Evidence Table H-5e. Biological therapies trials and observational studies

| **Author, year Country Overall Quality Rating** | **Study Type** | **Eligibility Criteria** | **Exclusion Criteria** | **Number screened/ eligible/ enrolled/ analyzed** | **Age Sex Race** | **Intervention Type:** | **Ulcer Type/Severity at Baseline (Intervention Onset)** | **Treatment A** | **Treatment B** | **Treatment C** | **Treatment D** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Danon, 1997121 Israel  Poor | Observational | Patients with PU hospitalized during a 1 year period in a geriatric hospital | No exclusion criteria | NR/NR/199  /199 | Age (Mean): 80 years  Female: 56%  Race: NR | Local Wound Applications:  Biologics | NR | Macrophage suspension (0.05 mL/injection) injected at 0.5-1 cm from the ulcer's edge all around the ulcer's periphery, at 1 cm between  injection points. Macrophage treatment only given one time  Ringer solution compress on a cotton gauze pad, kept moist  with Ringer solution, and changed daily  n=72 | Conventional treatments of ulcers, including Polydine, Eusol, Silverol, Debrizan, Ringer,  Saline, Granuflex, hydrogels, etc.  n=127 | NA | NA |

| Evidence Table H-5e: Biological Therapies Trials and Observation-al Studies, continued |  |  |  |  |  |  |  |  |  |  |  |
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| **Author, year Country Overall Quality Rating** | **Study Type** | **Eligibility Criteria** | **Exclusion Criteria** | **Number screened/ eligible/ enrolled/ analyzed** | **Age Sex Race** | **Intervention Type:** | **Ulcer Type/Severity at Baseline (Intervention Onset)** | **Treatment A** | **Treatment B** | **Treatment C** | **Treatment D** |
| Hirshberg, 2001122 US Poor | Trial | PU surface area between 15-120 cm2, calcium alginate mold weight of >10 g following debridement at baseline visit, target ulcer present for at least 4 weeks, serum albumin concentration >2.5 g/dL, ulcer, bacterial counts of <105per gram of tissue and no beta-hemolytic streptococci or malignancy on biopsy | Osteomyelitis, alginate mold weight <10 g after debridement, use of topical antibiotics, disinfectants, autolytic, enzymatic debridement experimental, nonapproved or investigational drug use within one month or during trial, malignancy, use of systemic corticosteroids >20 mg per day, immunosuppressive therapy, patients whose target ulcer failed to heal with previous cytokine therapy or who received radiation therapy, pregnant, nursing, or of childbearing age women (not using birth control). | 270/NR/NR/14 | Age (Mean):44  Female: 45%  Race: NR | Local Wound Applications:  Biologics | Stage III, IV | 1.0 mcg/cm2 transforming growth factor-beta3 (TGF-beta3) 1x daily plus standardized wound care n=4 | 2.5 mcg/cm2 TGF-beta3 1x daily plus standardized wound care.  n=5 | Placebo gel 1x daily plus standardized wound care.  n=5 | NA |
| Landi, 2003123 Italy Good | Trial | PU, from 1 cm2 to 30 cm2 in total area | Lesions developed >1 month before admission, terminal illness, diabetes, peripheral vascular disease | Number screened: NR/70/38/36 | Age (Mean): 80  Female: 72% Race: NR | Local Wound Applications:  Biologics | Stage II: N=3 N=3 Stage III: N=9 vs. N=13 Stage IV: N=5 vs. N=1 Stage V: N=1 vs. N=1 | 2.5S murine nerve growth factor solution 1x daily plus daily local care.) n=18 | Salt solution 1x daily plus daily local care.  n=18 | NA | NA |
