

A Novel Topical Drug Proved Superior Efficacy from Global Ph3 on Diabetic Foot Ulcers

Abstract no. OP03

Conflict of Interest

Source of Funding:

This study was supported by Oneness Biotech Co., Ltd.

Conflict of Interest:

Min-Liang Kuo is employed by Oneness Biotech Co., Ltd.

DFU - Severe & life-threatening

- DFU is the leading cause to disability and death of DM patients
- Global prevalence of DFU is **6.3%**¹ and the annual recurrence rate is **30-40%**²
- A lower limb amputation on DM patients occurs every **20 seconds**³ globally
- The survival of DFU amputees is less than **60%**⁴

Source:

1. IDF atlas 2018; 2. Armstrong, et. al, Diabetic Foot Ulcers and Their Recurrence, 2017, NEJM; 3. Pemayun TG, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital-based case-control study. Diabet Foot Ankle. 2015; 4. Survival of diabetes patients with major amputation is comparable to malignant disease; Diabetes & Vascular Disease Research 2015, Vol. 12(4) 265–271

Novel Phase 3 Topical Drug : ON101

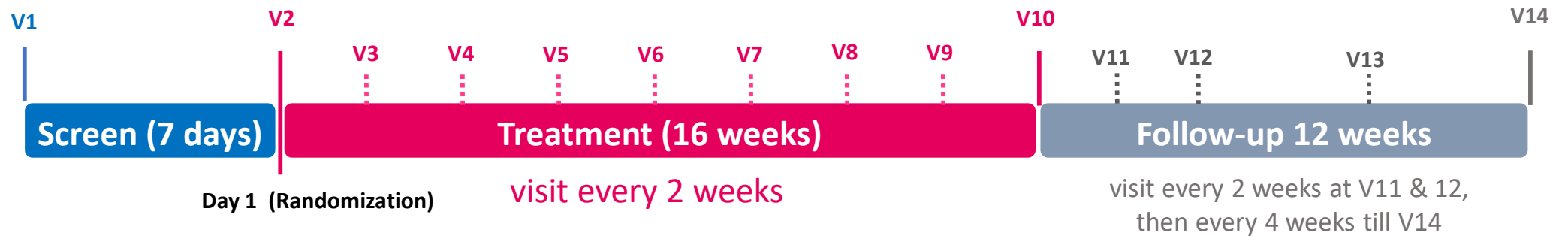
Product	ON101 Cream
Active Ingredients	PA-F4 (from <i>P. amboinicus</i>) & S1 (from <i>C. asiatica</i>)
Dosage Form	Topical/ External Use, 15g /tube
Dosing	Topical application, twice a day
Storage	Room temp. storage, good stability
Manufacturing	PIC/s GMP standard
Status	46 non-clinical pharmacological studies, 13 GLP tox studies, 8 MoA studies (in-vitro, in-vivo, ex-vivo, clinical) 4 clinical studies (including 1 Ph 3 study) Under NDA procedure in Taiwan and China

**Clinical Efficacy and Safety of ON101 in Treatment of
Diabetic Foot Ulcers:
A Phase 3, Active Controlled, Evaluator-Blinded,
Multicentre, Randomized Trial**

Phase 3 MRCT Design

212 evaluable subjects from Taiwan, China, US (21 sites)

ON101 (111 subjects) vs. Aquacel® Hydrofiber® Dressing (101 subjects)



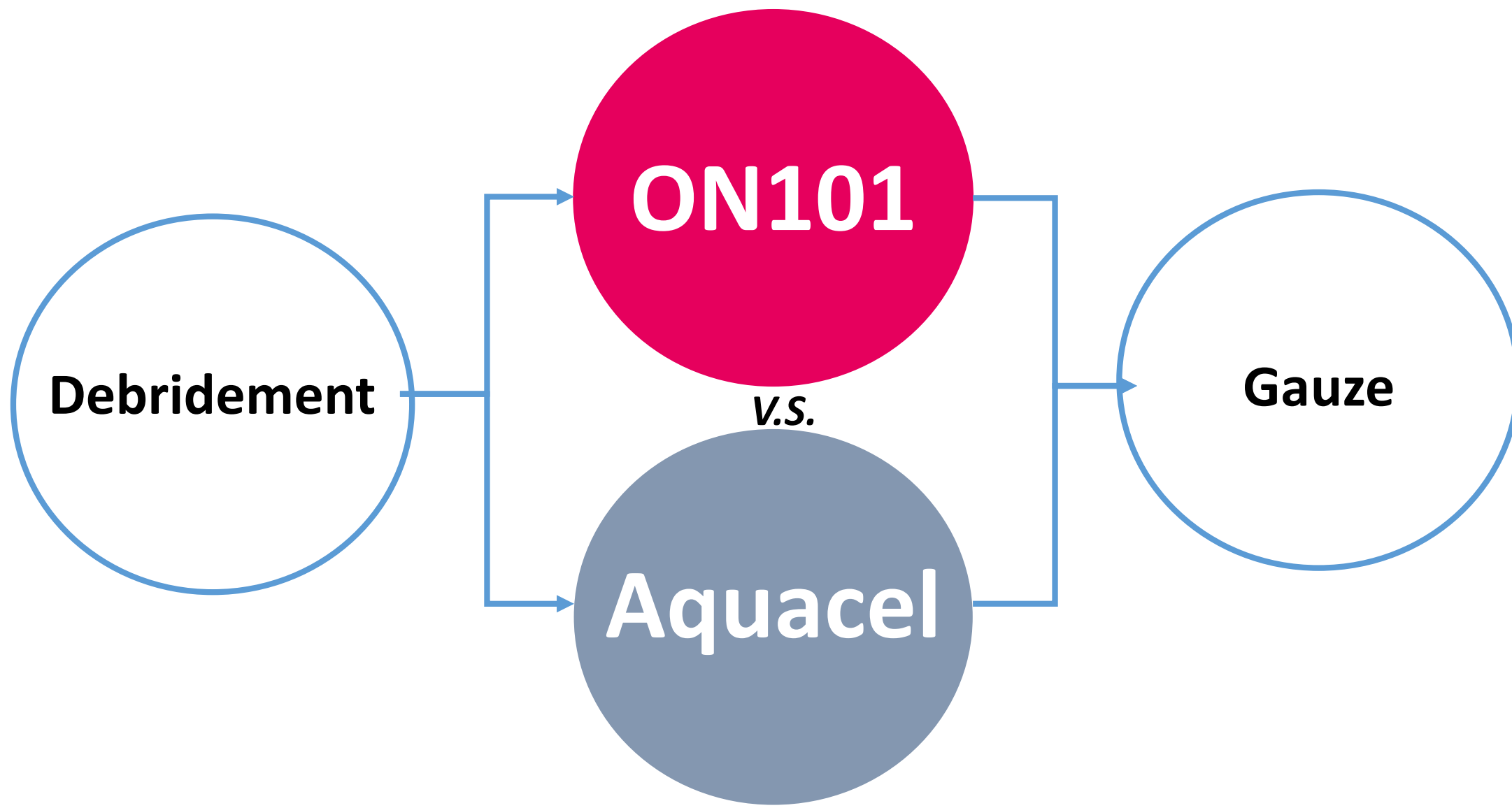
Key inclusion criteria

- ABI ≥ 0.8
- Wagner Grade 1 or 2
- Wound Size 1-25 cm²
- Wound present for at least 4 weeks
- HbA_{1c} < 12%
- Non-active infection

Primary Endpoint: the comparison of the incidence of complete healing of the target ulcer between the two treatment groups at the end of treatment.

According to Guidance for Industry – Chronic Cutaneous Ulcer and Burn by US FDA, complete healing means complete epithelialization which is maintained with no drainage for at least 2 weeks (consecutive 2 visits).

