

”ImproWin[®] treatment of gastric ulcer in trotter”

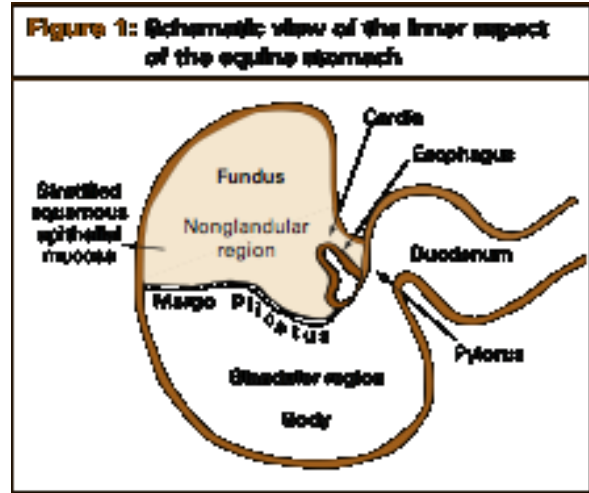
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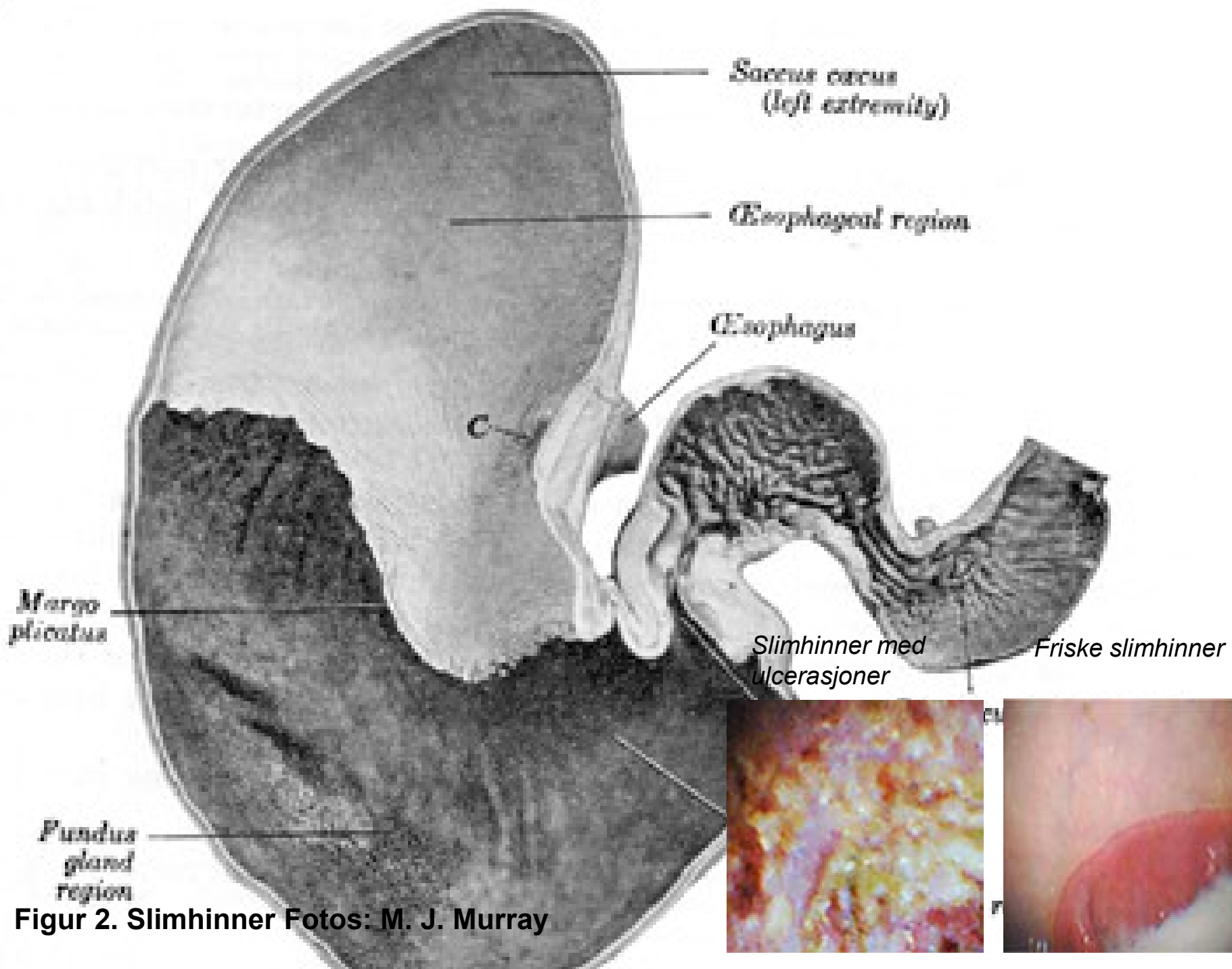
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Prevalence of gastric ulcer - is now well known