| Mustoe, 1994124 US  Poor | Trial | Stage III, IV PU in an adult, surface area between 4-100 cm2, no evidence of cellulitis or malignant neoplasms | Venous or arterial vascular disorder directly implicated in the cause of the ulcer; significant endocrine disease, immunosuppressive disease, sepsis, pregnancy or lactation, active abuse of alcohol/drugs, unstable renal hepatic, hematological or cardiac disease; evidence of malignant neoplasms; use of immunotherapy, cytotoxic chemotherapy, or investigational drugs | NR/NR/52/44  (41 had complete alginate mold weight data and were used as n for some analyses) | Age: 72years  Female: 66%  Race,:  Caucasian: 52% | Local Wound Applications:  Biologics | Treatment A:  Stage III: 27% vs. 25% vs. 21%  Stage IV: 73% vs75% vs. 79%,:  Location:  Ischium: 20% vs. 17% vs. 29%  Sacrum: 33% vs. 42% vs. 43%  Trochanter: 27  Other: 20 vs. 255 vs. 75 | 100 μg/mL rDPGF-BB topical spray 1x daily in addition to moist saline gauze dressings and mechanical debridement as needed  N=15 | 300 μg/mL rDPGF-BB topical spray 1x daily in addition to moist saline gauze dressings and mechanical debridement as needed  N=12 | Placebo  N=14 | NA |
| Payne, 2001125 US  Poor | Trial | PU involving any tissue from a bony prominence to the subcutaneous tissue (grad III, IV) | None | NR/NR/61/ 59  Complete follow-up data for 54 | Age: NR  Female:  NR  Race: NR | Local Wound Applications:  Biologics | NR | Sequential topical GM-CSF/bFGF 1x daily | bFGF alone 1x daily | GM-CSF 1x daily | Placebo 1x daily |
| Payne, 2004126 US  Good | Trial | Age>18 years; stage III sacral PU; ulcer free of necrotic tissue and debridement; ulcer present for 2-24 months; ulcer area is >5 cm2 and l<50 cm2; if more than one ulcer, the distance between ulcers is > 10 cm; ulcer is due solely to pressure damage. | Stage I, II, IV PU; more than 3 stage III, IV PUs; evidence of undermining, tunneling, or sinus tracts > 1 cm after debridement; previous treatment with a surgical flap procedure; bacterial colonization; decrease or increase in ulcer size of 50% during the screening period; underlying non-pressure ulcer etiology. | NR/NR/34/ 34 | Age (Mean): 69 years  Female: 32%  Race: Caucasian: 82%  African-American: 15%%  Other: 3% | Local Wound Applications:  Biologics | All Stage III  Location:  Sacral: 67%  Trochanter: 24%  Ischium: 9% | Dermagraft (human dermal fibroblast-derived substitute) up to 2x weekly in conjunction with conventional treatment  N=18 | Non-adherent dressing, saline-moistened gauze and Allevyn.  N=16 | NA | NA |
| Rees, 1999127 US Fair | Trial | ≥18 years, 1 - 3 chronic (stage III or IV NPUAP) PU (primary or recurrent) without involvement of bone tissue, PU volume between 10 ml and 150 ml, inclusive, following debridement at the baseline visit, PU present for at least 4 weeks despite previous treatment, located where pressure could be off loaded for the duration of the study, and albumin concentrations >2.5g/dl, total lymphocyte count> 1000 and concentrations of vitamin A and C within the normal range | Osteomyelitis, after debridement PU volume <10ml or >150ml, topical antibiotics, antiseptics, enzymatic debriding agents or other agents that would interfere with study evaluations used within 7 days preceding randomization, PU from electrical, chemical or radiation insult, cancer patients, concomitant diseases, treatment or medication that would deleteriously affect healing or interfere w/ evaluation of study medication, pregnant, nursing or of childbearing potential and not using birth control | NR/NR/124/124 | Age (Mean): 49 years  Female: 16%  Race: NR | Local Wound Applications: Biologics | NR | Becaplermin gel 100µg/g alternated with placebo gel every 12 hours  N=31 | Becaplermin gel 300 µg/g alternated with placebo gel every 12 hours  N=32 | Becaplermin gel 100 µg/g 2x daily  N=30 | Placebo gel  2x daily  N=31 |
