ORIGINAL ARTICLE

Within-trial cost-effectiveness of novel macrophage-regulating treatment on wound healing in patients with diabetic foot ulcers

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Abstract

An M1/M2 macrophage-regulating treatment, ON101 cream, has shown its superior healing efficacy for diabetic foot ulcers (DFUs) versus standard absorbent dressing, according to a phase III trial. Given its high cost, corroborating the economic value of ON101 treatment can facilitate clinical and policy decision-makings. This study sought to evaluate the cost-effectiveness of ON101 versus an absorbent dressing for patients with DFUs from Taiwan's healthcare sector perspective. This economic evaluation utilized effectiveness and cost data (in 2022 USD) from a randomized controlled trial of ON101, published literature, and Taiwan's National Health Insurance program. Incremental cost-effectiveness ratio (ICER) against willingness-to-pay (WTP) threshold was estimated to determine the cost-effectiveness of treatment. Over a mean follow-up of 12.69 weeks in the full analysis set of patients (n = 236), 6 patients would need to be treated with ON101 versus the absorbent dressing to obtain a case of complete healing, which costed US$21,128 per complete-healing case gained. This ICER value was below WTP threshold of US$32,788. Cost-effective findings were consistent across sensitivity analyses, and more remarkable for patients with Wagner grade 2 ulcers, HbA_{1c} >7%, and plantar ulcers. All these results were similar in modified intention-to-treat set. The high upfront drug cost of ON101 could be offset by its superior healing efficacy. Considering key prognostic factors for DFUs while optimizing the allocation of limited healthcare budgets, ON101 should be prioritized for severe cases with poor ulcer prognosis.

Keywords: Cost, Cost-effectiveness analysis, Diabetic foot ulcer, Number needed to treat

1. Introduction

Diabetic foot ulcers (DFUs) are the leading cause of infection, lower-extremity amputation, and hospitalization among patients with diabetes [1]. The treatment of DFUs aims to accelerate wound healing and closure [2]. Unfortunately, under current practice, which generally comprises pressure relief, debridement, infection management, and revascularization, only 35% of DFUs heal within 12 months, with a mean healing time of 4.4 months [3] and a recurrence rate of approximately 40% and 60% within 1 and 3 years, respectively [4]. Although adjunctive treatments (e.g., biological agents, silver-containing dressings) are available, they are supportive care rather than pharmacotherapy and often in limited use among a subset of patients who failed optimal standard care [5].

A novel treatment for DFUs, ON101 cream, was recently introduced to accelerate wound healing

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through the regulation of the balance between M1 and M2 macrophages and the attenuation of chronic inflammation of diabetic wounds [6]. A multicenter phase III clinical trial of DFU patients who had the ulcer size between 1 and 25 cm^2, lasted for at least 4 weeks, and at Wagner grade 1 or 2 demonstrated that a 16-week treatment using ON101 generated superior complete healing rates in the overall study population across patients with different risk factors for DFUs, with a shorter time to reach healing compared to that for an absorbent dressing, and reported no serious treatment-related adverse events [7].

A cost-effective treatment for DFUs is urgently needed not only for individual patients to optimize health outcomes and enhance quality of life, but also for healthcare systems to restrain the health and economic burdens of DFUs [8,9]. The economic burden associated with DFU treatments for public and private payers was estimated to be in the range of $9 and $13 billion annually. The annual per-patient incremental cost attributable to DFUs was $11,710 and $16,883, respectively, for public and private insurance [10].

In this study, we perform an economic evaluation as a secondary analysis of the ON101 phase III trial to provide clinicians, payers, and policy-makers with an empiric, quantitative assessment of the value of ON101 treatment versus an absorbent dressing (i.e., dressing containing sodium carboxymethylcellulose, Aquacel; ConvaTec Ltd) for DFUs.

2. Materials and methods

2.1. Data source and description of study subjects

This study was approved by the Institutional Review Board of National Cheng Kung University (B-ER-110-080). To ensure the transparency and reproducibility of the cost-effectiveness analysis (CEA), all analyses are reported in compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (eTable 1 in the Supplement (https://doi.org/10.38212/2224-6614.3537)) [11]. Subjects from the full analysis set (FAS) and modified intention-to-treat (mITT) set of the ON101 phase III trial were analyzed [7], where the FAS comprised all trial participants and the mITT set included only those who met the criteria of eligible target ulcers (eMethods in the Supplement) (https://doi.org/10.38212/2224-6614.3537). Patient characteristics and effectiveness data in this CEA were obtained from the ON101 phase III trial [7] and costs were obtained from the trial [7], literature, and Taiwan's National Health Insurance program. The impact inventory for this CEA from a healthcare sector perspective is given in eTable 2 in the Supplement (https://doi.org/10.38212/2224-6614.3537). Briefly, cost paid by a third-party payer and by patients (i.e., out-of-pocket) were considered in this study.

