Randomized, double-blind, and multicenter study of ENERGI-F703 gel as a topical treatment for patients with diabetic foot ulcers

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INTRODUCTION

Various factors contribute to non-healing chronic wounds. Well-known countermeasures currently include antibiotics for infection control, moisture for wound bed preparation, extracellular matrix for cell proliferation, and more. Additionally, offloading and debridement should be incorporated as physicians deem necessary. Among chronic wounds with different etiologies, diabetic foot ulcers (DFUs) are the most notorious, complex, and burdensome. There is also room for improvement in their care. Despite the variety of countermeasures, is there a more direct and central therapy available? The intriguing question is whether cells can be mobilized for re-epithelialization or wound closure by simply providing energy. More specifically, not energy or adenosine triphosphate (ATP) itself, but its precursor molecule: adenine. Preclinical studies have shown that adenine-treated cells migrate faster than controls. Consequently, the question arises whether such migration can be translated into wound healing for DFUs. ENERGI-F703 is an adenine-based topical gel. In this trial, ENERGI-F703 is applied to DFU patients, and the treatment group demonstrates more complete closure of the ulcers.

OBJECTIVE

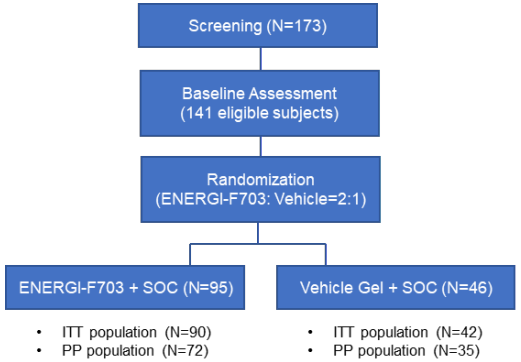
Diabetic foot ulcers (DFU) is a common problem with clinically serious sequelae. ENERGI-F703 gel is a topical treatment with twice-daily regimen. The active pharmaceutical ingredient (API) of ENERGI-F703 is adenine (0.02%), which has been used in humans for medical purposes for more than 50 years. The objective of this study was to evaluate the safety and efficacy of ENERGI-F703 in subjects with DFU.

METHOD

This study was designed as a randomized, double-blind, vehicle-controlled, multiple center and parallel trial, which involved eight medical centers in Taiwan. Patients with at least one cutaneous ulcer on the foot (including ulcers on the lower legs) and not healing for at least 4 weeks were assessed and classified according to the Wagner grading system (Grade 1-3 without active osteomyelitis). Patients who met all eligible requirements for the study were randomly assigned (2:1) to receive either one of topical application of ENERGI-F703 gel dose or vehicle gel, twice daily for 12 weeks or up to confirmed complete closure. The patients, investigators, and site personnel were masked to group allocation. The efficacy and safety conclusion were made on ITT population and safety population analysis results, respectively. The primary endpoint was the complete ulcer closure rate at the end of the treatment. Trial registration: This trial is registered with ClinicalTrials.gov, number NCT02672436.

Remark: this study was published in *eClinicalMedicine* 2022;51: 101497
Reference: Yang, Jui-Yung, et al. "ENERGI-F703 gel, as a new topical treatment for diabetic foot and leg ulcers: A multicenter, randomized, double-blind, phase II trial." *eClinicalMedicine* 51 (2022): 101497.

STUDY FLOW



RESULTS

173 patients were screened, where 32 were excluded as screen failure, resulting in a safety population of 141 (81.5%) patients who were enrolled and randomized to ENERGI-F703 gel treatment group (n=95) or vehicle group (n=46). In ITT population analysis, 90 patients in ENERGI-F703 group had 36.7% in response rate while those in vehicle group has 26.2%. Further analysis showed the 25% quartiles (QI) of the time to complete closure rate in ENERGI-F703 group had 69 days while those in the vehicle group had 84 days. Safety analysis of ENERGI-F703 group and vehicle group showed comparative incidence of serious adverse events of 25 patients (26.3%) and 11 patients (23.9%), respectively.

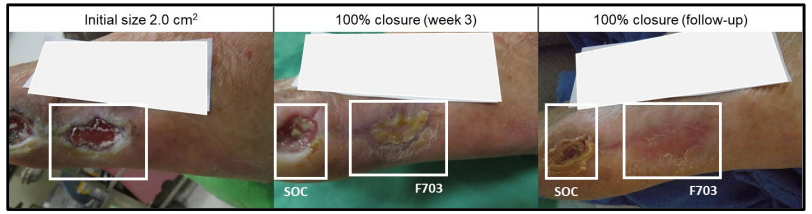
The most significant difference ($p<0.05$) between two groups was observed in patient subgroup of Grade 1~2 and size 1.5~25 cm2, 36.7%(ITT)/43.9%(PP) ulcer closure rate in the ENERGI-F703 while 9.1%(ITT)/10%(PP) in vehicle group.

SIGNIFICANT OUTCOME

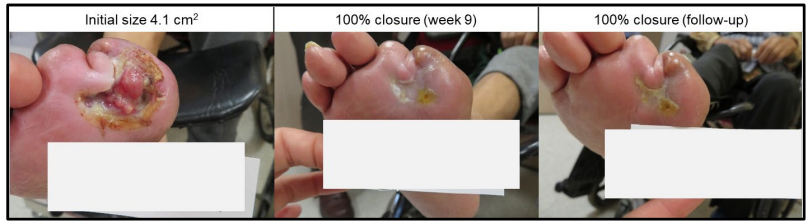
	Complete closure incidence	ENERGI-F703 gel		Vehicle group		P value
ITT analysis	All subjects (Grade 1~3, 1~36 cm^2)	33/90	36.7%	11/42	26.2%	0.264
	Subpopulation (Grade 1~2, 1.5~25 cm^2)	19/52	36.7%	2/22	9.1%	**0.017**
PP analysis	All subjects (Grade 1~3, 1~36 cm^2)	32/72	44.4%	10/35	28.6%	0.168
	Subpopulation (Grade 1~2, 1.5~25 cm^2)	18/41	43.9%	2/20	10%	**0.008**

CLINICAL CASES

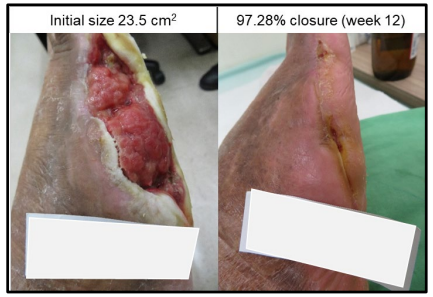
Case 1: Ulcer of Wagner grade 2 (2.0 cm^2) completed closure in 3 weeks with treatment by F703 gel.



Case 2: Ulcer of Wagner grade 3 (4.1 cm^2) completed closure in 9 weeks with treatment by F703 gel.



Case 3: Ulcer of Wagner grade 3 (23.5 cm^2) completed closure in the follow-up period after treatment by F703 gel for 12 weeks.



DISCUSSION

The study results suggest ENERGI-F703 gel is safe for topical treatment and appears to be efficacious in treating diabetic foot ulcers. The efficacy of ENERGI-F703 will be further confirmed in a larger study with a more precise design of targeted ulcer size and ulcer grade.

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