The 13th Malvern
Diabetic Foot Conference

EFFICACY AND SAFETY OF BEMIPARIN SODIUM AS A TREATMENT FOR DIABETIC FOOT ULCERS: MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND PHASE-III CLINICAL TRIAL. (Preliminary report)

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BACKGROUND (I)

- Diabetes Mellitus is becoming a worldwide health problem of epidemic dimensions
- Diabetic foot ulcers (DFU) are associated to:
  - High Incidence (1.0% - 4.1%) and prevalence (4% - 10%)
  - High risk of limb amputation
  - High social and sanitary costs
- Objective of wound care: to obtain an early ulcer healing
  - Reduction of ulcer infection
  - Reduction of ulcer recurrence
  - Reduction of lower limb amputation

HEPARIN AND WOUND HEALING

- Anti-inflammatory effect by
  - inhibiting TNF-α production
  - decreasing leukocyte migration and adhesion to injury site
- Stimulation of production of growth factors and induction of fibroblast proliferation
- Synthesis of the extracellular matrix component heparan sulfate by endothelial cells
- Increase of fibrin gel porosity which may positively influence microvascular functions
- Encouraging results from previous clinical trials with LMWH

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BEMIPARIN IN DIABETIC FOOT ULCERS
Exploratory Trial. Results

EFFICACY OUTCOMES (ITT) AT 3 MONTHS

Outcome measure	Bemiparin ($N = 37$) n (%)	Placebo ($N = 33$) n (%)	Difference % (95% CI)	P-value
Main analysis				
Improved ulcer*	26 (70.3)	15 (45.5)	24.8 (2.33, 47.30)	0.035
Ulcer area decreased ≥ 50%	21 (56.8)	14 (42.42)	14.3 (−8.9, 37.6)	0.231
Ulcer decreased at least one grade	17 (46.0)	13 (39.4)	6.6 (−16.6, 29.7)	0.580
Complete healing	13 (35.1)	11 (33.3)	1.8 (−20.45, 24.06)	0.874
Subanalysis depending on ulcer grade at baseline				
Improved ulcer				
Wagner II at baseline	12/14 (85.7)	2/5 (40)	45.7 (0.6, 77.8)	0.046
Wagner I at baseline	14/23 (60.9)	13/28 (46.4)	14.4 (−12.9, 39.4)	0.304
Complete healing				
Wagner II at baseline	7/14 (50)	0/5 (0)	50.0 (0.9, 50.0)	0.047
Wagner I at baseline	6/23 (26.1)	11/28 (39.3)	−13.2 (−35.1, 12.7)	0.320

*Primary efficacy end-point: ulcer area decreased ≥ 50% and/or decreased at least one grade in Wagner's classification (from Wagner grade II to I or from Wagner grade II or I to Wagner grade 0).

Rullan M, et al. Diabetic Medicine 2008

OBJECTIVES

- Main objective:
  - to analyze the efficacy and safety of bemiparin as a treatment to promote the healing of diabetic foot ulcers

- Secondary objectives:
  - acceptability of treatment with bemiparin sodium
  - potential effects on the quality of life
  - cost-benefit ratio.

STUDY COMMITTEES

- STEERING COMMITTEE
  - Dr. José Ramón March , Hospital de Getafe (Getafe, Spain)
  - Dr. Josep Marinel Lo, Hospital de Mataró (Mataró, Spain)
  - Dr. Rafael Gómez Medialdea, Hospital Virgen de la Victoria (Málaga, Spain)

- DATA SAFETY& MONITORING BOARD
  - Dr. José Real, Hospital Clínico (Valencia, Spain)
  - Prof. Francisco Lozano (Hospital Clínico Universitario (Salamanca, Spain)
  - Dr. José Manuel Ortega, Hospital de León (León, Spain)
  - Dr. Fidel Fernández Quesada, Hospital Clínico San Cecilio (Granada, Spain)

- INVESTIGATOR`S SITES

  *Croatia (5) *Poland (3) *Romania (17)

  *Russia (7) *Serbia (2) *Spain (15)