2.2. Effectiveness measure in CEA

Given its clinical relevance and increasing use in economic evaluations related to diabetes [12,13], the number needed to treat (NNT) was adopted in this CEA as the measurement of treatment effectiveness for clinical outcomes. In the light of the ON101 trial, clinical outcomes included 1) a complete healing event measured as a primary outcome over a 16-week treatment course, 2) a 50% reduction in wound surface area and infected target ulcer measured as secondary outcomes over a 16-week treatment course, and 3) ulcer recurrence which were ascertain as an exploratory outcome during 12 weeks of follow-up period. NNT was estimated based on the cumulative incidence (CI) of clinical events in each group (i.e., ON101 and absorbent dressing) and the corresponding absolute risk reduction (ARR) (eMethods in the Supplement) (https://doi.org/10.38212/2224-6614.3537).

Moreover, the Cox proportional hazard model with adjustment for clinically important patients' characteristics (i.e., sex, diabetes duration, ankle-brachial index, amputation history, ulcer size, plantar ulcers, and exposure to metformin), which may affect treatment outcome (e.g., healing), was performed. The estimated hazard ratios (HRs) were obtained and then transformed to estimate NNTs (Equation (3), eMethods in the Supplement (https://doi.org/10.38212/2224-6614.3537)) [14]. To support clinical interpretations and policy decisions based on meaningful CEA results, NNT measures were only estimated for clinical outcomes with a statistically significant difference ($p < 0.05$) between the study groups.

2.3. Cost measure in CEA

Total healthcare costs per person with DFUs from treatment initiation (i.e., ON101 or absorbent dressing) to the end of follow-up (i.e., 28 weeks) were assessed in each treatment group. The estimation of costs was based on the healthcare utilization records measured in the ON101 trial [7], including the diagnostic fee, ON101 or absorbent dressing treatment, medical services related to DFU care (i.e., inpatient, outpatient, and emergency service and debridement), and co-medications (i.e., antibiotics and glucose-lowering agents). Except for treatment

costs which were calculated from the beginning of trial until a healing event occurred or the end of treatment course (i.e., 16 weeks), all medical expenses were estimated over 28 weeks of the trial period. The total treatment cost for ON101 cream was calculated by multiplying the amounts utilized by individual subjects with the unit cost of the ON101 cream, provided by the pharmaceutical company. The consumption of ON101 was based on each subject's wound surface. The unit price of medical service and treatment was informed by the reimbursement scheme of Taiwan's National Health Insurance [15].

To account for the between-group difference in patient baseline healthcare costs, a two-step cost adjustment approach was used [12,13]. Details can be found in eMethods in the Supplement (Equations (4) and (5) (https://doi.org/10.38212/2224-6614.3537)). Costs were standardized into 2022 values using the medical care component of Taiwan's consumer price index [16] and then expressed in United States dollars (US$) using an average exchange rate of US$1:NT$30.98. Of note, discounting was not applied in this CEA because only 28 weeks of the ON101 trial period were considered as the time horizon.

2.4. Base-case and sensitivity analyses

The cost-effectiveness of ON101 relative to absorbent dressing for DFUs was assessed using the incremental cost-effectiveness ratio (ICER). Briefly, an ICER was estimated as the incremental cost of using ON101 versus absorbent dressing multiplied by the NNT estimate for a given clinical outcome of interest within a study period. In the base-case CEA, the components of ICER were the crude incremental cost during 28 weeks between ON101 and absorbent dressing with adjustment for baseline healthcare spending (Equations (4) and (5), eMethods in the Supplement (https://doi.org/10.38212/2224-6614.3537)), and NNT, which was derived from the incidence rates (IRs) (Equations (1) and (2), eMethods in the Supplement (https://doi.org/10.38212/2224-6614.3537)).

Several sensitivity and subgroup analyses were conducted. First, the ICER was re-estimated based on the NNT estimates derived from the HRs (Equation (3), eMethods in the Supplement (https://doi.org/10.38212/2224-6614.3537)) and the between-group cost difference, which was measured from the trial recruitment until the end of observation (28 weeks of the trial period). Second, the estimation of ICER was based on the NNT derived from IR (Equation (2), eMethods in the Supplement (https://doi.org/10.38212/2224-6614.3537)) with the cost measured only from 16 weeks of the treatment course. Third, the ICER was assessed using the NNT calculated from HRs (Equation (3), eMethods in the Supplement (https://doi.org/10.38212/2224-6614.3537)) with the cost measured only from 16 weeks of the treatment course. In addition, one-way sensitivity analysis was performed to determine the impact of effectiveness and the cost parameter variation/uncertainty, which was quantified using the 95% confidence interval of a parameter, on the ICER results. Moreover, Wagner grade 2 ulcers, a high HbA_{1c} value, plantar ulcers, a large wound area, and smoking are associated with poor wound healing outcome [17,18]. Therefore, the CEA for the complete healing outcome was further stratified by these clinical characteristics, in which the effectiveness and cost parameter data specific to each subgroup were applied (eTable 3 in the Supplement (https://doi.org/10.38212/2224-6614.3537)). All of the above subgroup analyses were conducted under both FAS and mITT settings.