ON101 Treatment Procedure in Phase 3



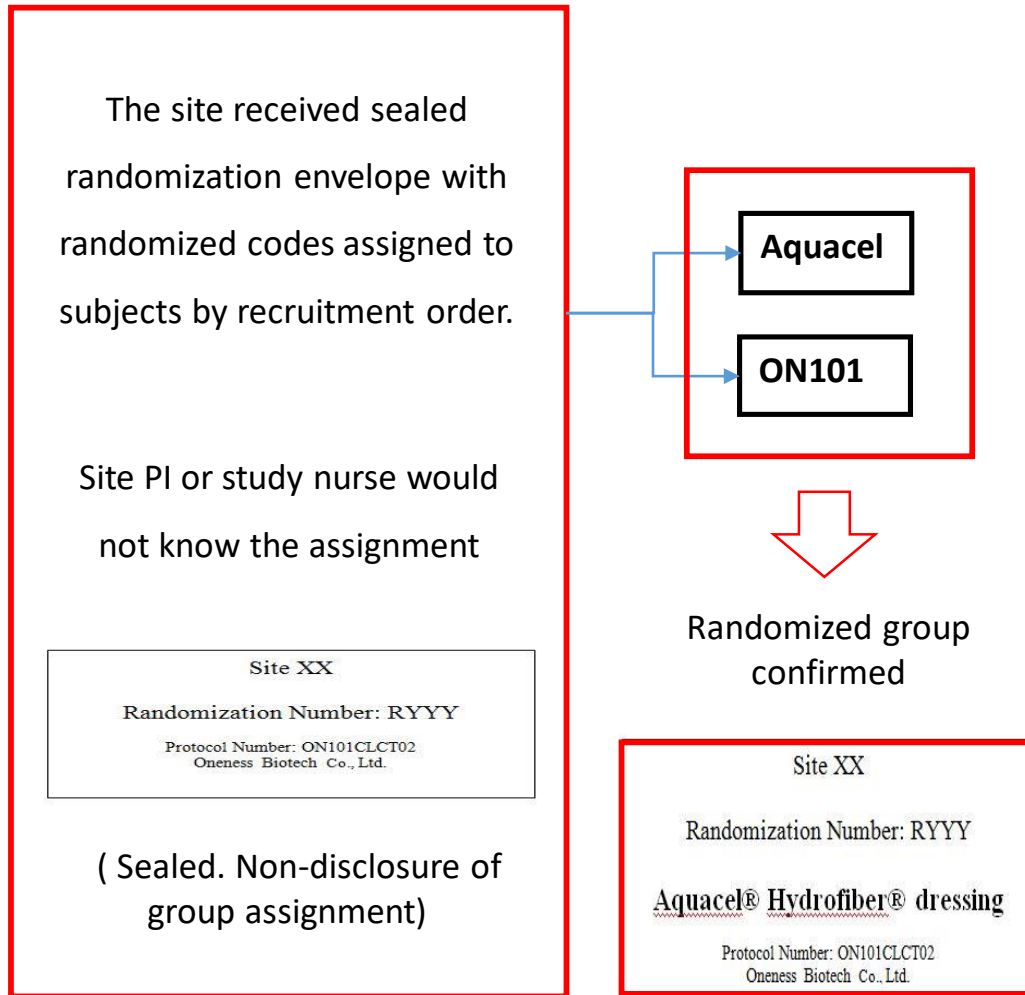
Open-label Design & Blinded Evaluation

For ethical consideration, it is adapted active-controlled concurrent design according to US FDA and Aquacel Hydrofiber dressing used widely in chronic wound care was selected to give adequate care in control group.

Since this is an open-label study, it is necessary that strict blinded evaluation was implemented.

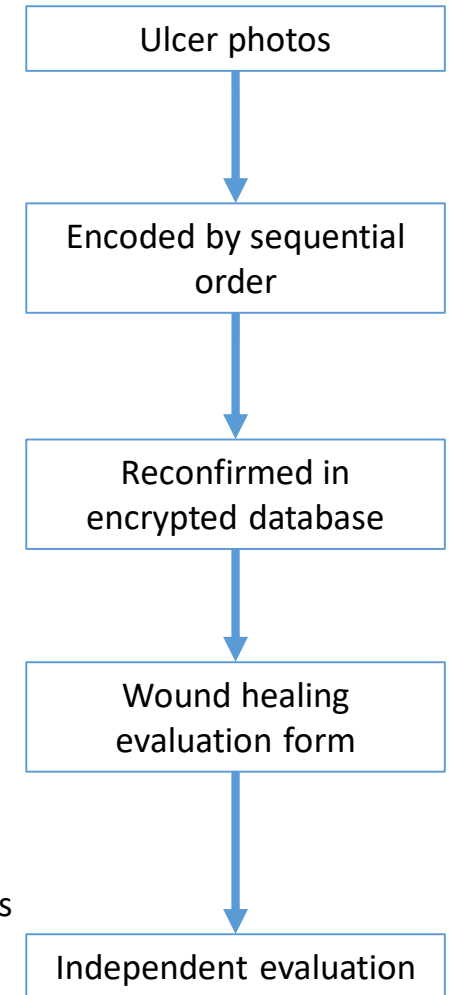
Implementation of Blindness – 1

① Blinded Block Randomization



② Standardized Blinded Procedure

1. Target Ulcer: 1. Whole foot x1
2. 3 closer takes from 3 angles
2. An independent staff encodes the photos of each subject by sequential order upon receipt
3. 2nd independent staff reconfirmed the sequential coding in encrypted database
4. Sequential coding filled in wound healing evaluation form and printed
5. 2nd independent staff brings laptop with photos of the subjects under sequential coding and evaluation form to the independent evaluator



Implementation of Blindness – 2

③ Standardized Camera and Photos

Standardized Camera Setting

1. Camera setting :
P mode auto
1. Still Image size : 5M
2. Shutter : Auto focus by pressing shutter halfway down and take photo by pressing shutter completely
3. EV : 0
4. ISO : 200
5. White balance : Auto
6. AF : Auto focus
7. Metering mode :
Centre-weighted
Average Metering
8. DRO : DRO Standard
9. Flash : off

Target Ulcer (Whole foot x 1)



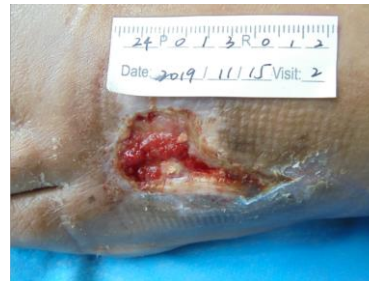
From 30 cm distance

**Label:
Visit, date,
group assignment,
patient number**

Target Ulcer (3 angles)



Front

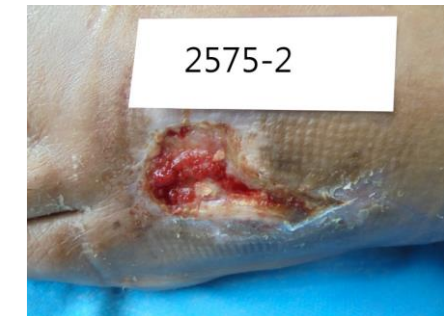


Left



Right

④ Independent Blinded Coding



Implementation of Blindness – 3

⑤ Independent Delivery for Blinded Evaluation

⑥ Blinded Independent Reviewer





Independent Blinded Evaluation for Wound Healing		
Protocol No.: ON101CLCT02	IP Name: WH-1 Ointment	Image No.: _____
Protocol Title: Randomized Controlled Study to Evaluate the Efficacy and Safety of WH-1 Ointment for the Treatment of Chronic Diabetic Foot Ulcers		
Wagner Staging	☐ Grade 0: pre-ulcerative lesions, healed ulcers ☐ Grade 1: Superficial ulcer ☐ Grade 2: Deep ulcers ☐ Grade 3: Deep ulcers with osteitis, abscess or osteomyelitis ☐ Others	
Healed Ulcer	☐ Yes ☐ No	☐ Epithelialized ☐ Macerated ☐ Scab ☐ Exposed tissue ☐ Granulation tissue
Signature of Reviewer: Date: 		