METHODS

- **DESIGN**: international, multi-centre, randomized, double-blind, parallel-group phase-III clinical trial
- **ClinicalTrials.gov Identifier**: NCT00448903
- **TREATMENT**: o.d. Subcutaneous injections of
  - Bemiparin 3,500 IU (0,2 ml)
  - Placebo (Saline sol., 0,2 ml)

  for 90 days or up to complete healing of the ulcer
- **SAMPLE SIZE CALCULATION**:
  - Expected response (complete healing or significant improvement) rates:
    - 70% bemiparin
    - 50% placebo
  - $\alpha = 0,95$; $\beta = 0,10$; Patient loss: 30%
  - N=354 patients
- **STATISTICAL ANALYSIS**
  - Chi-squared test (or Fisher's exact test when applicable)

EFFICACY ENDPOINTS

- Primary efficacy endpoint:
  - Complete healing (100% re-epithelisation of the ulcer surface) or
  - Significant improvement, defining as:
    - Reduction of ≥ 50% of the ulcer size, or
    - Decrease in one Wagner grade

  up to the end of the double-blind treatment period (3 months)
- Secondary efficacy endpoint:
  - Complete healing (100% re-epithelisation of the ulcer surface) up to the end of the double-blind treatment period (3 months)
- Exploratory efficacy endpoints and sub-analyses