As recommended for a country without a predefined willingness-to-pay (WTP) threshold for CEAs [19,20], one and three times the per capita gross domestic product of Taiwan in 2022, namely US$32,788 and US$98,364 respectively, were adopted in this CEA as the WTP thresholds to determine whether the use of ON101 versus absorbent dressing was highly cost-effective (i.e., US$0 < ICER $\leq$ US$32,788) or cost-effective (i.e., US$32,788 < ICER $\leq$ US$98,364).

3. Results

There were 236 and 230 patients in the FAS and mITT set, respectively. The mean (SD) age of patients in the FAS and mITT set was 57.0 (10.9) and 57.2 (10.8) years, respectively. The majority were male, 175 (74.2%) in the FAS and 172 (74.8%) in the mITT set. The proportions of patients with Wagner grade 2 ulcers, plantar ulcers, and current smoking, and using insulin in the FAS and mITT set were similar (77.9%, 49.6%, 23.0%, and 57.0%, respectively).

Table 1 presents the crude IRs of DFU-related events for the FAS and mITT subjects. Compared to absorbent dressing, the IRs in the ON101 group were higher for beneficial events (i.e., complete healing, a 50% reduction in wound surface area) and lower for harmful events (i.e., ulcer infection and recurrence). Only complete healing showed a statistically significant difference between the two groups; that is, patients with ON101 compared to those using absorbent dressing had better complete healing rates, with ARRs for FAS and mITT subjects of −0.19 and −0.21, respectively, and adjusted HRs for FAS

Table 1. Disaggregated results for diabetic-foot-ulcer-related clinical outcomes associated with 16-week treatment course of ON101 versus absorbent dressing in 28-week study period.

	Incidence rate per 1,000 person-weeks		Estimated cumulative incidence		Mean follow-up time (weeks)	ARR	Adjusted HR (95% CIs)[a]	NNT[b,c]	NNT[b,d]
	ON101	Absorbent dressing	ON101	Absorbent dressing					
Full analysis set (n = 236)									
Complete healing	50.25	26.29	0.47	0.28	12.69	−0.19[f]	2.01 (1.36, 2.97)[g]	−5.33 (−15.02, −3.24)	−4.07 (−8.83, −2.90)
50% reduction in WSA	51.74	53.73	0.56	0.58	16.00	0.01	1.08 (0.35, 3.34)	N/A	N/A
Infection of target ulcer	3.16	3.94	0.05	0.06	15.58	0.01	0.94 (0.70, 1.24)	N/A	N/A
Ulcer recurrence [e]	13.80	12.02	0.18	0.16	14.64	−0.02	1.52 (0.58, 3.98)	N/A	N/A
Modified intention to treat (n = 230)									
Complete healing	51.38	25.24	0.48	0.27	12.72	−0.21[f]	2.14 (1.44, 3.18)[g]	−4.87 (−12.06, −3.05)	−3.78 (−7.75, −2.79)
50% reduction in WSA	52.44	53.57	0.57	0.58	16.00	0.01	0.70 (0.20, 2.47)	N/A	N/A
Infection of target ulcer	2.17	4.01	0.03	0.06	15.59	0.03	0.97 (0.73, 1.29)	N/A	N/A
Ulcer recurrence [e]	14.01	10.75	0.19	0.15	14.68	−0.04	1.77 (0.64, 4.91)	N/A	N/A

Abbreviations: HR, hazard ratio; CI, confidence interval; ARR, absolute risk reduction; NNT, number needed to treat; WSA, wound (ulcer) surface area; N/A, not applicable.

[a] Adjusted for patient baseline characteristics (i.e., sex, diabetes duration, ankle-brachial index, amputation history, ulcer size, plantar ulcers, and exposure to metformin).

[b] NNT estimate was only estimated for study outcomes with a statistically significant difference between the two treatment groups (i.e., p-value of incidence rate <0.05 or p-value of hazard ratio <0.05). A negative value of NNT indicates the number of patients needed to be treated with ON101 versus absorbent dressing to gain a case with beneficial results (i.e., complete healing) in time t.

[c] NNT was estimated based on the incidence rate.

[d] NNT was measured based on the survival probabilities derived from Cox proportional model analysis with adjustment for clinically significant factors.

[e] Ulcer recurrence was only estimated from patients having complete healing. The number of patients with ulcer recurrence were 114 and 111 in the full analysis set and modified intention to treat set, respectively.

[f] $p < 0.05$.