2575

Independent Blinded Evaluation for Wound Healing		
Protocol No.: ON101CLCT02	IP Name: WH-1 Ointment	Image No.: 2575
Protocol Title: Randomized Controlled Study to Evaluate the Efficacy and Safety of WH-1 Ointment for the Treatment of Chronic Diabetic Foot Ulcers		
Wagner Staging	☐ Grade 0: pre-ulcerative lesions, healed ulcers ☒ Grade 1: Superficial ulcer ☐ Grade 2: Deep ulcers ☐ Grade 3: Deep ulcers with osteitis, abscess or osteomyelitis ☐ Others	
Healed Ulcer	☐ Yes ☒ No	☐ Epithelialized ☐ Macerated ☐ Scab ☐ Exposed tissue ☒ Granulation tissue
Signature of Reviewer: <u>Ha-Tei Shien</u> Date: <u>2019-11-20</u>		
Image No. <u>2575</u> Site No. <u>24</u> P <u>013</u> R <u>012</u> Visit No. <u>2</u> Recorder <u>W. of Admin</u> Date <u>2019-11-20</u>		

Implementation of Blindness – 4

⑦ Blinded Coding Delinks Visits

V5

Independent Blinded Evaluation for Wound Healing 2659

Protocol No.: ON101CLCT02	IP Name: WH-1 Ointment	Image No.: <u>2659</u>
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Protocol Title:
Randomized Controlled Study to Evaluate the Efficacy and Safety of WH-1 Ointment for the Treatment of Chronic Diabetic Foot Ulcers

Wagner Staging	☐ Grade 0: pre-ulcerative lesions, healed ulcers ☒ Grade 1: Superficial ulcer ☐ Grade 2: Deep ulcers ☐ Grade 3: Deep ulcers with osteitis, abscess or osteomyelitis ☐ Others	
	☐ Yes ☒ No	☐ Epithelialized ☐ Macerated ☒ Scab ☐ Exposed tissue ☐ Granulation tissue

Signature of Reviewer: Hayte Chin Date: 2019-12-25

Image No.	2659
Site No.	24 P 013 R 012
Visit No.	5
Recorder	Vif. Chin Date 2019-12-25

2 weeks
apart



V6

Independent Blinded Evaluation for Wound Healing 2685

Protocol No.: ON101CLCT02	IP Name: WH-1 Ointment	Image No.: <u>2685</u>
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Protocol Title:
Randomized Controlled Study to Evaluate the Efficacy and Safety of WH-1 Ointment for the Treatment of Chronic Diabetic Foot Ulcers

Wagner Staging	☒ Grade 0: pre-ulcerative lesions, healed ulcers ☐ Grade 1: Superficial ulcer ☐ Grade 2: Deep ulcers ☐ Grade 3: Deep ulcers with osteitis, abscess or osteomyelitis ☐ Others	
	☒ Yes ☐ No	☒ Epithelialized ☐ Macerated ☐ Scab ☐ Exposed tissue ☐ Granulation tissue

Signature of Reviewer: Hayte Chin Date: 2020-1-8

Image No.	2685
Site No.	24 P 013 R 012
Visit No.	6
Recorder	Vif. Chin Date 2020-01-08

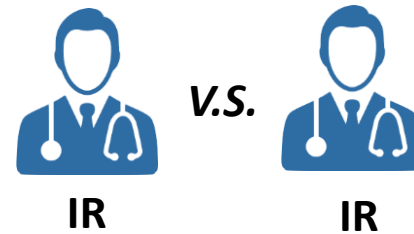
Evaluation results will be sent to study site and
recorded in CRF on the same day

Blinded Evaluation Consistency by Sensitivity Analysis

Healing status evaluated by independent evaluator (IR) and re-assessed by independent review committee (IRC) consisting of IR and 2 more experts based on photos of 2 visits for final evaluation

- According to the review comments of Taiwan Food and Drug Administration, an Independent Reviewer Committee was established to reconfirm the healing results consistency.
- The members of Independent Reviewer Committee consists of 3 physicians specialized in plastic surgery, wound care, etc.
- The trial sponsor shall provide the photos of target ulcer encoded under blinded randomization according to Trial Procedure Guidance to the independent CRO personnel without disclosing the relevant information of the subjects (including date of visit, visit number, treatment group, and subject number)

Intra-evaluation



Inter-evaluation



IRC results: According to the sensitivity analysis between intra-evaluation or inter-evaluation, the accuracy is **99.53%** which reflects the consistency in healing status evaluation and the strict blind evaluation execution.

Balanced Baseline Characteristics (FAS)

Patient Characteristics	ON101 cream (n=111)	AHD* (n=101)	P-value**
Characteristic, n (%)			
Age (years) (SD)	56·6(10·6)	55·9 (11·4)	0.639
Men	85 (76·58%)	73 (72·28%)	0.529
BMI	61 (54·95%)	61 (60·40%)	0.341
≥ 25 (kg/m²)			0.4871
Type 2 Diabetes	110(99·10%)	100 (99·01%)	>0.999
Diabetic duration			
≤ 2 years	18 (16·22%)	14 (13·86%)	0.134
>2 to ≤5 years	11 (9·91%)	11 (10·89%)	
> 5 to ≤10 years	23 (20·72%)	10 (9·90%)	
> 10 years	59 (53·15%)	66 (65·35%)	
Mean HbA _{1c} (%)(SD)#	8·1(1·5)	8·1 (1·8)	0.767
Diabetic complications			
Cardio-vascular disease	75 (67·57%)	72 (71·29%)	0.656
Diabetic kidney disease	23 (20·72%)	14(13·86%)	0.235
Diabetic retinopathy	38 (34·23%)	31 (30·69%)	0.660
Smoking	49(44·14%)	35(34·65%)	0.266