| Robson, 1992(a)128  Robson, 1992(b)129 US  Poor | Trial - double-blind, placebo-controlled, phase I/II study | Consenting adult inpatients (ages 21-56) with stage III or IV, of area 25-95 cm, was randomly allocated placebo or rPDGF-BB at 1 µg/ml, 10 µg/ml, or 100 µg/ml, daily for 28 days. | Patients with diabetes | NR/NR/20/20 | Age (Mean)33 years Female: NR Race: NR | Local Wound Applications: Biologics | NR | 1μg/ml recombinant homodimeric platelet derived growth factor (rPDGF- BB) 1x daily  N=4  Total test material applied daily was calculated from a dose of 0 01 ml/cm ulcer surface.  After the daily treatment, the wound was left open for 15 minutes to allow absorption of rPDGF-BB by the wound surface. The ulcer crater was packed with fresh sterile gauze and sealed closed with `Biobrane'  Pressure-relieving devices were used as appropriate. Patients were repositioned every 2 hours throughout the treatment period | 10 µg/ml rPDGF- BB 1x daily  Total test material applied daily was calculated from a dose of 0 01 ml/cm ulcer surface.  After the daily treatment, the wound was left open for 15 minutes to allow absorption of rPDGF-BB by the wound surface. The ulcer crater was packed with fresh sterile gauze and sealed closed with `Biobrane'  Pressure-relieving devices were used as appropriate. Patients were repositioned every 2 hours throughout the treatment period  N=4 | 100 µg/ml rPDGF- BB 1x daily  Total test material applied daily was calculated from a dose of 0 01 ml/cm ulcer surface.  After the daily treatment, the wound was left open for 15 minutes to allow absorption of rPDGF-BB by the wound surface. The ulcer crater was packed with fresh sterile N=5  gauze and sealed closed with `Biobrane'  Pressure-relieving devices were used as appropriate. Patients were repositioned every 2 hours throughout the treatment period | Placebo (not described)  N=7 |
| Robson, 1994130  US  Poor | Trial | Both sexes, >18 years old, 28 days of hospitalization, wound volume 10-100cm3 and a depth of >2cm or to the boney prominence, located on sacrum, ischium, trochanter | Pregnant or lactating women, significant renal, hepatic, cardiac, or hematologic disease, endocrine disease such as diabetes mellitus, neoplastic disease producing PU, arterial or venous disorders, lack of cooperation or suitability, inability to consent, whirlpool therapy, HIV positive, use of investigational drugs before study entry, treatment of PU with cytokines within last 3 months | NR/NR/26/26 | Age: NR Female: NR Race: NR | Local Wound Applications: Biologics | All grade III or IV | Interleukin:0.01 ug/cm2/day (1.0 ug/ml) | Interleukin: 0.1 ug/cm2/day (10 ug/ml) | Interleukin: 1.0 ug/cm2/day (100 ug/ml) | Placebo |
| Robson, 2000131 US Poor | Trial | Patients age 28-70 with PU on the truncal area involving any tissue from bony prominence to subcutaneous tissue (grade III/IV), ulcer duration of > 8 weeks, and an initial ulcer volume of 10-200 cm3 | Significant diabetes mellitus, renal insufficiency, vasculitis, or hepatic, immunologic, cardiac, or hemorrhagic disease; malignant or neoplastic disease, except for adequately treated skin cancers; significant malnutrition, systemic steroidal therapy, immunotherapy, or chemotherapy; cytokine therapy within 90 days or investigational drug study within 30 days | NR/NR/NR/61 | Age(Mean): 50 years  Female: NR  Race:  Caucasian – 84% Black – 11%  Hispanic: 5% | Local Wound Applications:  Biologics | All stage III or IV | Granulocyte-macrophage/colony-stimulating factor (GM-CSF) 1x daily for 35 days  N=15 | Basic fibroblast growth factor (bFGF) 1x daily for 35 days  N=15 | Sequential GM-CSF 1x daily for 10 days of GM-CSF followed by 1x daily for 25 days of bFGF  N=16 | Placebo  N=15 |