[g] $p < 0.001$.

and mITT subjects of 2.01 and 2.14, respectively. The NNT estimates derived from IRs were similar to those calculated based on adjusted HRs.

Table 2 shows that the crude medical cost per patient in the ON101 group was higher than that for patients using absorbent dressing (in FAS setting: US$4,458.95 versus US$668.64; in mITT setting: US$4,551.55 versus US$671.53). The higher cost in the ON101 group was mainly attributed to the higher acquisition cost of ON101 treatment. The expenses for using a dressing (i.e., absorbent dressing in a 12-week follow-up period) and wound drainage (i.e., during 28 weeks of the study period) in the ON101 group were lower than those for the absorbent dressing group (i.e., in the FAS setting, the costs of using absorbent dressing were US$88.32 versus US$116.19 and the costs of wound drainage were US$7.60 versus US$10.39 for the ON101 and absorbent dressing groups, respectively). Nevertheless, the adjusted costs per user in the ON101 group were US$3,967.42 and US$4,054.79 higher than those in the absorbent dressing group under the FAS and mITT settings, respectively.

The results of ICER in the base-case and sensitivity analyses are summarized in Table 3. Against a WTP threshold of US$32,788 (i.e., Taiwan's per capita gross domestic product), the base-case analysis indicated that using ON101 versus absorbent dressing was highly cost-effective for a complete healing outcome; that is, 6 and 5 patients would need to be treated with ON101 for a mean follow-up of 12.69 and 12.72 weeks to obtain one case of complete healing, resulting in US$21,128 and US$19,757 per case of complete healing gained under the FAS and mITT settings, respectively. The sensitivity analysis results for both the FAS and mITT settings (with ICER estimates ranging from US$15,344 to US$21,262 per case of complete healing gained) are consistent with the base-case analysis findings.

The complete healing rate in the ON101 group was generally higher than that in the absorbent dressing group across all subgroups (eTable 3 in the Supplement (https://doi.org/10.38212/2224-6614.3537)), suggesting that approximately 4–7 patients would need to be treated with ON101 relative to absorbent dressing to gain one case of complete healing under the FAS and mITT settings, with the most favorable result obtained for patients with plantar ulcers in the mITT setting (NNT: −3.70). eTable 4 in the Supplement (https://doi.org/10.38212/2224-6614.3537) shows that the between-group difference in adjusted medical costs is in the ranges of US$3,348 to US$5,482 and US$3,463 to US$5,463 across the subgroups under the FAS and mITT settings, respectively. The obtained incremental costs of ON101 compared to absorbent dressing in both the

Table 2. Disaggregated results of adjusted medical costs per patient over 28 weeks of study period for cost-effectiveness analysis.

	ON101 cream (per person, US$)	Absorbent dressing (per person, US$)	ΔCost (/person, US$)
Full analysis set (n = 236)			
Baseline healthcare costs	797.67	735.87	61.80
Crude total medical costs during 28 weeks of study period	4,458.95	668.64	3,790.31
Cost of using ON101/absorbent dressing in a 16-week treatment period	4,193.80	391.00	3,802.80
Costs of using antibiotics in a 16-week treatment period	23.04	8.72	14.32
Costs of using absorbent dressing in a 12-week follow-up period	88.32	116.19	−27.87
Costs of outpatient visits during 28 weeks of study period	146.18	142.34	3.84
Costs of wound (ulcer) drainage during 28 weeks of study period	7.60	10.39	−2.79
Adjusted total medical costs during 28 weeks of study period[a]	4,669.35	701.93	3,967.42
Modified intention to treat (n = 230)			
Baseline healthcare costs	805.08	737.10	67.99
Crude total medical costs during 28 weeks of study period	4,551.55	671.53	3,880.02
Cost of using ON101/absorbent dressing in a 16-week treatment period	4,289.36	396.30	3,893.06
Costs of using antibiotics in a 16-week treatment period	19.70	3.94	15.75
Costs of using absorbent dressing in a 12-week follow-up period	87.66	118.27	−30.60
Costs of outpatient visits during 28 weeks of study period	146.98	142.50	4.47
Costs of wound (ulcer) drainage during 28 weeks of study period	7.86	10.52	−2.65
Adjusted total medical costs during 28 weeks of study period[a]	4,759.83	705.04	4,054.79

Abbreviations: ΔCost, difference in costs per subject between ON101 and absorbent dressing groups over 28 weeks of study period.
Note: Except for drug acquisition cost derived from Huang et al.,[7] all costs were informed from the reimbursement scheme of Taiwan's National Health Insurance.

[a] Costs were measured from the recruitment of trial to withdrawal from trial, or the end of study (in a total of 28 weeks, which comprised 16 weeks of treatment and 12 weeks of follow-up), whichever came first. The total medical costs were adjusted for patients' baseline medical costs and clinical characteristics (i.e., age, gender, diabetes duration, complications [including myocardial infarction, ischemic heart disease, heart failure, arrhythmia, nephropathy, retinopathy, neuropathy, hypoglycemia, peripheral vascular disease], and treatments [including insulin and oral antidiabetic drug exposure]) using multivariable regression model analyses.