- Gastric ulceration affects a large number of horses and foals
- Since the introduction of endoscopic examination in veterinary practice been identified as a common occurrence in all types of horses.
- Prevalence in mature horses ; in the range from 58 to 93%
- Prevalence in standard bred trotters ; 44 to 70%
- Earlier studies reported mainly lesions in the squamous mucosa
- More recently lesions in the glandular mucosa, the pylorus region and proximal duodenum
- 50% of horses suffered from lesion in the squamous mucousa, 8% in the glandular mucosa of the stomach body, 58% in the pylorus or the antrum and 10% had duodenal lesions





Figur 2. Slimhinner Fotos: M. J. Murray

The aetiology of Equine gastric ulcer syndrome (EGUS)

The aetiology of EGUS is believed to be multifactorial;

- Most probably; an imbalance of the protective and ulcerogenic factors
- Stomach has a stratified pH, neutral in the dorsal oesophageal region but reduces near the margo plicatus and continuously decreasing towards the pylorus
- exposure to a pH below 4 is considered ulcerogenic in many species
- hydrophobic mucus barrier that overlies the gastric glandular mucosa is key in protecting the glandular mucosa to the acidic environment
- mucosal blood flow is essential for maintaining this barrier and is dependent on prostaglandin synthesis and nitrous oxide
- production of gastric acid is continuous and feed deprivation is associated with highly acidic conditions in the stomach and induction of ulcers.

Table 1: EGUS: Intrinsic and protective factors involved in the gastroduodenal mucosal environment	
Intrinsic protective factors	Intrinsic initiating factors
<ul style="list-style-type: none">• Adequate mucosal blood flow• Mucus-bicarbonate layer• Mucosal prostaglandin E₂• Tight intercellular junctions• Epidermal growth factor• Gastroduodenal motility	<ul style="list-style-type: none">• Hydrochloric acid• Acetylcholine• Bile acids• Pepsin

Source; Marqués, Fernando J, Diplomate ACVIM "Equine Gastric Ulcer Syndrome", Presented in the Rounds of the Department of Large Animal Clinical Sciences of the Western College of Veterinary Medicine, University of Saskatchewan

Housing or turnout

Housing has been suggested as a risk factor but no effect was detected on intragastric pH in horses fed hay adlib stabled or during 72 hr turnout in a paddock

A significant reduction in proximal gastric pH was found during the early hours regardless of housing or turnout.

=> This could possibly be explained by normal feeding behaviour decrease in these hours and feed deprivation induces squamous mucosal ulceration.

Risk factors associated with higher incidence of grade 2 EGUS

- lack of water available in the paddock,
- feeding of starch
- use of straw as only forage compared to hay

Degradation of starch in the stomach, presumed to happen due to microbial fermentation, causes production of lactic acid and volatile fatty acids (VFA) which may contribute to formation of gastric ulcers and grain causes secretion of gastrin (ref. 23, 24). Additionally, calcium carbonate supplements or in form of alfalfa has been shown to reduce the incidence of gastric ulceration of the nonglandular mucosa in response to VFA (ref.24).

Helicobacter species

- well established as the main cause of gastric ulcers in man.
- helicobacter has not been documented for horses.
- helicobacter equorum found to be highly prevalent in foals under 1 (6) month,
- but no detected connection to pathological disease after experimental infection with this bacteria (ref. 25, 26).

The study of gastric ulcer and the effect of ImproWin

Material description

- Trotters suffering from endoscopic verified gastric ulcers
- Norwegian cold blooded and standard bred racehorses past the age of 3 years
- 78 horses with endoscopically verified ulcers in nonglandular mucosa of severity grade 2 or above
- The two treatment groups were found clinically equal regarding distribution of gender and breed
- 11 horses were blindly classified as violators to the protocol either due to use of other ulcer treatment or change in the feeding procedure during the study period
- No significant interaction between the treatment groups, gender, breed and age.

