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

| **Author, yearCountryOverall Quality Rating** | **Study Type** | **Eligibility Criteria** | **Exclusion Criteria** | **Number screened/ eligible/ enrolled/ analyzed** | **AgeSexRace** | **Intervention Type:** | **Ulcer Type/Severity at Baseline (Intervention Onset)** | **Treatment A**  | **Treatment B** | **Treatment C** | **Treatment D** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Danon, 1997121IsraelPoor | Observational | Patients with PU hospitalized during a 1 year period in a geriatric hospital | No exclusion criteria  | NR/NR/199/199  | Age (Mean): 80 yearsFemale: 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 betweeninjection points. Macrophage treatment only given one timeRinger solution compress on a cotton gauze pad, kept moistwith Ringer solution, and changed dailyn=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, yearCountryOverall Quality Rating** | **Study Type** | **Eligibility Criteria** | **Exclusion Criteria** | **Number screened/ eligible/ enrolled/ analyzed** | **AgeSexRace** | **Intervention Type:** | **Ulcer Type/Severity at Baseline (Intervention Onset)** | **Treatment A**  | **Treatment B** | **Treatment C** | **Treatment D** |
| Hirshberg, 2001122USPoor | 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):44Female: 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, 2003123ItalyGood | 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): 80Female: 72% Race: NR | Local Wound Applications:Biologics | Stage II: N=3 N=3Stage III: N=9 vs. N=13Stage IV: N=5 vs. N=1Stage 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, 1994124USPoor | 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: 72yearsFemale: 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: 27Other: 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 neededN=15 | 300 μg/mL rDPGF-BB topical spray 1x daily in addition to moist saline gauze dressings and mechanical debridement as neededN=12 | PlaceboN=14 | NA |
| Payne, 2001125USPoor | Trial | PU involving any tissue from a bony prominence to the subcutaneous tissue (grad III, IV) | None | NR/NR/61/ 59Complete follow-up data for 54 | Age: NR Female: NRRace: 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, 2004126USGood | 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 yearsFemale: 32% Race: Caucasian: 82%African-American: 15%%Other: 3% | Local Wound Applications:Biologics | All Stage IIILocation:Sacral: 67%Trochanter: 24%Ischium: 9% | Dermagraft (human dermal fibroblast-derived substitute) up to 2x weekly in conjunction with conventional treatmentN=18 | Non-adherent dressing, saline-moistened gauze and Allevyn. N=16 | NA | NA |
| Rees, 1999127USFair | 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 yearsFemale: 16%Race: NR |  Local Wound Applications: Biologics | NR | Becaplermin gel 100µg/g alternated with placebo gel every 12 hoursN=31 | Becaplermin gel 300 µg/g alternated with placebo gel every 12 hoursN=32 | Becaplermin gel 100 µg/g 2x dailyN=30 | Placebo gel2x dailyN=31 |
| Robson, 1992(a)128Robson, 1992(b)129US 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 yearsFemale: NRRace: NR | Local Wound Applications: Biologics | NR | 1μg/ml recombinant homodimeric platelet derived growth factor (rPDGF- BB) 1x dailyN=4Total 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 dailyTotal 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 periodN=4 | 100 µg/ml rPDGF- BB 1x dailyTotal 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=5gauze 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, 1994130USPoor | 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: NRFemale: NRRace: 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, 2000131USPoor | 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 yearsFemale: 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 daysN=15 | Basic fibroblast growth factor (bFGF) 1x daily for 35 daysN=15 | Sequential GM-CSF 1x daily for 10 days of GM-CSF followed by 1x daily for 25 days of bFGF N=16 | PlaceboN=15 |
| Robson, 1992(c)132USPoor | 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 yearsFemale: 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=35Drug 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, 2010133ItalyPoor | Prospective randomized controlled open clinical pilot trial | Patients were in a compensated stablenutritional status. | Metabolic, endocrine and collagen pathologies,ischemic cardiopathy, corticosteroid orimmunosuppressive therapy, obesity, malignancies,and organ failure | NR/NR/13/13PU N=16  | Age: NRFemale: 23%Race: NR | Local Wound Applications: Biologics  | Location:Sacral: 10Ischiatic: 6 | (GEL dressing) Allogenic Platelet Gel Protocol -gel applied directly to the clean wound bed using a sterile syringe; theulcer was then covered with a polyurethanesponge/semi-permeable film dressing systemPlatelet 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 ChlorideUlcers were treated 2x/week for 8 weeks (total of 16 applications) N=8 | (NO GEL dressing) Standard Protocol – Detorsion: Saline at room temperatureDressing: Packing with 10% iodoform impregnated gauzes or Sodium/Alginate foams or Cadexomer Iodine powder and/orVacuum Assisted Closure therapyPerilesional areas: Zinc Oxide paste or Silver Sulfadiazine in high contamination risk area (i.e. perineum) N=8 |  NA | NA |