Table 3. Results of cost-effectiveness analysis of ON101 versus absorbent dressing for complete healing outcome over mean follow-up period of 12.69 and 12.72 weeks under FAS and mITT settings, respectively.

Scenario setting[b]	Number needed to treat (NNT)[a]	ΔC per person between groups (US$)	Costs per case of complete healing gained over 16 weeks (US$)
Full analysis set (n = 236)			
Base-case analysis	−5.33	3,967.42	21,127.73
First sensitivity analysis	−4.07	3,967.42	16,143.61
Second sensitivity analysis	−5.33	3,992.61	21,261.89
Third sensitivity analysis	−4.07	3,992.61	16,246.12
Modified intention to treat (n = 230)			
Base-case analysis	−4.87	4,054.79	19,756.75
First sensitivity analysis	−3.78	4,054.79	15,343.95
Second sensitivity analysis	−4.87	4,083.24	19,895.38
Third sensitivity analysis	−3.78	4,083.24	15,451.62

Abbreviation: HR, hazard ratio.

1. Base-case analysis: NNT was derived from incidence rate with the between group difference in medical costs (ΔC) measured from the trial recruitment until the end of trial.

2. First sensitivity analysis: NNT was derived from adjusted hazard ratio estimates with the between group difference in medical costs (ΔC) measured from the trial recruitment until the end of trial.

3. Second sensitivity analysis: NNT was derived from incidence rate with the between group difference in medical costs (ΔC) measured from 16 weeks of treatment course.

4. Third sensitivity analysis: NNT was derived from adjusted hazard ratios with the between group difference in medical costs (ΔC) measured from 16 weeks of treatment course.

[a] Negative NNT value refers to fewer patients required to be treated by ON1010 versus absorbent dressing to obtain a case with complete healing.

[b] Each analysis varied by the estimation of effectiveness (i.e., NNT) and cost parameters, which are as follows.

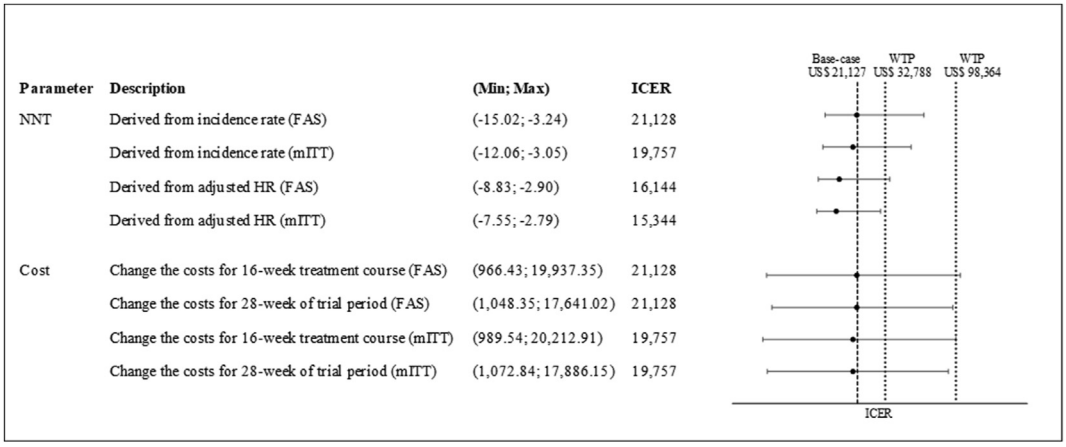
FAS and mITT settings among the subgroup analyses were generally higher than those (US$3,967.42 for FAS and US$4,054.79 for mITT) in the base-case analysis of overall study population, except for the subgroups of patients with HbA_{1c} >7%, non-plantar ulcers, wound area $\leq$5 cm^2, and non-current smokers. The subgroup CEA results (i.e., ICERs) are given in eFig. 1 in the Supplement (https://doi.org/10.38212/2224-6614.3537).

Fig. 1 summarizes the results of a one-way sensitivity analysis of the uncertainty (quantified using the 95% confidence interval) of effectiveness and cost parameters for a complete healing outcome. Generally, the ICER estimates were more sensitive to changes in cost parameters compared to the effectiveness data. As a result, using ON101 versus absorbent dressing remained highly cost-effective (i.e., ICER $\leq$ US$32,788) or cost-effective (i.e., ICER $\leq$ US$98,364) for complete healing across the sensitivity analyses using different effectiveness parameters. Moreover, the break-even analysis (Fig. 2) shows that if the per tube cost of ON101 doubles, using ON101 remains cost-effective compared to absorbent dressing.