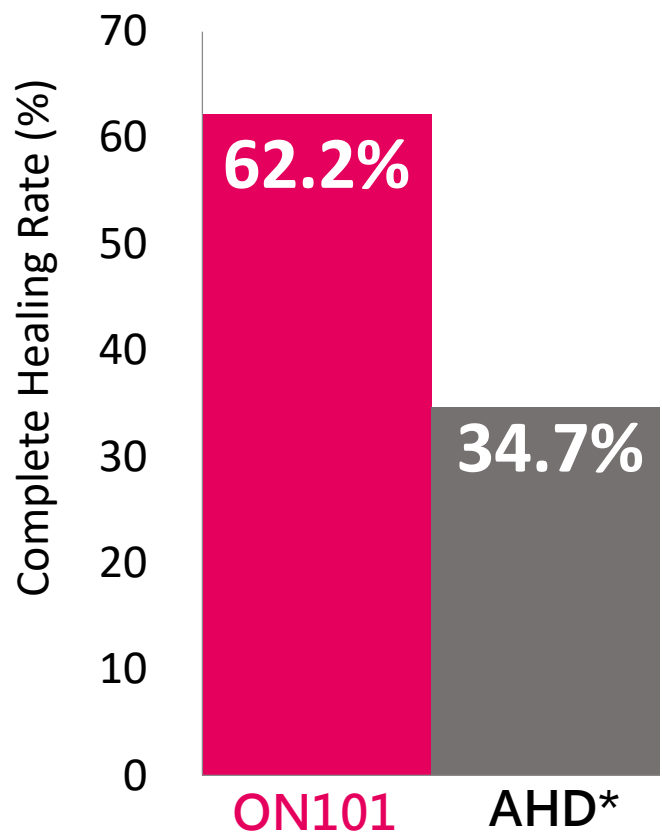
Wound Characteristics	ON101 cream (n=111)	AHD* (n=101)	P-value**
Ulcer etiology			
Neuropathy	74(66·67%)	62 (61·39%)	0.740
Peripheral vascular disease	25 (22·52%)	24 (23·76%)	
Neuro-ischemia	6 (5·41%)	6 (5·94%)	
Other	6 (5·41%)	9 (8·91%)	
Amputation history due to DFU	50 (45·05%)	50 (49·50%)	0.582
Ankle-brachial index (SD)	1·1(0·2)	1·1 (0·1)	0.291
Ulcer location			
Non-plantar	49 (44·14%)	51 (50·50%)	0.409
Plantar	62 (55·86%)	50 (49·50%)	
Ulcer duration (months)(SD)	7·7 (13·5)	7·3 (14·4)	0.849
1~6 months (n)(%)	75 (67·56%)	70(69·3%)	
≥ 6 months (n)(%)	36(32·43%)	31(30·7%)	
0.883			
Ulcer severity (Wagner grade)			
Grade 1	29 (26·13%)	23 (22·77%)	0.633
Grade 2	82 (73·87%)	78 (77·23%)	
Ulcer size (cm²)(SD)	4·50 (0·43)	4·60 (0·42)	0.886
1.01 -5	83 (74·77%)	72 (71·28%)	
>5	28 (25·22%)	29 (28·71%)	
0.642			

*Aquacel® Hydrofiber® Dressing ** ANOVA test for continuous variables and Fisher's exact test for categorical variables

Phase 3 Execution and Results

- With randomization equality, the baseline characteristics between 2 groups are well-balanced.
- Under strict blinded evaluation, the healing efficacy has been assessed by IR and IRC with consistency.
- ON101 has achieved the best complete healing rate in DFU in the last 20 years based on the above criteria.

Primary Endpoint : Complete Healing (FAS)

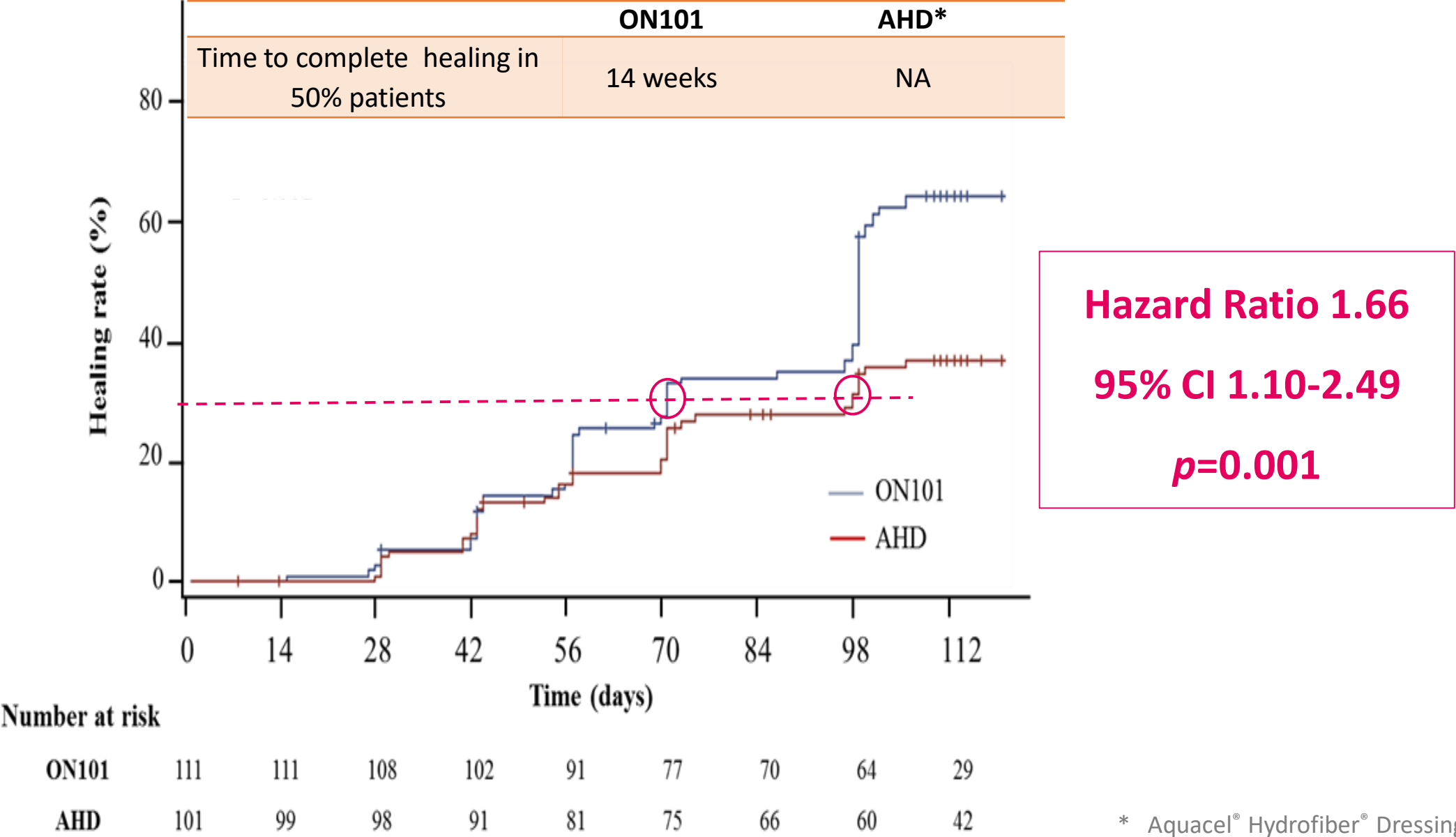


	ON101	AHD*	P-value
N	111	101	
Complete healing	69 (62.2%)	35 (34.7%)	0.0001
Non-complete healing	42 (37.8%)	66 (65.3%)	