| Robson, 1992(c)132 US Poor | Trial - randomized, blinded, placebo-controlled trial | Patients 18-65 years, PUs: 10-200 cm3 as measured by alginate mold, hospitalized, mechanical debridement (if necessary): at least 24 hours before initiation of treatment, laboratory findings: normal or clinically insignificant abnormalities on pretreatment CBC, coagulation, chemistry, urinalysis panels | Arterial or venous disorder, or vasculitis as cause for ulcerated wound, clinically significant systemic disease, significant malnutrition, recent use of steroidal therapy, penicillin allergy | NR/NR/50/49 | Age (Mean): 38 years Female: 25% Race:  Caucasian37%  Black:46% Hispanic:16% | Local Wound Applications: Biologics | NR | Recombinant basic fibroblast growth factor (bFGF): 1x daily/22 days  Tier 1: Low-dose bFGF (100 mcg/mL/cm2)  Tier 2: High-dose bFGF (1000 mcg/mL/cm2)  Tier 3: Intermediate-dose bFGF (500 mcg/mL/cm2)  N=35 Drug application was performed according to the specific tier after irrigation of the ulcer crater with normal saline. The given drug dosage was applied from a spray applicator, after which the wound was exposed to the ambient air for 15 minutes to allow the medication to adsorb to the wound surface. After this time, the ulcer crater was packed with fresh saline-moistened sterile gauze. 12 hours later the saline-moistened gauze was changed, but no additional medication was applied. | Placebo 1x daily (not described)  N=14 | NA | NA |
| Scevola, 2010133 Italy Poor | Prospective randomized controlled open clinical pilot trial | Patients were in a compensated stable nutritional status. | Metabolic, endocrine and collagen pathologies, ischemic cardiopathy, corticosteroid or immunosuppressive therapy, obesity, malignancies, and organ failure | NR/NR/13/13  PU N=16 | Age: NR Female: 23% Race: NR | Local Wound Applications: Biologics | Location:  Sacral: 10  Ischiatic: 6 | (GEL dressing) Allogenic Platelet Gel Protocol - gel applied directly to the clean wound bed using a sterile syringe; the ulcer was then covered with a polyurethane sponge/semi-permeable film dressing system  Platelet gel prepared in a Petri dish blending 4–8 ml of concentrated platelet preparation, including at least 2 × 1010 platelets, with 2–4 ml of plasma activated with Calcium Chloride  Ulcers were treated 2x/week for 8 weeks (total of 16 applications) N=8 | (NO GEL dressing) Standard Protocol –  Detorsion: Saline at room temperature  Dressing: Packing with 10% iodoform impregnated gauzes or Sodium/Alginate foams or Cadexomer Iodine powder and/or Vacuum Assisted Closure therapy  Perilesional areas: Zinc Oxide paste or Silver Sulfadiazine in high contamination risk area (i.e. perineum)  N=8 | NA | NA |
| Zuloff-Shani, 2010134 Israel Poor | Observational | Admitted to the rehabilitation wards following acute stroke, hip fractures, amputations, or deconditioning following acute illnesses. Patients were eligible once they suffered at least one PU at stage III and/or IV, as defined by the EPUAP lasting >30 days, regardless of gender or associated comorbidities. Could also have anemia, renal or hepatic disease, hypoalbuminemia, use of steroids, chemotherapy, or other immuno-compromising drugs | PU at stages other than stage III and/or IV, or a significant acute life threatening medical condition that might interfere with treatment results | NR/NR/131/100  PU N=213 | Age (Mean): 78 years,  Females: 59% Race: NR | Local Wound Applications: Biologics |  | SOC:  Wounds were surgically debrided, if necessary, and then treated by a variety of SOC treatments, including alginate containing dressings, polyurethane dressings, carboxymethylcellulose dressings, activated charcoal dressings with silver, hydrocolloids, hydrogels, silver containing dressings, gauze pads absorbed with Ringer (Hartman) solution, eusol, antibiotics and ointments containing