4. Discussion

This economic analysis using empirical data from a randomized clinical trial supports the cost-effectiveness of using ON101 versus absorbent dressing. Such promising economic results are consistent across sensitivity analyses using different settings and estimations of effectiveness and cost parameters and subgroup analyses stratified by clinically significant characteristics for DFU progression (i.e., Wagner grade, HbA_{1c} value, plantar ulcers, wound area, and smoking status). These results thus strengthen the validity of the cost-effectiveness of using ON101 for the treatment of DFUs through enhanced wound healing. In fact, the cost-effectiveness of promoting wound healing through other DFU intervention strategies (e.g., TLC-NOSF dressing [21], becaplermin [22]) has been reported previously.

The results of one-way sensitivity analyses (Fig. 1) suggest that the economic analyses were robust across different estimations of effectiveness parameters and sensitive to changes in the cost parameters. That is, the range and magnitude of the variation in ICERs caused by changes in the cost parameters were considerably larger than those derived from different estimations of NNTs (Fig. 1). Moreover, the difference in healthcare costs between the 16 weeks of the treatment course and the 28 weeks of the trial period is minimal (e.g., crude costs in 16 weeks and 28 weeks under the FAS setting in the ON101 group are US$4,626.38 versus US$4,737.37 per case). A large proportion of the



Parameter	Description	(Min; Max)	ICER
NNT	Derived from incidence rate (FAS)	(-15.02; -3.24)	21,128
	Derived from incidence rate (mITT)	(-12.06; -3.05)	19,757
	Derived from adjusted HR (FAS)	(-8.83; -2.90)	16,144
	Derived from adjusted HR (mITT)	(-7.55; -2.79)	15,344
Cost	Change the costs for 16-week treatment course (FAS)	(966.43; 19,937.35)	21,128
	Change the costs for 28-week of trial period (FAS)	(1,048.35; 17,641.02)	21,128
	Change the costs for 16-week treatment course (mITT)	(989.54; 20,212.91)	19,757
	Change the costs for 28-week of trial period (mITT)	(1,072.84; 17,886.15)	19,757

Fig. 1. ***One-way sensitivity analysis for impact of cost and effectiveness parameter variations (quantified by 95% CIs) on ICER for complete healing outcome.*** *Abbreviations: FAS, full analyses set; mITT, modified intention to treat; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay; CI, confidence interval. Notes: 1. One-way sensitivity analysis was only conducted for clinical outcome with statistically significant difference between treatment (i.e., healing outcome). 2. For complete healing outcome, there were mean follow-ups of 12.69 and 12.72 weeks under FAS and mITT settings, respectively. 3. The lower and upper bounds of 95% confidence interval from the effectiveness estimates (i.e., incidence rate and HR) were utilized to calculate the minimum and maximum values of NNT. The Wald method was applied to determine the minimum and maximum values for the cost parameters (including costs in the 16-week treatment course and costs in overall 28-week trial period). Black solid dot indicates the point estimate of ICER. The range for the black solid dot (i.e., ICER estimate) were calculated using the minimum and maximum values of NNT and of the cost parameters under different settings (i.e., FAS or mITT). 4. The baseline medical cost was not examined in one-way sensitivity analysis because it was estimated based on patient baseline characteristics using a regression model analysis (Chen et al. 2020), where between-group difference in baseline characteristics (i.e., ON101 and Absorbent dressing) was relatively small.*

healthcare costs in the 16 weeks of the treatment course was contributed by the treatment (i.e., ON101). Therefore, one can expect that the drug acquisition cost of ON101 was the key factor in the economic analyses. However, the break-even cost analysis suggests that the use of ON101 would remain cost-effective even if its cost is doubled.

Consistent with the results for all study patients, a superior complete healing effect of ON101 versus absorbent dressing (supported by statistically