Design and randomisation

- A randomised, double blind and single centre study with stratified cross-over design.
- Cold-blooded trotters and standard breed defined the two study strata.
- Within the the **two strata** the horses were allocated to either ImproWin or equal looking placebo treatment for three weeks by block randomisation with a fixed block size of eight.
- **Responders** defined as improvement of 1 grade or more on the 5 point EGUC ulcer scale.
- Responders to the given three weeks treatment continues additionally 2 or 4 weeks.
- Patients in which the ulcers were grade 0 or 1 was considered healed and discontinued.
- **Non-responders** was blindly crossed to other treatment.
Non-responder in placebo group was crossed to ImproWin for 2 or 4 weeks

Study procedure

Bjerke Animal Hospital (Rikstotoklinikken Bjerke AS) recruited the patients. Owners/trainers were asked to fill out a questionnaire during the study period, recording any change in training/stabling/feeding.

Prior to start; horses examined and endoscopically verified.

The number and degree of ulcers were recorded according to EGUC recommendations.

0 = epithelium is intact without appearance of hyperaemia or hyperkeratosis

4 = extensive lesions with areas of apparent deep ulceration

The degree of ulceration was recorded on a 10 cm Visual Analogue Scale (VAS)

Treatment started the same day as initial examination

The horses were all trained as usually during the treatment period and they were allowed to participate in races

After three weeks a new endoscopic investigation. And followed the further treatment as earlier described.

The non-responders to ImproWin were all crossed to Proton Pump Inhibitor therapy

Statistical Analysis

Assumed continuously distributed variables

95% confidential interval

All tests are performed two-tailed with a significance level of 5%.

To calculate the number of horses to be included in the study, a power analysis was performed in the planning phase.

Conclusion; 32 horses in each group had to be included

Significance level of 5%, a power of 90% an a clinical relevant difference between the groups of one time the standard deviation,

Results of the study

The degree of ulceration recorded on 10 cm Visual Analogue scale from start to three week and to end of treatment.

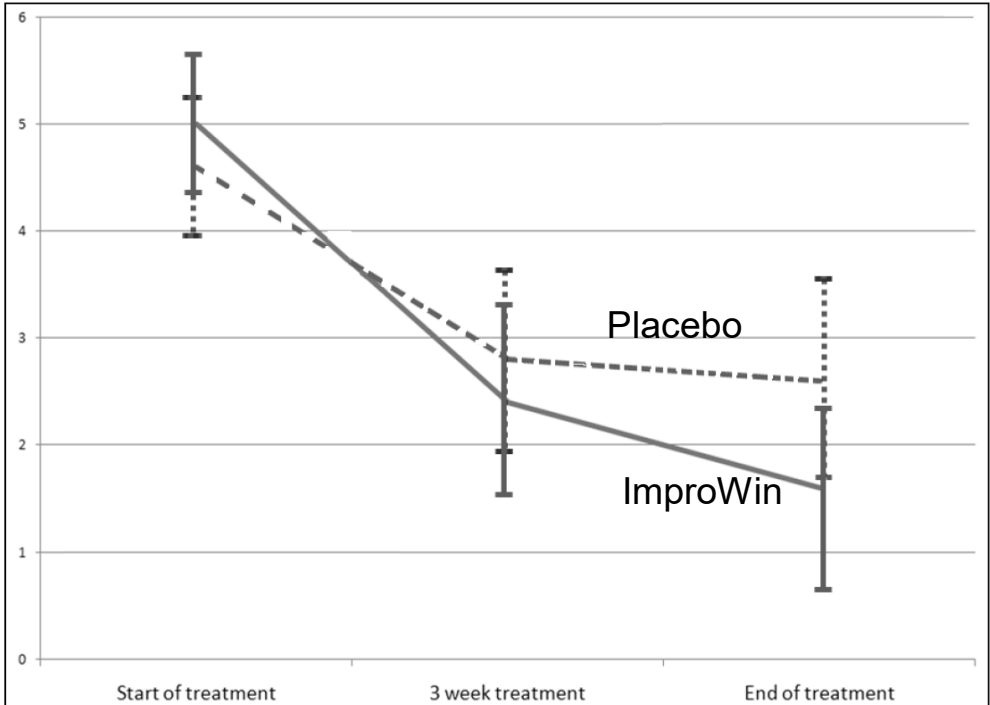
The results are expressed as mean values with 95% confidence interval in brackets

The two treatment groups was found comparable at start of treatment.