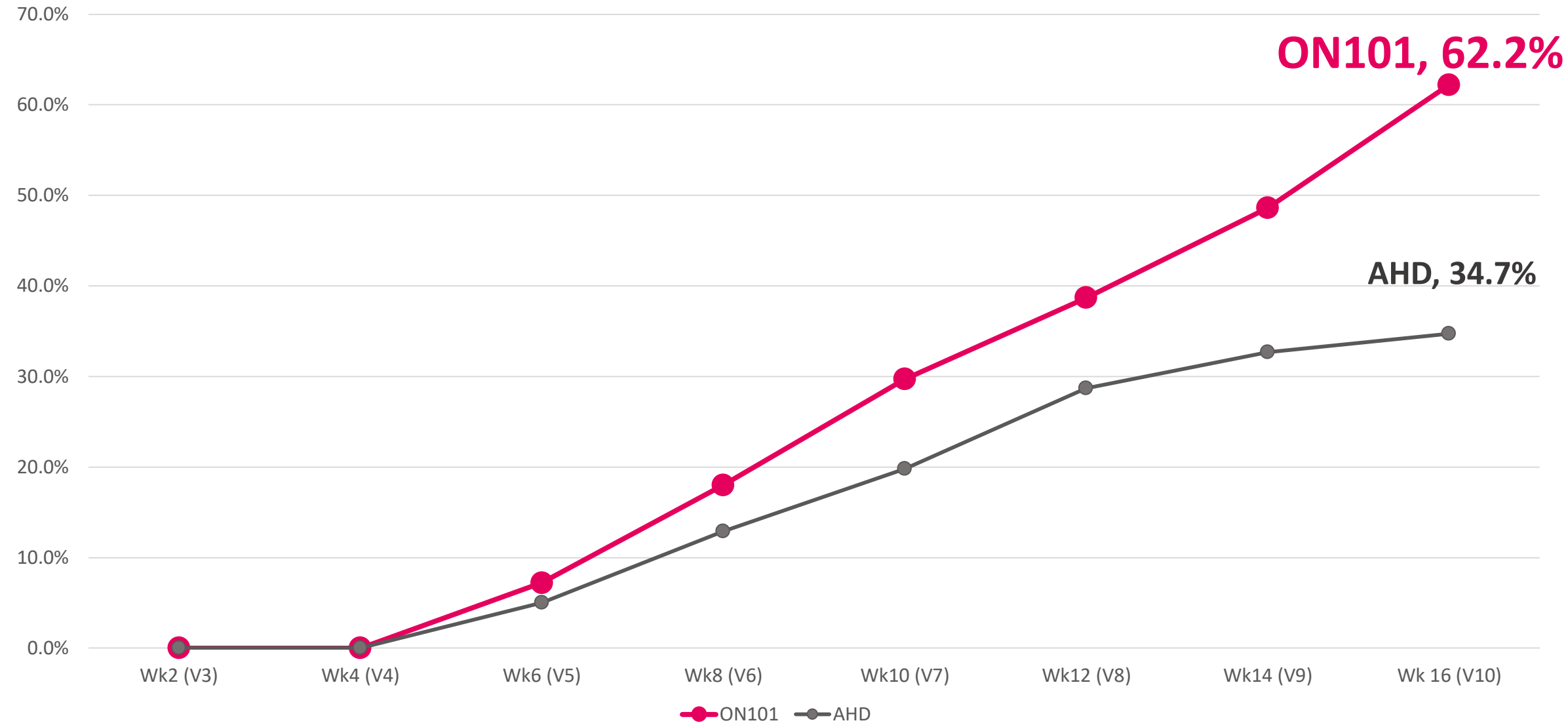
P = 0.0001 ($\alpha < 0.03476$)

* Aquacel® Hydrofiber® Dressing

Secondary Endpoint: Time to Healing (FAS)



Complete Healing Curve



Hard-to-heal Prognostic Indicators

Wounds

- **Wound Severity**
- **Wound Location**
- **Wound Size**
- **Wound Duration**

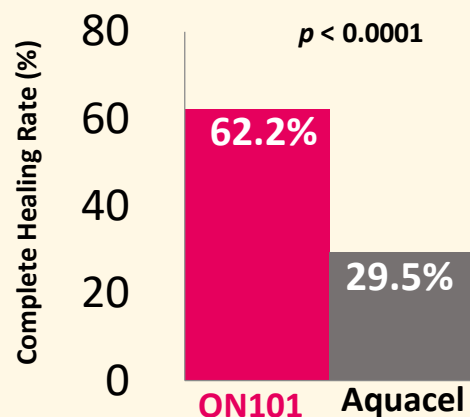
Patients

- **HbA_{1c}**
- **BMI**
- **Smoking Status**
- **Neuropathy**

Hard-to-heal Analysis

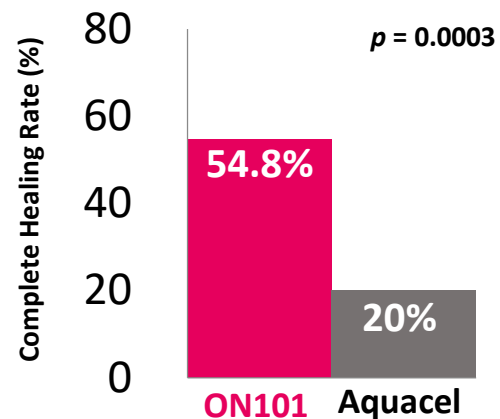
Wagner Grade 2 Wounds

Complete Healing Rate (FAS)



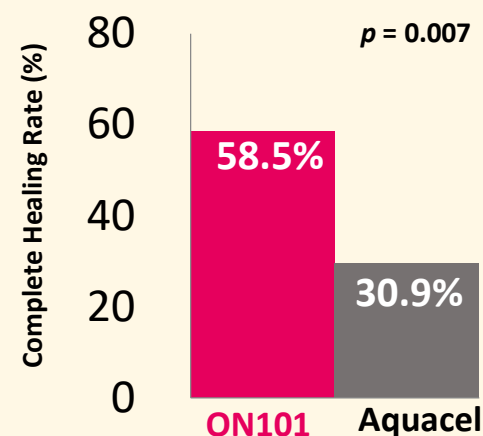
Plantar Wounds

Complete Healing Rate (FAS)



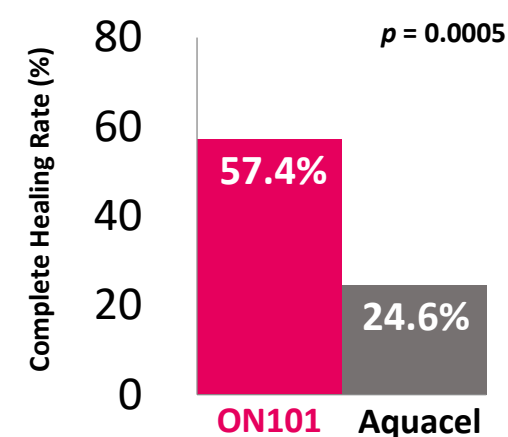
HbA_{1c} >7%

Complete Healing Rate (FAS)



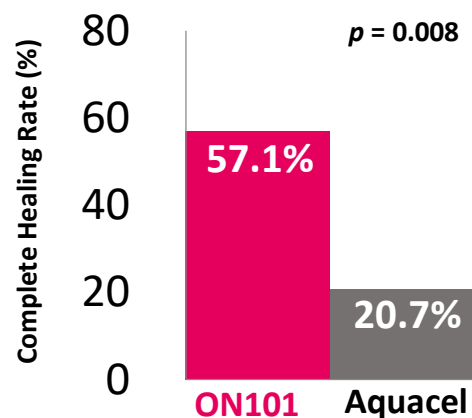
BMI ≥ 25

Complete Healing Rate (FAS)



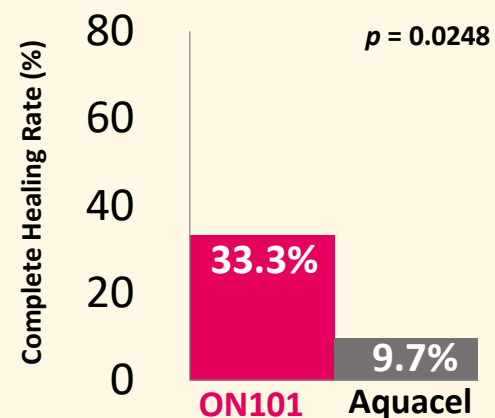
> 5 cm² Wounds

Complete Healing Rate (FAS)



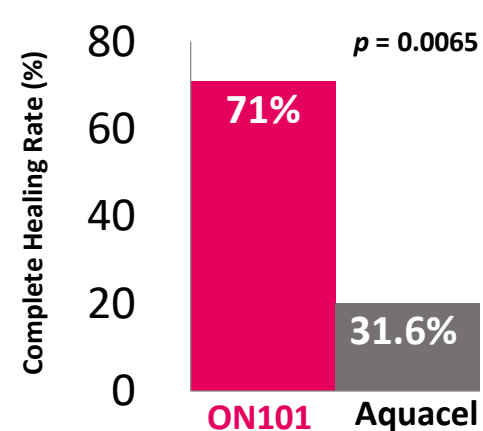
≥ 6 m Duration

Complete Healing Rate (FAS)