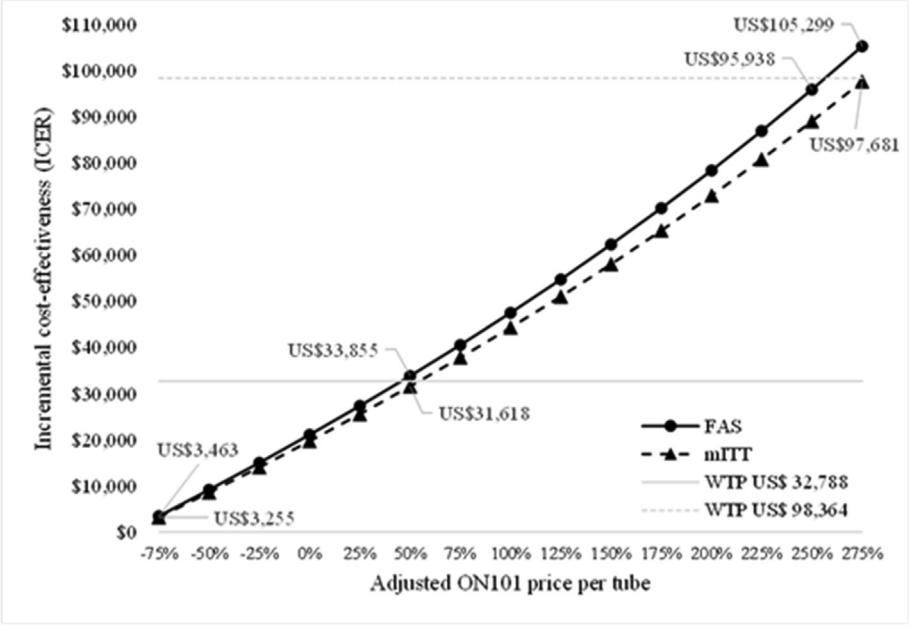


Fig. 2. ***Break-even analysis for ON101 treatment cost.*** *Abbreviations: FAS, full analyses set; mITT, modified intention to treat; ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay. Note: ICER estimates were calculated based on the effectiveness estimated from the number needed to treat for complete healing event and the costs derived from 28 weeks of trial period.*

significant ARR estimates) was found across the subgroups of patients, with greater healing efficacy (i.e., larger magnitudes of ARR and lower NNTs) among those with severe ulcers, foot plantar ulcers, and poor glycemic control compared to their counterparts and even the overall study population (e.g., ARRs/NNTs in the FAS setting for patients with wound area >5 cm^2, wound area ≤5 cm^2, and all study patients are −0.25/−3.99, −0.16/−6.44, and −0.19/−5.33, respectively; eTable 3 in the Supplement (https://doi.org/10.38212/2224-6614.3537)). Furthermore, the results of subgroup economic analyses not only corroborate the base-case analysis findings but also suggest the subgroup of patients who can most benefit from ON101 intervention. That is, the ICERs of the subgroup analyses were generally comparable to or lower than those of the base-case analysis (eFig. 1 in the Supplement (https://doi.org/10.38212/2224-6614.3537)), showing the high cost-effectiveness of using ON101 versus absorbent dressing for accelerating wound healing. In addition, compared to other subgroups, the smaller variations (in terms of 95% confidence intervals) in ICER estimates among patients with Wagner grade 2 ulcers, HbA_{1c} >7%, and plantar ulcers, which are associated with poor ulcer progression or delayed wound healing time [17,18,23], imply that the economic benefit of ON101 therapy among these patients is most robust and prominent. Hence, given limited healthcare resources and restrained budgets, these findings are important for supporting health policy-makers for the prioritization of ON101 treatment for patients at high risk for poor progression of ulcer wounds.

According to clinical treatment recommendations for DFUs, the primary goal is to achieve wound healing in a timely manner to prevent undesired consequences and complications (e.g., infection, amputation) [2]. This highlights the importance of prompt intervention to achieve this goal in the early stages of DFU development [24]. The present economic analysis found that the total medical costs for patients with minor ulcers (i.e., wound area ≤5 cm^2, Wagner grade of 1) were lower compared to those for patients with major or severe ulcers (i.e., wound area >5 cm^2, Wagner grade of 2). The medical costs in 12 weeks of follow-up for the ON101 group were generally lower than those for the absorbent dressing group, implying lower subsequent healthcare consumption for ON101-treated patients owing to the prompt wound control achieved by the treatment. This economic analysis thus supports the prompt use of ON101 for early DFU cases (e.g., patients with minor ulcers in term of size and severity) to ease the economic burden on the healthcare system through faster wound healing and reduce the downstream medical costs associated with the complications of DFUs (e.g., amputations).

The present study had some unique and strengths. First, the trial-based CEA supplements the previous model-based CEA findings [25] to support rational use of ON101. Specifically, the timeframe of this trial-based CEA was aligned with the follow-up length of its original clinical trial (i.e., 28 weeks) to deliver the economic benefit of the treatment which reflects the ideal setting (i.e., optimal treatment in the trial) and captures immediate and meaningful clinical outcomes (e.g., healed events typically occurring in one to six months) following the treatment. In particular, NNT, which is an intrinsically understandable metric and widely adopted across different disease types [13,26,27], was used to quantify the effectiveness of treatment in this trial-based economic analysis, which therefore enhances the understanding and interpretation of economic results for clinicians and facilitates decision-making in clinical practice. In contrast, the model-based CEA often requires multiple data sources and assumptions, and is typically conducted to estimate long-term economic consequences following the intervention of interest (i.e., ON101) with adoption of a generic measure of health burden, namely quality-adjusted life years (QALYs), as the main effectiveness outcome to quantify the overall treatment impact over a person's disease journey. Therefore, although the results from these two types of CEAs which focused on different aspects of economic outcomes of ON101 from the short-term or long-term time horizon and adopted different input parameters (e.g., costs) and outcome measures (e.g., healed event versus QALYs) might not be compared directly, they are complimentary and can be taken together to support the clinical decision for adoption of ON101.

