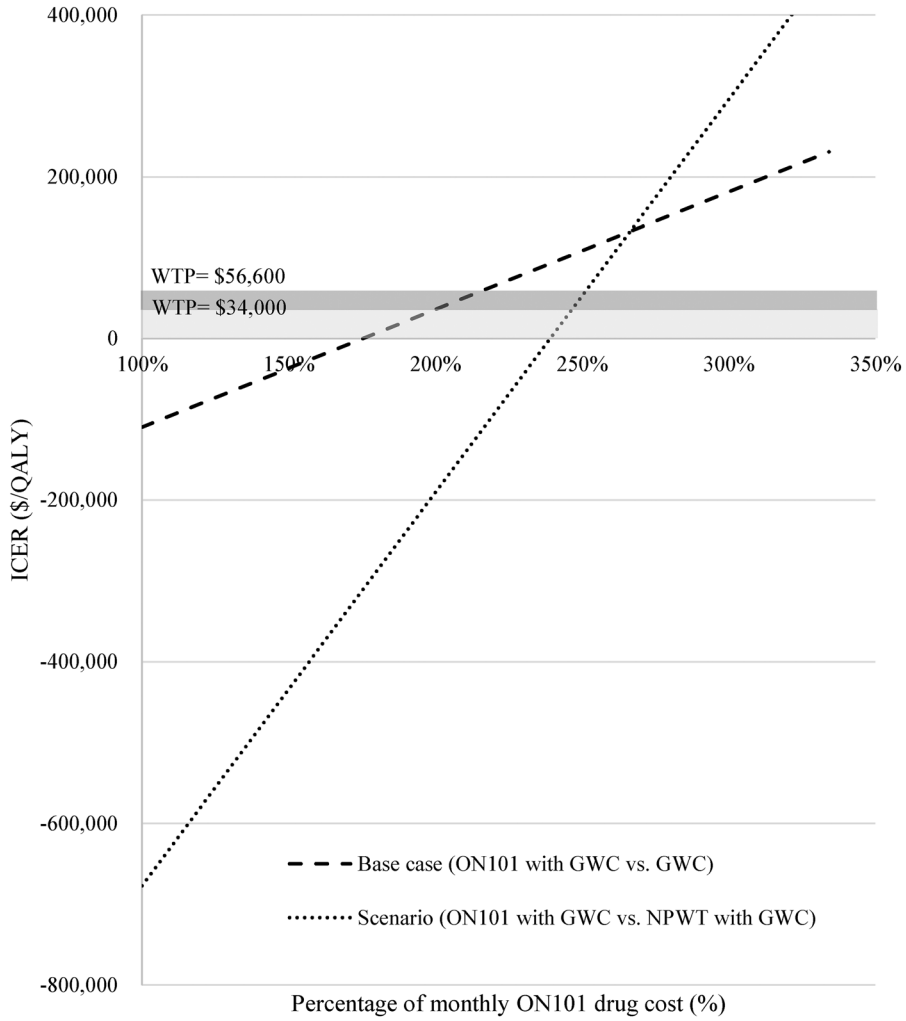


FIGURE 4 Impact of ON101's drug acquisition cost on incremental cost-effectiveness ratio (ICER) values in base-case and scenario analyses (i.e., negative pressure wound therapy [NPWT] with general wound care [GWC]). *X* axis shows percentage of monthly ON101 drug cost, with 100% indicating the base-case value. *Y* axis shows ICER estimate for a given ON101 drug cost. Light and dark shaded regions indicate the acceptable values of ON101 for willingness-to-pay (WTP) range of $0–$34 000 and $34 000–$56 600 per quality-adjusted life year (QALY) gained, respectively. For instance, if WTP is $34 000, then monthly ON101 drug cost could increase to 199% and 240% of the base-case value in the base-case and scenario analyses, respectively.

the monthly drug cost of ON101 increased from $1256 to $2496 (i.e., 99% increase) and $3013 (i.e., 140% increase) in the base-case and scenario analyses with NPWT as an add-on therapy to GWC, respectively.

4 | DISCUSSION

This study evaluated the cost-effectiveness of ON101 as an add-on therapy to GWC compared to GWC alone among patients with DFUs from the Singaporean healthcare sector perspective. The high upfront cost of adding ON101 to GWC is balanced by a subsequent reduction in medical costs attributable to the decreased incidence of costly adverse DFU-associated complications and reduced time spent managing these harmful events. The cost-effectiveness results were robust through a series of subgroup and scenario sensitivity analyses. Our findings thus provide supporting evidence for the rational use of ON101 as an add-on therapy to GWC in clinical practice for a multi-ethnic Southeast Asian country with a high-income economy. In addition, the value-based price of ON101 for various WTP thresholds was estimated, thereby facilitating policymakers' decision-making in reimbursement policies and pricing for this treatment.