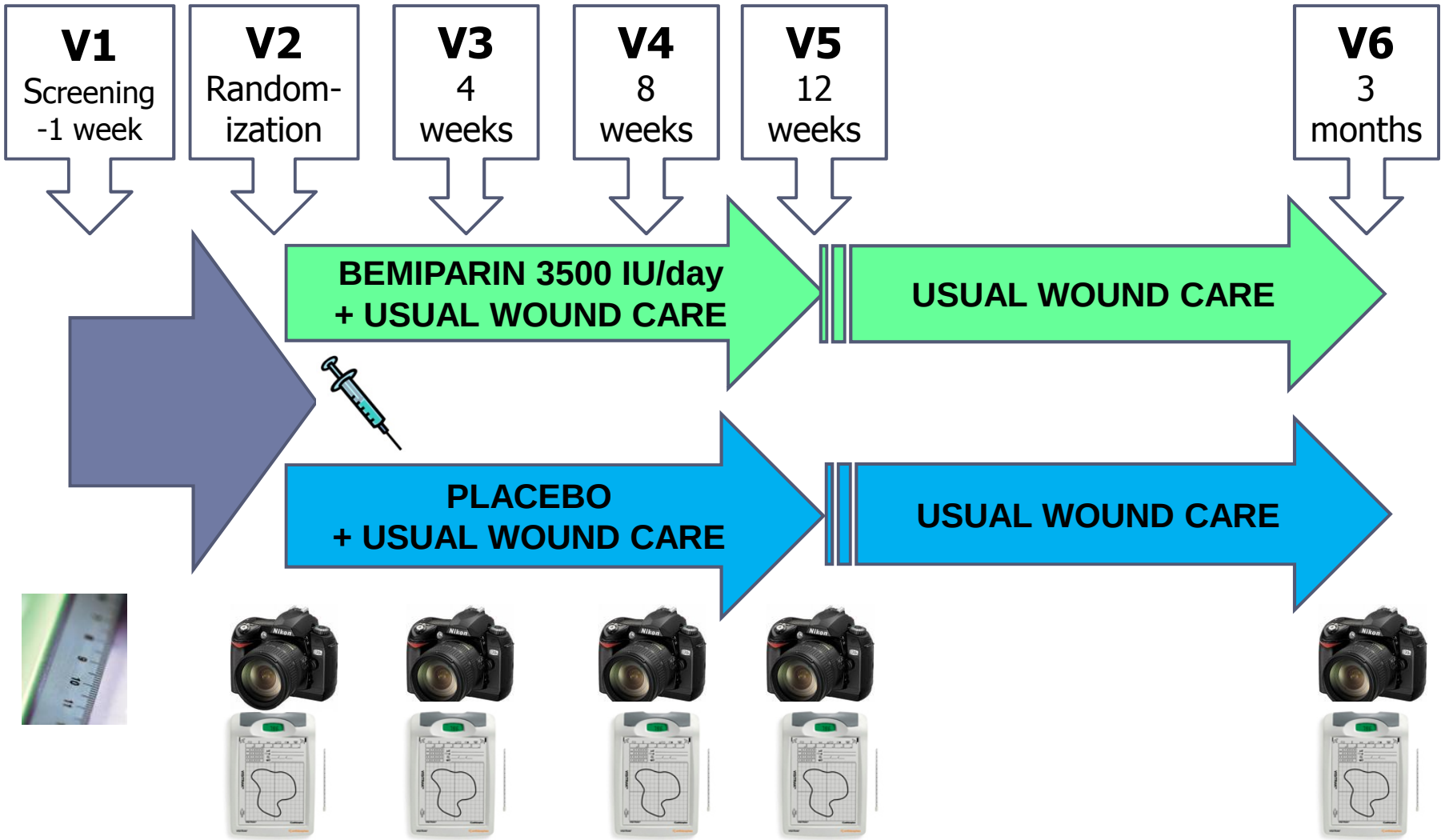
SAFETY ENDPOINTS

- Primary Safety endpoints:
  - Major bleeding events
  - Adverse events
- Secondary Safety endpoints:
  - Severe thrombocytopenia
  - Minor bleeding events
  - Clinically significant laboratory abnormalities
  - Discontinuation due to adverse events

ASSESSMENTS

- ULCER AREA
  - Visitrak method
  - Central reading by CRO
- COMPLETE HEALING
  - Photograph
  - Investigator's clinical assessment confirmed by the Steering Committee
- WAGNER GRADE: Investigator's clinical assessment
- BLEEDING EVENTS: major/minor classified by DSMB
- ADVERSE EVENTS:
  - Serious/non-serious classified by DSMB
  - Relationship with study drug evaluated by DSMB

METHODS. STUDY DESIGN



METHODS. INCLUSION CRITERIA

1. Age ≥ 18 y.
2. Diagnostic criteria of type I or II DM according to ADA criteria
3. Presence of:
   - Chronic neuropathic inframalleolar ulcer
   - Starting at least 2 months before
   - Grade I or II of Wagner's classification
   - With no significant improvement (size reduction ≥ 25%) in the 15 days prior to inclusion
4. Ulcer area ≥ 0.5 cm^2
5. ABI ≥ 0.7
6. Patient's written informed consent