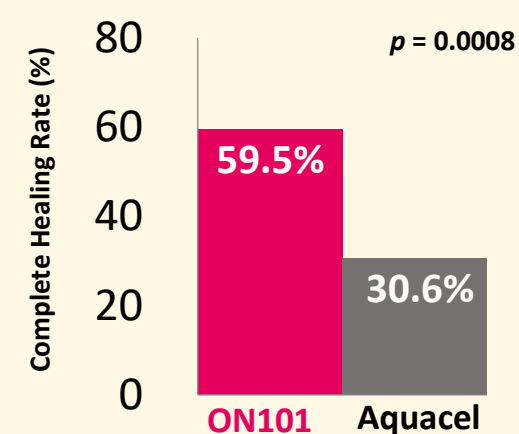
Current Smokers

Complete Healing Rate (FAS)



Neuropathy

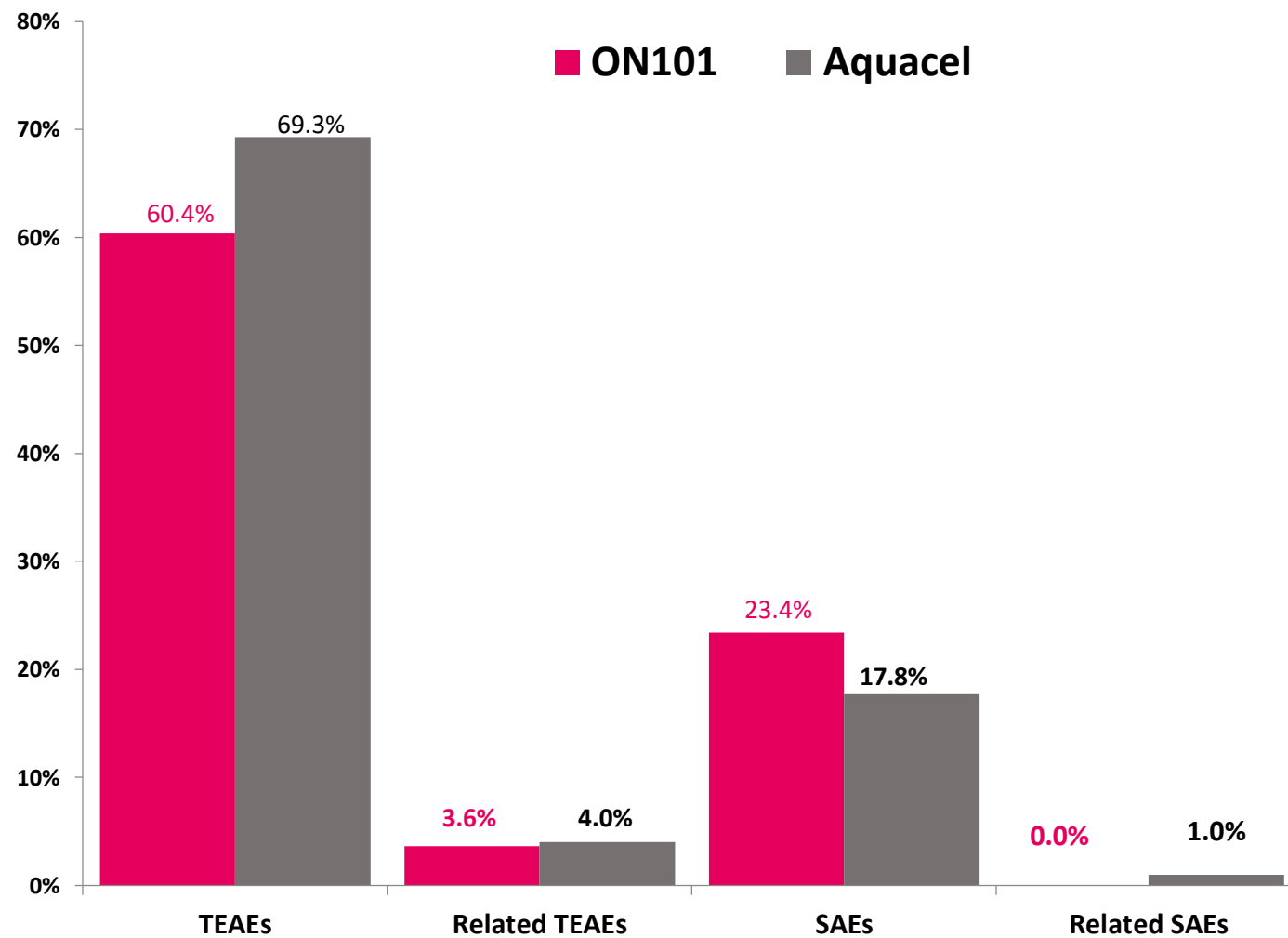
Complete Healing Rate (FAS)



Clean Safety Profile

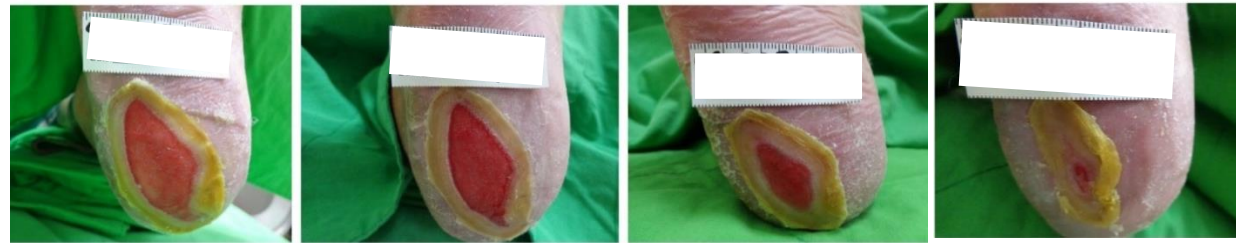
ON101 is well tolerated with clean safety profile for the treatment in DFUs.

- ① **TEAE or related TEAE is lower than comparator group**
- ② **None of treatment related SAE occurred in ON101 group**



Case (1)

DM>10 y ;Ulcer duration 6 mons
Wagner Grade 2; Plantar



V1
Area: 6.49 cm²

V2
Area: 4.99 cm²

V3
Area: 2.18 cm²

V4
Area: 0.14cm²



V5
Healing

V6
Healing



Follow-up
Area: 0.0 cm²



Follow-up
Area: 0.0 cm²

Complete healing
in 8 wks

Case (2)

DM>10 y; Ulcer duration 4 mons; Wagner G2;
Plantar; Smoker (5 pack-year); 7.92cm²