steroids, silver containing ointments  N=30 (leg ulcers) | AMS: Injected by a sterile disposable 2 ml syringe with a 25G needle. The AMS suspension (0.1 ml/injection) was injected at the entire wound bed, at 1 cm between injection points. (for deep wounds, AMS was poured directly into the wound). Following AMS, sterile gauze well soaked with AMS was applied for 24 hours. Wounds were covered either with gauze pads absorbed with lactated Ringer’s (Hartman) solution or one of the following dressings: alginate containing dressings, polyurethane dressings, or carbo-xymethylcellulose dressings. In case of extensive exudates, silver containing dressings were applied. AMS injection was repeated in accordance with the wound condition (mean time between injections - 4 weeks) n= 45 (leg ulcers) | NA | NA |

| **Evidence Table H-5e: Biological Therapies Trials, continued** |  |  |  |  |  |  |  |  |  |
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| **Author, year Country Overall Quality Rating** | **Duration of Treatment/ Followup** | **Study Setting** | **Outcomes: Complete Wound Healing** | **Outcomes: Wound Surface Area** | **Outcomes: Healing Time** | **Outcomes: Infection Rate** | **Outcomes: Osteomyelitis Rate** | **Outcomes: Recurrence Rate** | **Other Outcomes: Specify** |
| Danon, 1997121 Israel  Poor | Single treatment / 12 months | Geriatric Hospital | Treatment A:  27% (n=36) complete wound healing.  Treatment B:  6% (n=15)  (p<0.001) | NR | NR | NR | NR | NR | NR |
| Hirshberg, 2001122 US Poor | 16 weeks or until ulcer healed | Wound care center | Treatment A: None  Treatment B:  n=1 achieved complete wound closure with no drainage | Treatment A:  Mean relative surface area of target ulcer at visit 4, cm2 0.8  Mean relative surface area of target ulcer at termination of trial, cm2 0.3  Treatment B/C  Mean relative surface area of target ulcer at visit 4, cm2 Treatment B: 0.5 Treatment C: 0.9  Mean relative surface area of target ulcer at termination of trial, cm2 Treatment B: 0.4 Treatment C: 0.7  Significant reduction in mean relative surface areas, Treatment B vs. Treatment C, during initial weeks of trial p<0.05 | NR | NR | Treatment A:  None  Treatment B:  n=2 | NR | Surface volumes Volume decreased significantly, Treatment A vs. Treatment C, p<0.05  Mean relative volumes (cm3) at termination were Treatment A 0.7, Treatment B 0.2, Treatment C 0.3 |
| Landi, 2003123 Italy Good | 6 weeks | Nursing home | Treatment A:  44%) (N=8)  Treatment B:  6%, (N=1) (p=0.009) | Treatment A:  6 weeks Mean area, mm2: 274 +/- 329  Reduction in ulcer area (raw), mm2: 738 +/- 393  Reduction in ulcer area (adjusted), mm2: natural log of area reduction 6.5 +/- 0.3  Treatment B: 6 weeks Mean area, mm2: 526 +/- 334, p=0.022   Reduction in ulcer area, mm2: 485 +/- 384, p=0.034   Reduction in ulcer area (adjusted), mm2: natural log of area reduction 5.9 +/- 0.3, p<0.001  adjustment for confounders including baseline ulcer area, location, ulcer duration | Topical application of Treatment A showed statistically significant acceleration of healing process (no p-value provided)  4 weeks total area reduced by nearly 50% in all ulcers of treatment A  Complete healing within 3 weeks,  Treatment A:  n=2  Treatment B:  n=1  Complete healing within 4 weeks, n=2 Complete healing within 5 weeks, n=1 Complete healing within 6 weeks, n=3 | NR | NR | NR | Treatment A vs. Treatment B Ulcer improvement by >3 stages, 28%(n=5) vs. 0 Ulcer improvement by 2 stages, 50%(n=9) vs. 11%(n=2) Ulcer improvement by 1 stage, 22%(n=4) vs. 44%(n=8), (p<0.001) No ulcer improvement, 44%(n=8) of Treatment B |