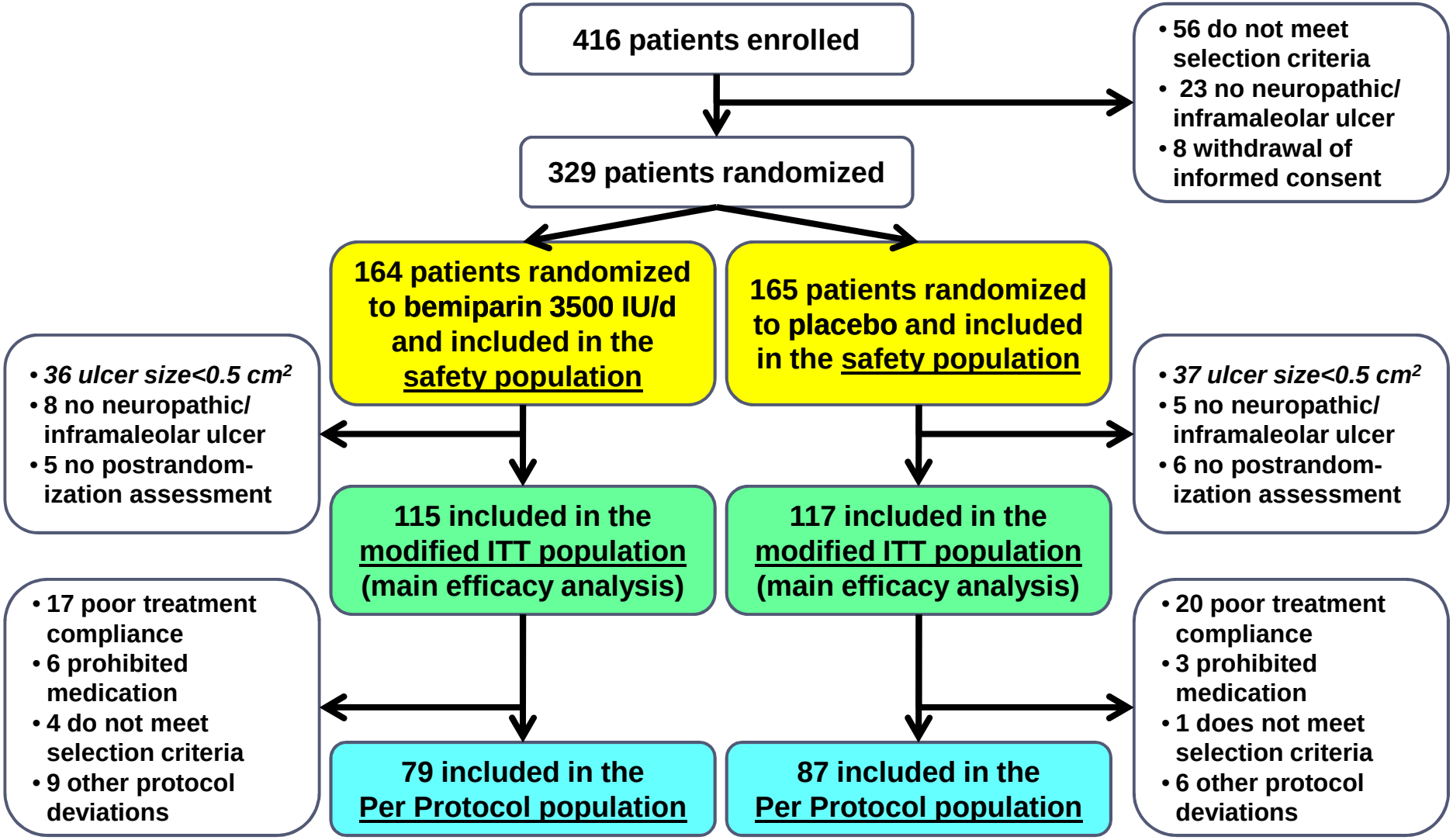
EXCLUSION CRITERIA (I)

1. Limb infection threatening the extremity or life
2. Bone exposure or clinical signs of osteomielytis
3. Limb ischemia (ABI <0.7 or toe pressure ≤30 mmHg)
4. Co-morbidities:
   - increasing bleeding risk
   - liver insufficiency or severe renal failure
   - connective tissue diseases
   - Acute bacterial and slow endocarditis
   - Antithrombin, protein C and S deficit
5. HbA1C >12%
6. Known hypersensitivity to bemiparin sodium, heparin or porcine-origin substances
7. History or suspect heparin-associated thrombocytopenia

EXCLUSION CRITERIA (II)

8. Pregnant women or with child-bearing potential not using an effective contraceptive method, or nursing women
9. Patients treated with:
   - anticoagulants (at the time of inclusion or 15 days prior to it)
   - pentoxyphylline (30 days prior to inclusion)
   - systemic corticosteroids or immunosupressants (3 months prior to inclusion)
   - becaplermin (15 days prior to inclusion)
10. Life expectancy less than 6 months
11. Unable to complete the study period
12. Participating in another clinical trial (30 days prior to inclusion)

PATIENTS DISPOSITION



BASELINE CHARACTERISTICS (1)

	BEMIPARIN (n=115)	PLACEBO (n=117)
Age [years], *mean ± SD*	61.5 ± 10.9	61.0 ± 11.1
Male/female, *n (%)*	82 (71.3) / 33 (28.7)	91 (77.8) / 26 (22.2)
Weight [kg], *mean ± SD*	82.7 ± 15.0	86.5 ± 17.4
Diabetes type I/type II, *n (%)*	17/98 (14.8/85.2)	15/102 (12.8/87.2)
Concomitant anti-platelet therapy	**37 (32.2)**	**33 (28.2)**
ABI, *n (%)* 0.9 ≥ ABI ≥ 0.7 ABI > 0.9	 36 (31.6) 78 (68.4)	 39 (33.6) 77 (66.4)
HbA1C, *n (%)* < 7.5% 7.5% - 10% > 10%	 51 (44.3) **53 (46.1)** **11 (9.6)**	 44 (37.6) **65 (55.6)** **8 (6.8)**