V1
Area: 8.04 cm²

V2
Area: 7.92 cm²

V3
Area: 3.17 cm²

V4
Area: 2.13 cm²



V5
Area: 0.41 cm²



V6
Healing

V7
Healing

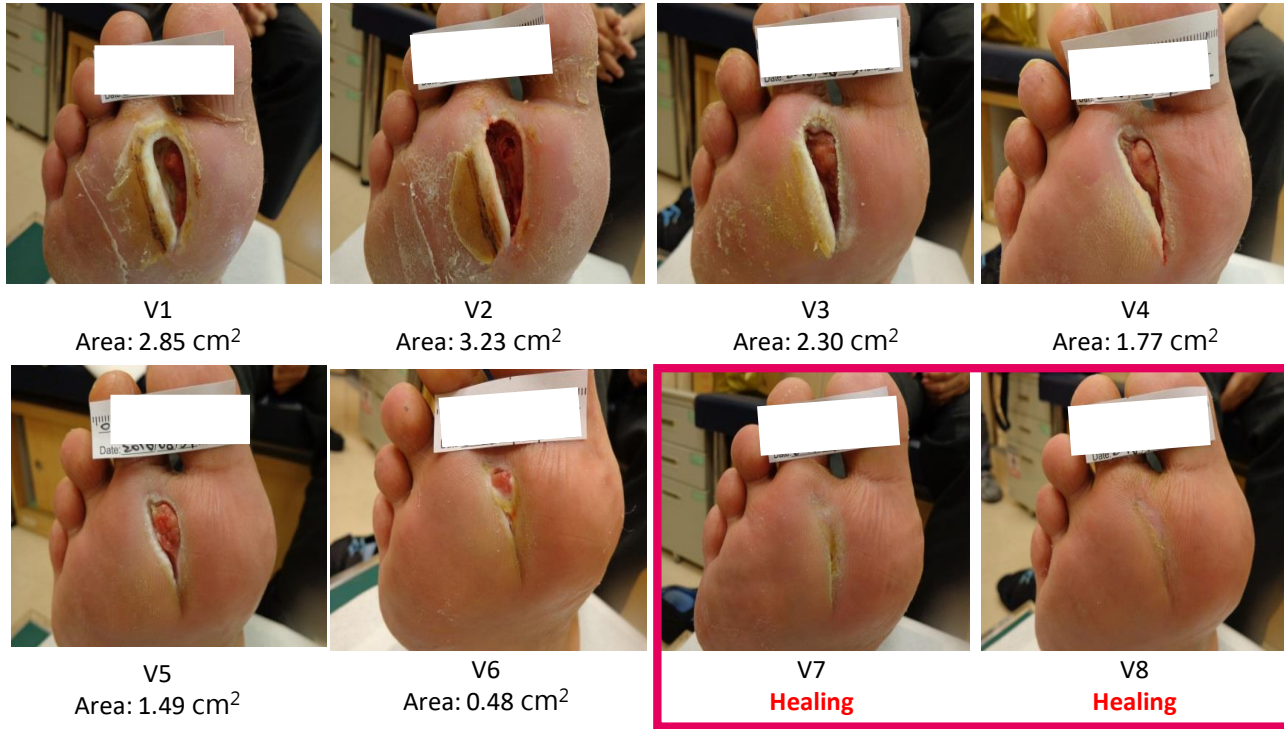


Follow-up
Area: 0.0 cm²

Complete healing
in 10 wks

Case (3)

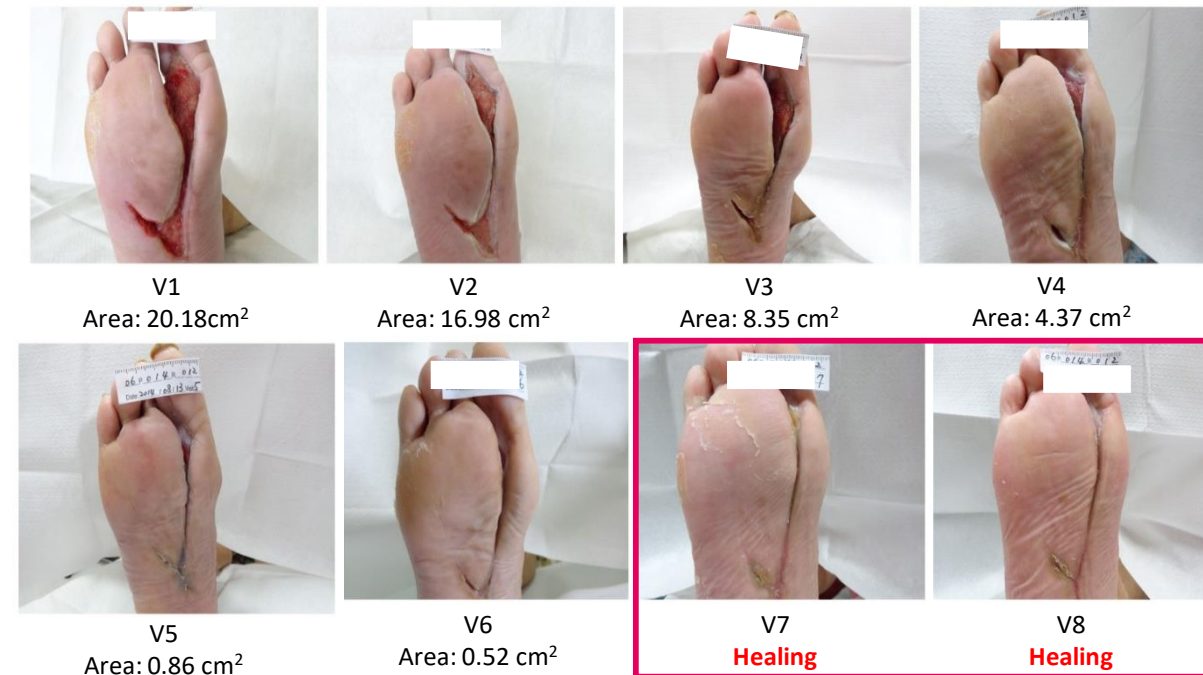
Wagner Grade 2 ; Plantar
HbA_{1c}: 9.2%;



Complete healing
in 12 wks

Case (4)

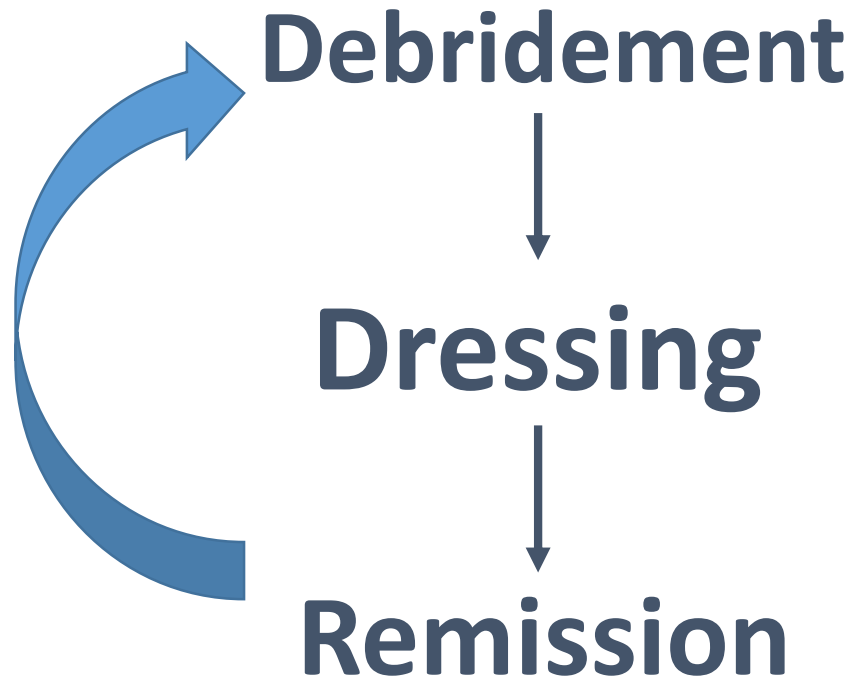
DM > 10 yrs; Ulcer duration 4 months;
Wagner Grade 2; Plantar; wound size 16.98 cm²