| Mustoe, 1994124 US  Poor | 28 days/5 months | Nursing homes and hospitals | Treatment A 38% of PU had complete wound healing at 5 months  Treatment B  21%  Treatment C 14% of PU had complete wound healing at 5 months | % Decrease in volume at day 29:  Treatment A  71%  Treatment B  60%  Treatment C  17%  (p=0.056) | No statistically significant difference in 50% healing time | NR | NR | Treatment A:  0%  Treatment B:  40% of PU healed during treatment and recurred during followup | NR |
| Payne, 2001125 US  Poor | 35 days/1 year | Nursing Home | No difference between complete healing in groups | NR | No difference in healing times between groups | NR | NR | Overall recurrence rate of 17% | NR |
| Payne, 2004126 US  Good | Variable treatment/26 weeks | Multi-center | Treatment A:  11% complete wound healing  Treatment B:  13% | Treatment A:  Median ulcer area reduction at week 12:  50% for patients who had complete healing  39% for patients who had incomplete healing  Median ulcer volume reduction 41% for patients who had complete healing  Treatment B:  Median ulcer area reduction 34% for patients who had complete healing  17% for patients who had incomplete healing  Median ulcer volume reduction 17% for patients who had complete healing | NR | Treatment A:  17% (n=3 )  Treatment B:  19% (n=3) | NR | NR | NR |
| Rees, 1999127 US Fair | 16 weeks | Multi-center | Treatment A:  23%  Treatment B:  19%  Treatment C:  0%  Treatment A vs. Treatment C:  (p=0.005)  Treatment B vs. Treatment C:  (p=0.008) | NR | NR | Treatment D  3%  Treatment C:  3% in 100 μg/g BID | Treatment A: 6%  Treatment B: 3%  Treatment C: 3%  Treatment D: 0% | NR | Becaplermin 100µg/g vs. 300μg/g vs. 100µg/g BID vs. placebo  Incidence of ≥90% healing: 58% vs. 59% vs. 405 vs. 29%, 100µ/g vs. placebo (p=0.021), 300μg/g vs. placebo (p=0.014)  Median relative ulcer volume at 16 weeks: 0.07 vs. 0.05 vs. 0.15 vs. 0.27, 100µ/g vs. placebo (p=0.013), 300μg/g vs. placebo (p=0.011) |
| Robson, 1992(a)128 Robson, 1992(b)129 US  Poor | 29-day trial/ followup at 2 weeks and 1, 2, 3 and 5 months post discharge and treatment | NR | NR | NR | NR | NR | NR | NR |  |
| Robson, 1994130  US  Poor | 28 days | Hospital | NR | NR | NR | NR | NR | NR | Ulcer volume reduction was the response examined, no significant differences were found between treatment groups |
| Robson, 2000131 US Poor | 35 days/1 year | Hospital | NR | NR | NR | NR | NR | NR | Treatment A vs. B  vs. C vs. D  Day 36 ulcer  volume, mean  (cm3):  12.02+/-11.88 vs.  7.24+/-6.11 vs.  16.83+/-25.75 vs.  14.24+/-13.66  All patients:  12.65+/-16.24  Day 36 ulcer  volume, median  (cm3):  9.29 (range 0.88-  40.62) vs. 4.42  (range 0.22-20.80)  vs. 7.48 (range  0.22-99.65) vs.  8.85 (range 2.12-  45.84), p=0.57  All patients: 7.26  (range 0.22-99.65)   Percent wound  closure on day 36,  mean:  67+/-24 vs. 75+/-  19 vs. 68+/-21 vs.  71+/-11  All patients: 70+/-  19   Percent wound  closure on day 36,  median (range):  70 (3-93) vs. 79  (42-99) vs. 73 (29-  98) vs. 72 (39-84),  p=0.69  All patients: 73 (3-  99)  Text: significantly  more patients  treated with  cytokine achieved  >85% decrease in  ulcer volume  (p=0.03);  significantly more  patients in  Treatment B had  >85% (p=0.02) |
| Robson, 1992(c)132 US Poor | 30 days acute phase of followup then patients discharged with followup evaluations at 1, 3 and 5 months | Hospital | >70% Wound Closure at 21 days: 69% (N=9)3, (p=0.041) | 70% volume reduction: Treatment A:  60%(n=21)  Treatment B:  29%(n=4) | NR | NR | NR | NR | NR |
| Scevola, 2010133 Italy Poor | 8 weeks/14 weeks after start of treatment (6 weeks after end of treatment) | NR | NR | NR | NR | NR | NR | NR | Pre-albumin (p=0.08) and albumin (p=0.041) values appeared slightly improved in both groups at the end of the study |