ImproWin group; the ulceration was significantly reduced from 5,0 to 2,4 after 3 weeks and further at the end of treatment to 1,6.

Placebo group; the ulceration was reduced from 4,6 to 2,8 after 3 weeks and further nearly no reduction to 2,4 at the end of treatment (not significant).

Treatment period	Treatment groups		p-values
	ImproWin (n=36)	Placebo (n=31)	
Start of treatment	5,0 (4,4 – 5,7)	4,6 (4,0 – 5,2)	0,37
3 week treatment	2,4 (1,6 – 3,3)	2,8 (1,9 – 3,7)	0,49
End of treatment	1,6 (0,7 – 2,6)	2,6 (1,7 – 3,5)	0,16



Classification of responders after 3 weeks and at the end of treatment in the groups

- A Only ImproWin from start to the end of treatment.**
- B Placebo and ImproWin the last period.**
- C Only Placebo from start to the end of treatment.**

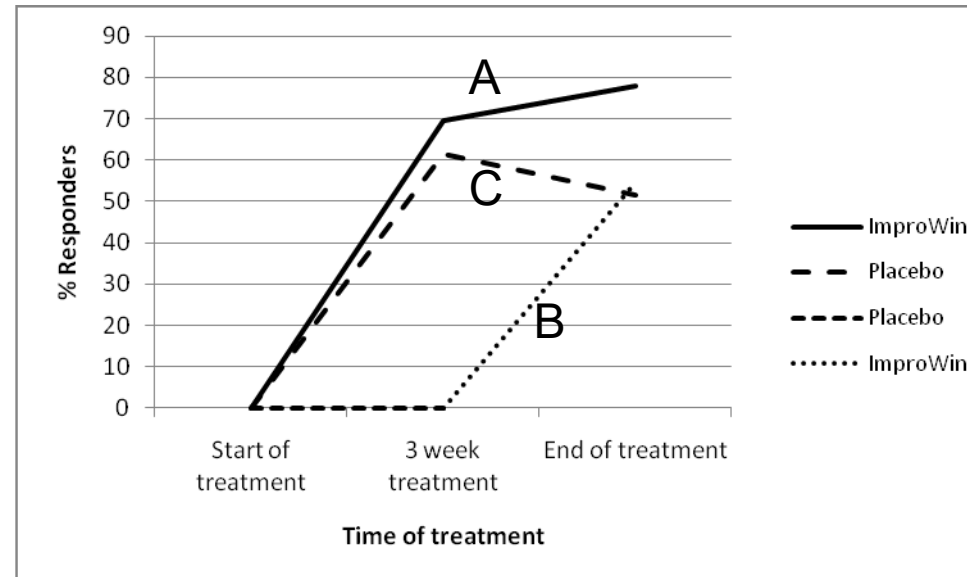
The results are expressed as number of responders and percent responders with 95% confidence interval

Table II (see attached at the end of this Presentation) shows that 22/36 were completely healed of the IW group (grade 0), And 27/36 with grade 0 or 1 (defined as healed in the study) which means 75%.

78% of the ImproWin group are responders (more than 50% improvement) which is significantly higher than the 51,6% in the placebo group at the end of treatment.

The comparing figures for the Placebo group are 16/31 with grade 0 or 1 at the end of treatment, which means 51,6%

	A	B	C
Treatment period	ImproWin/ImproWin (n=36)	Placebo/ImproWin (n=11)	Placebo/Placebo (n=31 / n=20)
3 weeks	25/36 69,4 (51,9 – 83,7)	0/11 0,0 (0,0 – 28,5)	19/31 61,3 (42,2 – 78,2)
End of treatment	28/36 77,8 (60,9 – 89 - 9)	6/11 54,6 (23,4 – 83,3)	16/31 51,6 (32,7-68,7)



Discussion

The improvement after 3 weeks in both groups are not entirely surprising.

Environmental factors are well known to influence development and healing of gastric ulcer.

Environmental factors; i.e. feeding or training regimes

Key assumption;

- *Horses not responding after 3 weeks would still not be responders at the end of treatment*

11 non-responders in the placebo group were crossed to IW treatment with 55% responders.