DFUs incur a substantial economic burden on individual patients and healthcare systems. The presence of DFUs was associated with an extra annual medical cost ranging from $11 710 to $16 883 per person, which is nearly double the healthcare cost of diabetic care.[3] Nonetheless, current treatment for DFUs remains suboptimal as the healing rate is only 35% within 12 months, with a mean time-to-healing of 4.4 months.[20] The safety and efficacy of ON101, which regulates the M1/M2 macrophage balance, in accelerating wound healing for DFUs has been demonstrated.[6] This study, along with a previous CEA conducted from a Taiwanese healthcare sector

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perspective,[9] demonstrated the cost-effectiveness of ON101 with GWC versus GWC alone, particularly for subgroups with complex baseline DFU status. The effectiveness and drug price of ON101 were the most influential drivers of the economic results. The current study extended the cost-effectiveness results from a monoethnic country to a multi-ethnic Asian population comprising Chinese, Malay, Indian and other ethnicities in Singapore.

Moreover, reduced total healthcare costs were observed for the use of ON101 versus GWC alone, which might be explained by the decrease in costly adverse DFU-associated complications, such as gangrene and post-amputation, and the increase in the number of healing events (Figure 2A). Specifically, the reduced costs in the ON101 group are mainly attributable to the lower costs of gangrene and uninfected DFUs (i.e., 53.1% and 39.4% of the reduced costs, respectively) (Figure 2B); amputation accounted for only 5.6% of the reduced costs. The recurrence of DFUs is of great concern, with the risk as high as 42% at 1 year, 58% at 3 years and 64% at 5 years in patients with healed DFUs.[21] This highlights the importance of timely intervention (e.g., adding ON101 to GWC) for DFUs to avert healthcare costs and regular follow-up to prevent recurrent DFUs.

Furthermore, our findings align with existing economic evaluations of DFU treatments, supporting the cost-effectiveness of newer or advanced interventions, such as guideline-concordance wound care, advanced dressings, becaplermin gel (an active pharmacotherapy for DFUs) and adjunctive supportive therapies integrated with GWC. The observed cost-effective and in some cases cost-saving results underscore that effective DFU treatments, which promote wound healing and reduce healing time, could contribute to beneficial health effect at an affordable cost.[22–24]

NPWT is widely accepted as an adjuvant treatment for complex DFUs owing to its proven efficacy in accelerating wound healing.[25] In Singapore, it has recently been reimbursed for post-operative DFUs as an add-on therapy to GWC.[17] A scenario analysis comparing ON101 with GWC to NPWT with GWC was conducted. Adding NPWT to GWC amplifies the difference in total costs between the two intervention groups (i.e., from −$16 237 to −$29 978 per patient), resulting in ON101 with GWC being a more cost-saving alternative to NPWT with GWC. We also performed a two-way sensitivity analysis, in which the two most influential drivers of the ICER results, namely the relative risk of ON101 and that of NPWT for ulcer healing, were simultaneously varied to mitigate the effect of the uncertainty of these parameters. Generally, the intervention with ON101 was cost-effective compared to NPWT with GWC across various combinations of relative risks (Figure S3). This finding confirms the robustness of our analysis. Moreover, these results could be applied to countries with similar healthcare systems and reimbursement policies where NPWT is considered an adjuvant treatment for managing DFUs.