| Zuloff-Shani, 2010134 Poor | 12 months/NR |  | Treatment A:  Complete wound healing: (leg ulcer subset) Complete wound healing: (leg ulcer subset): 18% vs. 69.9%, p<0.001  Number of patients with all wounds fully closed: 2 (5.3%) vs. 39 (59.1%), p<0.001  Wounds Completely Closed: wound level - 13.3% vs. 69.5%, p<0.001 patient level - 33.7% vs. 76.2%, p<0.001  Treatment B:  Complete wound healing  (All patients, includes diabetic ulcers): Percentage of completely closed wounds significantly better for AMS. (p<0.001 ) | NR | Treatment A:  Median healing time: 117.7 (38–368) days   Median healing time: (leg ulcer subset):  SOC – 125 days (range: 26-368)  (p>0.05)  Treatment B:  Median healing time: 86.7 (15–422) days, p=0.49  Median healing time: (leg ulcer subset): AMS – 57 days (range:1-394)  (p>0.05) | NR | NR | NR | NR |

| **Evidence Table**  **H-5e: Biological Therapies Trials, continued** |  |  |  |  |  |  |  |  |  |
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| **Author, year Country Overall Quality Rating** | **Harms: Pain** | **Harms: Dermatologic Complications** | **Harms: Bleeding** | **Harms: Infection** | **Other Harms: Specify** | **Severe Adverse Events** | **Withdrawal due to  Adverse Events** | **Overall Adverse Events Rate** | **Funding Source** |
| Danon, 1997121 Israel  Poor | NR | NR | NR | NR | NR | NR | NR | NR | Teva Medical LTD, Israel. |
| Hirshberg, 2001122  US Poor | NR | NR | NR | NR | NR | NR | Treatment B: n=2 developed osteomyelitis  Treatment C: n=1 due to unsatisfactory therapeutic effects | 21% | Office of Research and Development, Medical Research Service, Department of Veterans Affairs |
| Landi, 2003123 Italy Good | NR | NR | NR | NR | NR | NR | NR | NR | Progetto Finalizzato Invecchiamento  of the Italian National Research Council, inter*RAI* |
| Mustoe ,1994124 US  Poor | NR | Treatment A:  Tunneling of the ulcer, exuberant granulation tissue, erythema with purulent drainage  Treatment B:  NR | NR | Treatment A: None  Treatment B:  n=1 | Treatment A:  Tunneling of the ulcer: n=1  exuberant granulation tissue: n=1  erythema with purulent drainage: n=1  Treatment B: NR | None | None | 10% | Amgen Inc. |
| Payne, 2001125 US  Poor | NR | NR | NR | NR | NR | NR | NR | NR | NIAMS, National Institutes of Health, Schering-Plough Research Institute, Scios, Inc. |
| Payne, 2004126 US  Good | NR | NR | NR | NR | NR | NR | NR | NR | Smith and Nephew, Inc. |
| Rees, 1999127 US Fair | NR | Skin ulceration, rash erythema-numbers, NR | NR | Treatment A n=0  Treatment B:  n=0  Treatment C:  n=1  Treatment D:  n=1 | Becaplermin 100µg/g vs. 300μg/g vs. 100µg/g BID vs. placebo Sepsis: 0 vs. 1 vs. 0 vs. 0 Condition aggravated: 0 vs. 1 vs. 1 vs. 0 | None | Treatment A: 3.2%(N=1) | NR | Johnson & Johnson, Inc. |
| Robson, 1992(a)128  Robson, 1992(b)129 US  Poor | NR | NR | NR | NR | NR | NR | NR | NR | Grant from California Biotechnology, Inc. |
| Robson, 2000131 US Poor | NR | NR | NR | NR | NR | NR | NR | NR | National Institutes of Health; Schering-Plough Research Institute; Scios, Inc. |
| Robson, 1992(c)132 US Poor | NR | NR | NR | See outcomes | Surgical ablation not required by any patients in Treatment C but required in 8 patients from other groups combined (p=0.09) | NR | NR | NR. | NR |
| Robson, 1994130  US  Poor | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Scevola, 2010133 Italy Poor | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Zuloff-Shani, 2010134  Israel Poor | NR | NR | NR | NR | NR | NR | NR | There were no adverse and/or serious adverse events related to AMS treatment. However, during the study an overall of 18.2% (12/66) of the patients in the AMS group and 23.7% (9/38) in the SOC group died (p=0.61). | RoseTree London, MDA Israel |