Complete healing
in 12 wks

Revolutionary Intervention to DFU

Before ON101

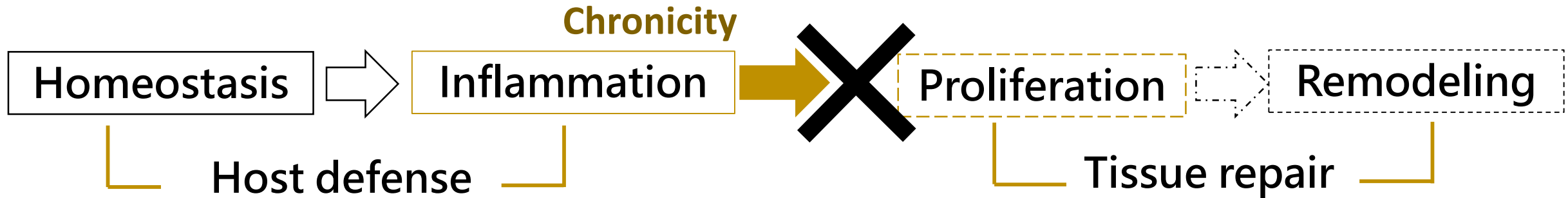


After ON101

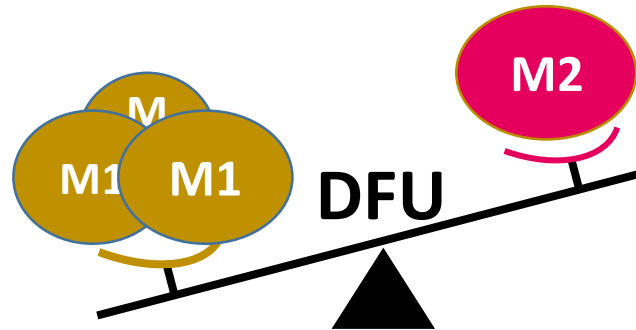


Redefine DFU Treatment Guidance

Chronic Ulceration: Imbalance M1-to-M2



- Excessive M1 Φ observed in diabetic wounds.
- Aberrant inflammatory cytokine profile caused prolonged chronic inflammation.
- Continuous tissue damage delayed wound healing.



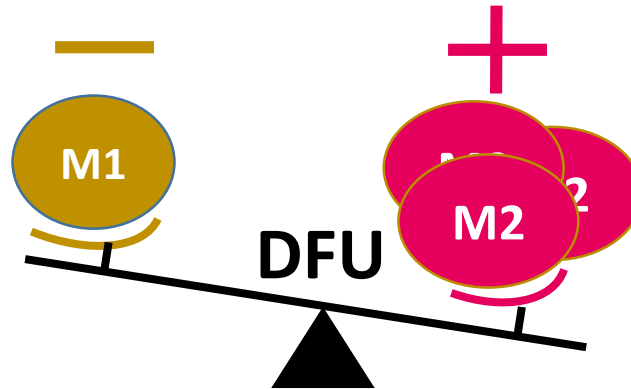
- A delayed M1/ M2 Φ transition observed in diabetic wounds.
- Less angiogenesis, keratinocyte activity, and collagen deposition.
- Delayed tissue repair and remodeling.
- Delayed wound healing.

ON101 MOA : Rebalance M1-to-M2



ON101 regulates Macrophage

- Suppressed M1 polarization.
- Promote M2 recruitment.
- Balanced the M1/ M2 ratio.
- Suppressed the secretion of pro-inflammatory cytokines (IL-1 β , IL-18, IL-6, etc.).
- Inhibited the NRPL3- mediated inflammasome activity.
- Promote the secretion of specific chemokine and growth factors.

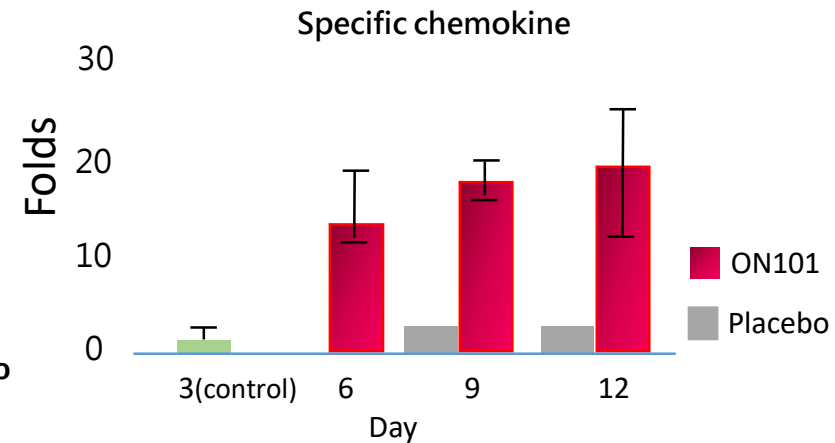
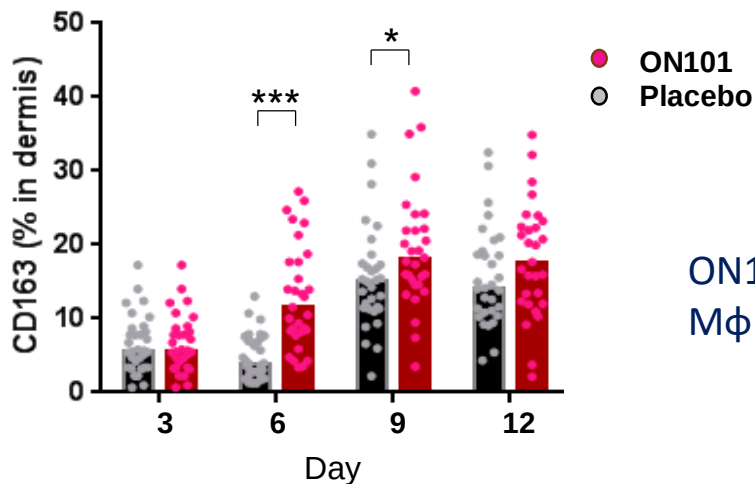
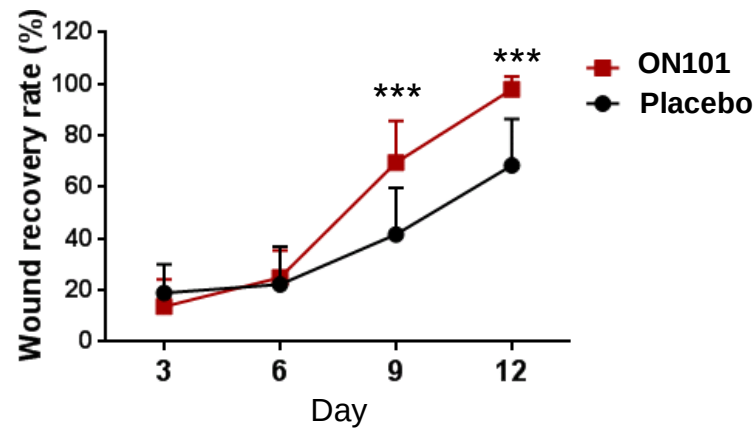


ON101 regulates the surrounding cells

- Suppressed inflammation state.
- Promote keratinocyte proliferation and migration.
- Promote collagen deposition.
- Promote the recruitment of CD71⁺ progenitor cells.
- Promote wound healing

DFU to Normal Wound

First finding of specific chemokine that accelerates DFU healing



ON101 regulates specific chemokine and growth factor which guided Mφ phenotypic switch from M1 to M2 inducing tissue repair.

ON101 MOA Summary

1. ON101 transits **CHRONIC** wound to **NORMAL** wound by driving **M ϕ** phenotypic switch from **M1** to **M2**.
2. Polarization to M2 exhibiting anti-inflammatory, matrix deposition, angiogenesis enables transition from the **inflammatory** phase to **proliferation** phase.
3. ON101 will extend indications in other chronic ulcers, including **venous leg ulcers** and **pressure ulcers**.

Highlights

- **1st successful global Ph3 MRCT in DFU since 1997**
- **Consistent healing across various types of DFU,
including multi-factoral hard-to heal ulcers**
- **Proven efficacy to revolutionize DFU treatment
landscape and patient journey**
- **Novel mechanism proven scientifically in
transiting DFU to normal wounds**

Thank You for Your Attention !



Globalization by Innovation

Contact

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