In Singapore, patients with DFUs tend to be elderly, with poorly controlled HbA1c.[26] We found that in the subgroup analyses, populations with more complex DFU status at the baseline (i.e., HbA1c ≥9%, ulcer size >5 cm^2 and ulcer duration ≥6 months) compared to their counterparts were more likely to benefit from the intervention of ON101. Specifically, we found greater cost-savings and more QALYs gained among these vulnerable populations receiving ON101 in addition to GWC compared to those receiving GWC alone. These findings are expected, as healing efficacy (i.e., odds ratio for healing) for patient subgroups with HbA1c ≥ 9%, ulcer size >5 cm^2 and ulcer duration ≥6 months was remarkably superior when compared to both the overall population and those with less complex DFUs (i.e., HbA1c < 9%, ulcer size ranges from 1 to 5, and ulcer duration <6 months).[6] Such an enhanced healing effect among these vulnerable populations is likely to contribute to a reduction in the subsequent treatment costs associated with DFU complications. In addition, these characteristics have been identified as risk factors that contribute to detrimental ulcer complications such as amputation and recurrent DFUs.[27,28] Given the financial constraint of healthcare systems, policymakers may prioritize these vulnerable subgroups with complex DFUs for the use of ON101. We also estimated the acceptable drug price of ON101 across scenario and subgroup analyses and for various WTP thresholds based on the appraisal outcomes of a CEA submitted to the Agency of Care Effectiveness in Singapore,[16] which ranged from $11 320 to $79 237 (Table S4). Hence, our results support health policy decisions regarding drug subsidies and financial assistance schemes for DFU patients with diverse clinical characteristics.

As artificial intelligence (AI) becomes widely utilized in medical research, its potential to optimize DFU treatments could be expected. For example, AlphaFold in drug discovery and clinical image-based AI models,[29,30] demonstrate how AI could enhance existing treatment regimens, provide individualized treatment plans, predict potential outcomes and allocate healthcare resources more efficiently. Therefore, future research may consider integrating AI technology in DFU care to improve patients' outcomes and enhance the efficiency of the healthcare system.

4.1 | Study limitations

First, the effectiveness data on wound healing for ON101 was collected from a trial setting with a short-term follow-up period.[6] A series of sensitivity analyses were thus conducted, including those where the effectiveness data of ON101 and simulation time horizons were varied. The consistent results of the cost-effectiveness of the use of ON101 mitigate this concern and confirm the robustness of our findings. Second, although Singapore is a multi-ethnic country, comprising Chinese, Malay, Indian and other ethnicities, this CEA was not stratified by ethnicity due to a lack of race-specific data. Type 2 diabetes patients of Malay and Indian descent, compared to those of Chinese descent, generally have poorer glycaemic control and thus are at a higher risk of foot complications.[27,31] Moreover, Malays have the highest smoking prevalence in Singapore and possess a greater proportion of peripheral vascular disease compared to the Chinese ethnicity.[27] In fact, the characteristics of the populations of Malay and

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Indian descent are comparable to the vulnerable subsets in our analysis; therefore, a greater cost-effective benefit of the use of ON101 for these racial groups is expected. Some socioeconomic status and lifestyle differences among these ethnicities need to be acknowledged. For example, Chinese patients with type 2 diabetes tend to have higher educational and income levels, be more physically active and be less likely to be current smokers than Malay and Indian patients.[32] Future economic studies that consider health accessibility and disparities among ethnic groups are warranted. Third, our modelling analysis might have oversimplified real-world practice. For instance, the transition probabilities between modelled health states and associated health utilities were assumed to be the same for both treatment interventions and constant across the simulation period, regardless of comorbidities, recurrent events and aging. However, the self-administration of ON101 at home after wound debridement reduces the frequency of follow-up visits, thereby enhancing patients' quality of life, benefits that may be underappreciated against the current assumption. This relatively conservative approach was adopted due to the limited empirical experience with ON101 in Singapore. To ameliorate these worries, PSAs with all variables varied simultaneously and scenario analyses with various time horizons were carried out. Their results were consistent with those of the base-case analysis. While future research based on real-world ON101 data is warranted to demonstrate the robustness of our findings. Fourth, this study was performed from the Singaporean healthcare sector perspective; hence, it did not consider the substantial indirect costs, such as productivity loss due to DFUs.[1] This might have led to an underestimation of the cost benefits related to the use of ON101. Finally, this study was conducted in an Asian region, applying the study results to scenarios other than the current study setting requires comprehensive consideration and careful interpretation.

5 | CONCLUSION

Our results showed that the use of ON101 with GWC compared to GWC alone was cost-effective among type 2 diabetes patients with DFUs from the Singaporean healthcare sector perspective. Greater economic benefits for patient subgroups with complex DFUs prove the value of the use of ON101 to facilitate resource allocation and prioritization for these vulnerable subsets.

AUTHOR CONTRIBUTIONS

H.Y.S. designed the study, analysed and interpreted the data and wrote the manuscript. K.Y.C. reviewed and edited the manuscript. N.G. provided study materials and reviewed the manuscript. H.T.-O. provided study materials, designed the study, interpreted the data and wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16473.

DATA AVAILABILITY STATEMENT

All data and material relevant to this analysis are presented in the outlined publication and Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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