Moreover, this trial-based CEA has several methodology strengths against the model-based CEA to enhance the validity of economic results. Specifically, unlike model-based economic studies [25] in which target populations, disease progression states, and treatment consequences are generally presumed based on data from multiple sources, this economic study adopted empirical data from a randomized clinical trial. Therefore, the concern regarding heterogeneity and uncertainty of study parameters in this CEA is negligible; the internal validity of the economic findings is thus improved. Several methodological enhancements were also adopted, including 1) different approaches for the estimation of NNTs (i.e., IR- or HR-based) were performed and consistent findings supported the study validity, 2) log-transformation was adopted to

reduce the skewness of cost data, and 3) a regression model-based adjustment for the between-group difference in the baseline medical costs was performed to eliminate the possibility of influence from patient baseline characteristics.

However, several limitations should be acknowledged. First, effectiveness measurements in this cost-effectiveness analysis were aligned with the clinical trial setting of ON101 which had a limited study period (i.e., 28 weeks). Also, NNTs, common effectiveness metrics in economic analyses, are typically applied for clinical events or outcomes with statistically significant difference between treatment groups (e.g., healing event in this study). So, inference from this within-trial economic analysis findings might not be extended to the DFU outcome which was clinically meaningful but not statistically significant between treatments under a short follow-up period (e.g., ulcer recurrence). Hence, future analyses which consider long-term clinical outcomes (e.g., ulcer recurrence, amputation) of DFU treatments are warranted. Second, regarding the nature of the trial design, our study subjects were well-controlled or closely monitored cases, which may result in limited generalizability to real-world settings where patients' adherence to DFU treatments and care is suboptimal and thus compromises DFU prognosis. Third, this economic analysis was based on trial data with a relatively small sample size and thus concern regarding the precision of the results might not be fully eliminated. Such a concern would be even amplified in the subgroup analyses with very small patient numbers. Hence, future economic analyses based on the data derived from large-scale patient populations comprising diverse clinical characteristics in real-world settings are warranted to confirm our findings. However, patients with Wagner grade 2 ulcers accounted for the majority of the trial population with DFUs (78%); this proportion is close to the distribution of Wagner grades among real-world patients with DFUs [28]. Fourth, since the costs in this study were derived from the trial data, the potential protocol-driven costs [29] have been considered. However, only direct medical utilization/medications and associated costs related to management of DFUs and T2D were included in the analyses. The resource utilization and costs used to identify or recruit the trial participants, as part of the protocol-driven costs, were not included in the analyses. The monitoring and testing performed for the trial participants were not more regular than those occurring in the usual clinical practice. Also, the cost of ON101 treatment was measured according to the actual consumption specific to the ulcer size of the trial participants. Fifth, Due to the unavailability of the well-established WTP threshold for the complete healing cases, one to three times the per capita gross domestic product as commonly recommended in Taiwan and worldwide [19,20] were thus adopted in this economic analysis. Future research may be needed to estimate the WTP threshold specific for clinically meaningful outcomes in some disease populations of interest. Lastly, this CEA from a healthcare sector perspective did not include costs from informal healthcare and non-healthcare sectors.

5. Conclusions

Compared to absorbent dressing, the greater pharmaceutical costs associated with ON101 for DFUs are substantially offset by its benefit of enhancing wound healing. This benefit is more remarkable for patients with Wagner grade 2 ulcers, HbA_{1c} >7%, and plantar ulcers, suggesting the prioritization of ON101 to severe cases and the rational use of ON101 with consideration of the key prognostic factors for DFUs. Prompt intervention with ON101 for early development of DFUs should be considered as it would reduce unnecessary medical consumption for wound care and alleviate downstream medical costs attributable to adverse complications.

Author contributions

H.Y.S. designed the study, performed the literature review, analyzed and interpreted the data, and wrote the manuscript. C.Y.Y. designed the study, analyzed and interpreted the data, and wrote the manuscript. Y.H.C. analyzed and interpreted the data. H.T.O. provided study materials, designed the study, interpreted the data, and wrote the manuscript. S.G.C. reviewed and edited the manuscript. J.C.C. reviewed and edited the manuscript. H.J.H. reviewed and edited the manuscript. S.K. designed the study, performed the literature review, interpreted the data, and reviewed and edited the manuscript. All authors approved the final manuscript.

Availability of data and material

All data and material relevant to this analysis are presented in the outlined publication and supplementary information.

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Conflict of interest

Huang-Tz Ou received a grant from Oneness Biotech Co., Ltd. Shyi-Gen Chen, Jui-Ching Chen, and Hui-Ju Ho are affiliated with Oneness Biotech Co., Ltd. No other disclosures are reported.

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