3 horses classified as non-responders (less than 50% improvement) were still given IW to the end of study and all horses responded.

Horses responding to the placebo treatment after 3 weeks but were not healed continued with Placebo treatment. At the end of treatment 4 out of 6 horses became non-responders. Changes in this assumption would have given an additional advantage for the IW group result.

- *The trainers and owners do no changes in the horse management*

It is likely to believe that some implemented changes in feeding and training.

It was reported that for some horses the feeding and environment was changed significantly.

These were classified as violators and removed from the study.

Even the study was performed double blind the trainers/owners might have been able to identify the treatment due to different smell.

Animal welfare and ambition to get the horse back in good performance as fast as possible might have influenced the result

Discussion continue.....

Placebo effect

Normal definition of placebo;

The direct specific effect of the placebo drug on top of the unspecific changes attributed to natural healing and context effect.

In this study we may assume that the Placebo had no direct effect on healing of ulcerations. If this is true, the placebo effect in this study consists of natural changes, i.e.;

- the body's own healing processes
- the more specific changes instigated by the owner consciously or unconsciously
- i.e. changes in daily routines, as feed, exercise, transport, competitions, housing etc are factors which have shown to be major factor in the development of EGUS in horses.

=> The placebo effect is likely quite large

Mode of action

- Buffering in the GI tract
- Reducing the population of pathogenic bacteria ; E-coli, Salmonella, Helicobacters ++
- Helicobacter-like DNA has been found in gastric mucosa
 - possible pathogenic effect of bacteria in the stomach regards to EGUS is involvement bacterial effect on fermentation of soluble carbohydrates to produce products such as Volatile fatty acids (VFAs) and lactic acids.
VFAs and HCl has been shown to penetrate the gastric mucosa at low pH and disrupt cellular transport and cause cell swelling, cell death and ulceration in vitro
 - The effect of treating horses with ImproWin on established ulceration in the glandular mucosa may be particularly interesting due to possible involvement of bacteria in these cases.

Further work needs to be done to establish the full underlying etiology of EGUS, particularly those in the glandular mucosa, and the possible role of bacteria in EGUS in horses.

Conclusions to the results

ImproWin is a feed supplement without restrictions on racing and quarantine times for competing.

The conclusion from our results is that

ImproWin has a positive effect on ulcer healing in horses.

The effect we have shown attributed to ImproWin adds a significant benefit on the healing of gastric ulcerations in the squamous mucosa in horses on top of management changes and placebo effect.

The length of IW treatment seems to have an impact on the response rate, with higher response after 7 weeks than 2 or 3 weeks treatment.

It is recommendable to use ImproWin complementary to Proton Pump Inhibitor therapy as a daily supplement. ImproWin should be used as posttreatment and preventive as a supplement.

Thanks for the attention!

Table I: Distribution of gender and breed within the materials and treatment group. The results are expressed as numbers within categories.

		Per protocol material		Violators	
Treatment	Gender	Type of trotters		Type of trotters	
		Cold blooded	Standard	Cold blooded	Standard
ImproWin	Mare	2	12	0	0
	Stallion	1	5	0	1
	Gelding	3	13	0	3
Placebo	Mare	0	12	0	4
	Stallion	0	5	0	1
	Gelding	7	7	0	2
Total	78	13	54	0	11

Table II: The degree and change in degree of ulceration from start to three week and to end of treatment recorded on the 5 point scale as defined by Andrews et al, 1999.

Treatment	Weeks of recording	Degree of ulceration	Recorded degree of ulceration at start			Total	
			2	3	4		
ImproWin	3 weeks	0	5	3	4	12	
		1	1	4	0	5	
		2	3	6	1	10	
		3	0	4	1	5	
		4	1	1	2	4	
	Total			10	18	8	36
	End of treatment	0	6	10	6	22	
		1	2	3	0	5	
		2	1	1	0	2	
		3	0	3	0	3	
4		1	1	2	4		
Total			10	18	8	36	
Placebo	3 weeks	0	7	2	0	9	
		1	3	0	1	4	
		2	2	2	3	7	
		3	2	8	0	10	
		4	0	0	1	1	
	Total			14	12	5	31
	End of treatment	0	10	4	1	15	
		1	0	0	1	1	
		2	1	0	1	2	
		3	3	8	0	11	
4		0	0	2	2		
Total			14	12	5	31	