BASELINE CHARACTERISTICS (2)

	BEMIPARIN (n=115)	PLACEBO (n=117)
Size of the ulcer [cm^2], *mean ± SD (range)*	3.68 ± 7.11 (0.5 – 59.5)	3.24 ± 4.24 (0.5 – 32.3)
Location of the ulcer, *n (%)*		
Plantar	47 (40.9)	45 (38.5)
Dorsal	11 (9.6)	10 (8.5)
Digital	34 (29.6)	47 (40.2)
Interdigital	4 (3.5)	5 (4.3)
Heel	19 (16.5)	10 (8.5)
Wagner grade I/grade II, *n (%)*	32 (27.8) / **83 (72.2)**	37 (31.6) / **80 (68.4)**
Evolution time of the ulcer [weeks], *median (range)*	**16** (180 – 8)	**16** (117 – 3)
Signs of ulcer infection, *n (%)*	6 (5.2)	10 (8.5)

EFFICACY PRELIMINARY RESULTS. UP TO END OF TREATMENT (1)

	BEMIPARIN (n=115)	PLACEBO (n=117)	P-value
PRIMARY OUTCOME (complete healing or significant improvement), *n (%)*	**76 (66.1)**	**77 (65.8)**	**0.965**
COMPLETE HEALING, *n (%)*	29 (25.2)	30 (25.6)	0.941
Reduction of ≥50% ulcer area, *n (%)*			
One Wagner grade decrease, *n (%)*	[n=79] 41 (51.9)	[n=78] 43 (55.1)	
Time to complete healing [days], *mean ± SD (range)*	74.5 ± 21.8 (28 – 102)	74.9 ± 21.9 (26 – 100)	
Total amputations, *n (%)*	11 (6.7)	10 (6.1)	

EFFICACY PRELIMINARY RESULTS. UP TO END OF TREATMENT (2)

WAGNER GRADE II	BEMIPARIN (n=83)	PLACEBO (n=80)	P-value
COMPLETE HEALING, *n (%)*	19 (22.9)	15 (18.8)	0.515
Complete healing or significant improvement), *n (%)*	56 (67.5)	53 (66.3)	
Time to complete healing [days], *mean ± SD (range)*	76.0 ± 23.0 (28 – 102)	76.2 ± 21.3 (26 – 100)	

WAGNER GRADE I	BEMIPARIN (n=32)	PLACEBO (n=37)	P-value
COMPLETE HEALING, *n (%)*	10 (31.3)	15 (40.5)	0.423
Complete healing or significant improvement), *n (%)*	20 (62.5)	24 (64.9)	
Time to complete healing [days], *mean ± SD (range)*	72.0 ± 20.3 (28 – 91)	73.1 ± 23.1 (26 – 97)	

SAFETY PRELIMINARY RESULTS

From randomization up to the end of the study, *n (%)*	BEMIPARIN (n=164)	PLACEBO (n=165)	P-value
Patients with at least one adverse event	57 (34.8)	49 (29.7)	0.3
Patients with at least one serious adverse event	29 (17.7)	21 (12.7)	0.2
Major bleeding events	1 (0.6)	1(0.6)	
Minor bleeding events	0	0	
Deaths	1(0.6)	1(0.6)	
Severe thrombocytopenia	0	0	

CONCLUSIONS

- Bemiparin (3500 IU/day for up to 3 months) did not show superiority over placebo in the rate of patients achieving complete healing or significant improvement (reduction of ≥50% of the ulcer size, or decrease in one Wagner grade) of their diabetic foot ulcers
- The response rate in the placebo group was unexpectedly high
- Bemiparin showed a good safety profile, and the incidence of bleeding events was extremely low
- All exploratory analyses and sub-analyses have not been performed yet