| Zuloff-Shani, 2010134IsraelPoor | Observational | Admitted to the rehabilitation wards followingacute stroke, hip fractures, amputations, or deconditioningfollowing acute illnesses. Patients were eligible once they sufferedat least one PU at stage III and/or IV, as defined by theEPUAP lasting >30 days, regardless of gender or associatedcomorbidities. Could also haveanemia, renal or hepatic disease, hypoalbuminemia, use ofsteroids, chemotherapy, or other immuno-compromising drugs | PU at stages other than stage III and/or IV, or a significant acute life threatening medical conditionthat might interfere with treatment results | NR/NR/131/100PU 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 alginatecontaining dressings, polyurethane dressings, carboxymethylcellulosedressings, activated charcoal dressings with silver, hydrocolloids,hydrogels, silver containing dressings, gauze padsabsorbed with Ringer (Hartman) solution, eusol, antibiotics andointments containing steroids, silver containing ointmentsN=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, yearCountryOverall 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, 1997121IsraelPoor | 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, 2001122USPoor | 16 weeks or until ulcer healed | Wound care center | Treatment A: NoneTreatment B:n=1 achieved complete wound closure with no drainage | Treatment A:Mean relative surface area of target ulcer at visit 4, cm20.8Mean relative surface area of target ulcer at termination of trial, cm20.3Treatment B/CMean relative surface area of target ulcer at visit 4, cm2Treatment B: 0.5Treatment C: 0.9Mean relative surface area of target ulcer at termination of trial, cm2Treatment B: 0.4Treatment C: 0.7Significant reduction in mean relative surface areas, Treatment B vs. Treatment C, during initial weeks of trial p<0.05  | NR | NR | Treatment A:NoneTreatment B:n=2 | NR | Surface volumesVolume decreased significantly, Treatment A vs. Treatment C, p<0.05Mean relative volumes (cm3) at termination were Treatment A 0.7, Treatment B 0.2, Treatment C 0.3 |
| Landi, 2003123ItalyGood | 6 weeks  | Nursing home | Treatment A: 44%) (N=8) Treatment B: 6%, (N=1) (p=0.009) | Treatment A:6 weeksMean area, mm2: 274 +/- 329Reduction in ulcer area (raw), mm2: 738 +/- 393Reduction in ulcer area (adjusted), mm2: natural log of area reduction 6.5 +/- 0.3 Treatment B:6 weeksMean 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<0.001adjustment 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 weekstotal area reduced by nearly 50% in all ulcers of treatment AComplete healing within 3 weeks, Treatment A:n=2Treatment B:n=1Complete healing within 4 weeks, n=2Complete healing within 5 weeks, n=1Complete healing within 6 weeks, n=3 | NR | NR | NR | Treatment A vs. Treatment BUlcer improvement by >3 stages, 28%(n=5) vs. 0Ulcer 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, 1994124USPoor | 28 days/5 months | Nursing homes and hospitals | Treatment A38% of PU had complete wound healing at 5 monthsTreatment B21%Treatment C14% of PU had complete wound healing at 5 months | % Decrease in volume at day 29:Treatment A71%Treatment B60%Treatment C17% (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, 2001125USPoor | 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, 2004126USGood | Variable treatment/26 weeks | Multi-center | Treatment A:11% complete wound healingTreatment B:13% | Treatment A:Median ulcer area reduction at week 12: 50% for patients who had complete healing39% for patients who had incomplete healingMedian ulcer volume reduction 41% for patients who had complete healingTreatment B:Median ulcer area reduction 34% for patients who had complete healing17% for patients who had incomplete healingMedian 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, 1999127USFair | 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 D3% 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. placeboIncidence 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)128Robson, 1992(b)129USPoor | 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, 1994130USPoor | 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, 2000131USPoor | 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)132USPoor | 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, 2010133ItalyPoor | 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, 2010134Poor | 12 months/NR |  | Treatment A:Complete wound healing: (leg ulcer subset)Complete wound healing: (leg ulcer subset): 18% vs. 69.9%, p<0.001Number of patients with all wounds fully closed:2 (5.3%) vs. 39 (59.1%), p<0.001Wounds Completely Closed:wound level - 13.3% vs. 69.5%, p<0.001patient level - 33.7% vs. 76.2%, p<0.001Treatment 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=0.49Median 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, yearCountryOverall 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, 1997121IsraelPoor | NR | NR | NR | NR | NR | NR | NR | NR | Teva Medical LTD, Israel. |
| Hirshberg, 2001122USPoor | 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, 2003123ItalyGood | NR | NR | NR | NR  | NR | NR | NR | NR | Progetto Finalizzato Invecchiamentoof the Italian National Research Council, inter*RAI* |
| Mustoe ,1994124USPoor | NR | Treatment A:Tunneling of the ulcer, exuberant granulation tissue, erythema with purulent drainageTreatment B:NR  | NR | Treatment A: NoneTreatment B: n=1 | Treatment A:Tunneling of the ulcer: n=1 exuberant granulation tissue: n=1 erythema with purulent drainage: n=1Treatment B: NR | None | None | 10% | Amgen Inc. |
| Payne, 2001125USPoor  | NR | NR | NR | NR | NR | NR | NR | NR | NIAMS, National Institutes of Health, Schering-Plough Research Institute, Scios, Inc. |
| Payne, 2004126USGood |  NR | NR | NR |  NR | NR | NR | NR | NR | Smith and Nephew, Inc. |
| Rees, 1999127USFair | NR | Skin ulceration, rash erythema-numbers, NR  | NR | Treatment An=0 Treatment B:n=0Treatment C:n=1Treatment D: n=1 | Becaplermin 100µg/g vs. 300μg/g vs. 100µg/g BID vs. placeboSepsis: 0 vs. 1 vs. 0 vs. 0Condition aggravated: 0 vs. 1 vs. 1 vs. 0 | None | Treatment A: 3.2%(N=1)  | NR | Johnson & Johnson, Inc. |
| Robson, 1992(a)128Robson, 1992(b)129USPoor | NR | NR | NR | NR | NR | NR | NR | NR  | Grant from California Biotechnology, Inc. |
| Robson, 2000131USPoor | NR | NR | NR | NR | NR | NR | NR | NR | National Institutes of Health; Schering-Plough Research Institute; Scios, Inc. |
| Robson, 1992(c)132USPoor |  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, 1994130USPoor | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Scevola, 2010133ItalyPoor | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Zuloff-Shani, 2010134IsraelPoor |  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 |