**Table D-1. Study design characteristics of studies evaluating treatments for chronic venous ulcers**

| **Author, year** | **Study design** | **N enrolled (N screened)** | **Enrollment year****Followup duration** | **Source population** | **Country** | **Run in period?****Washout period?****Compliance measured?** | **Exclusion criteria** | **Other exclusion criteria comments** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Alinovi, 1986**[**82**](#_ENREF_82) | RCT; parallel arms | 48 (NR) | 1983 to 1984 20 days | Primary care | Italy | No run-in | Ulcer duration: < 4 weeksComorbids excludedDiabetes excluded | Ulcers with clinical signs of infection, ulcers with negative bacteriologic cultures, ulcers with non-venous main cause, arterial insufficiency |
| **Arnold, 1994**[**39**](#_ENREF_39) | RCT; parallel arms | 70 (NR) |  Year NR10 weeks | pop source NR | US, UK | No run-inNo compliance | clinical infectionComorbids excluded | arterial insufficiency, dermatological conditions |
| **Backhouse, 1987**[**43**](#_ENREF_43) | RCT; parallel arms | 58 (NR) | Year NR12 weeks | wound center | NR | NR run-inNo compliance | no CVU | Ulcer size > 10cm2 Doppler indicating arterial cause |
| **Barwell, 2000**[**62**](#_ENREF_62) | cohort; NA | (669) | 1995 to 19993 years | pop source NR | UK | Yes run-inNo compliance | ABI: < 0.85 |  |
| **Barwell, 2004**[**60**](#_ENREF_60) | RCT; parallel arms | 500 (1418) | 1999 to 20025 years | nursing home, Primary care medical specialists | UK | Yes run-inYes compliance | Ulcer duration: <4 weeksABI: < 0.85 | Complete color duplex imaging not possible; veins completely occluded; Those unable to give informed consent; were unfit for surgery; compression was not practical; malignant ulcers |
| **Beckert, 2006**[**31**](#_ENREF_31) | RCT; parallel arms | 119 (137) | 2002 to 200420 weeks | wound center | Europe | Yes run-inNo compliance | Age: <18ABI: < 0.8 | Ulcerations due to CVI, severe cardiac , respiratory, gastrointestinal, liver, or renal disease, malignancy or signs of wound infection Pregnant women and nursing mothers, ulcer area < 3 cm |
| **Bello, 1999**[**71**](#_ENREF_71) | cohort | 111 (325) | 1994 to 1997NR | a single Venous ulcer assessment clinic | UK | No run-inNo compliance | ABI: < 0.8 | No venous reflux on duplex scanning |
| **Cambal, 2008**[**69**](#_ENREF_69) | Cohort, retrospective | 793 (NR) | 19735 years | Surgery | Slovakia | No run-in | no CVUNo compliance |  |
| **El-Hafez, 2004**[**68**](#_ENREF_68) | Cohort | 36 (NR) | 2000 to 200112 months | surgical outpatient clinic | Egypt and Saudi Arabia | No run-in | No CVUUlcer duration: < 4 weeksABI: < 0.9 | ulcer diameter 2 to 7cm |
| **Falanga V, 1999**[**51**](#_ENREF_51) | RCT; parallel arms |  (NR) | Year NR12 months | pop source NR | US | No run-inNo compliance | no CVUAge: <18 & >85Ulcer duration: <52 weeksComorbids excludedDiabetes excluded | receiving immunosuppressive agents, radiation therapy or chemotherapy within 1 month of entry into study |
| **Falanga, 1998**[**38**](#_ENREF_38) | RCT; parallel arms | 309 (NR) | Year NR12 months | outpatient setting but type not specified | US | No run-inNo compliance | no CVUAge: <18 & >85ABI: < 0.65Comorbids excludedDiabetes excluded | receiving immunosuppressive agents, radiation therapy or chemotherapy within 1 month of entry into study cellulitis, exudation indicative of heavy bacterial contam, eschar, obvious necrotic material that could interfere with graft/healing pregnancy, lactation collagen vascular diseases |
| **Franks, 2007**[**28**](#_ENREF_28) | RCT; factorial | 156 (NR) | 200224 weeks | Primary care hospital inpatient | United Kingdom | NR run-inNo compliance | Age: <18Ulcer duration: <2 & >52clinical infectionABI: < 0.8Systemic antimicrobials excluded | Pregnant, dry non-exuding wounds |
| **Galimberti, 1988**[**66**](#_ENREF_66) | Retrospective  | 118 (NR) | NR40 months | Dermatology clnic, vascular clinic | Italy | NR run-inNo compliance  | NR | NR |
| **Gatti, 2011**[**45**](#_ENREF_45) | NR; parallel arms | 24 (NR) | Year NR8 weeks | pop source NR | Brazil | No run-inNo compliance | no CVUUlcer duration: >260 weeks | Unable to receive dressing once per week associated arterial disease not adhering to treatment not accepting the use of Unna's boot |
| **Gethin, 2009**[**24**](#_ENREF_24) | RCT; parallel arms | 108 (256) | 2003 to 200612 weeks | wound center hospital inpatient vascular clinic | Ireland | No run-inYes compliance | no CVUAge: <18clinical infectionABI: < 0.8Comorbids excludedSystemic antimicrobials excluded | Having < 50% wound bed covered in slough Ulcer > 100cm2; Pregnant women or lactating mothers; Having a cavity wound |
| **Gohel, 2007**[**59**](#_ENREF_59) | RCT; parallel arms | 500 (1418) | 1999 to 20024 years | nursing home, Primary care hospital inpatient | UK | NR run-inNo compliance | Ulcer duration: <4 weeksABI: < 0.85 | Healed ulcer >6months; Those in whom duplex scan was not possible; those unwilling or refused to give consent; Those with deep venous occlusion; Malignant ulceration; Those unfit for surgery; Multiple layered compression not practical |
| **Gottrup, 2007**[**27**](#_ENREF_27) | RCT; parallel arms | 122 (NR) | 2005 to 200647 days | pop source NR | 6 European countries, Great Britain, Lithuania, Denmark, Germany, Czech Republic, Finland | NR run-inNo compliance | Age: <18Ulcer duration: <8 weeksclinical infectionDiabetes excludedSystemic antimicrobials excludedPain: Less than moderate pain on 5-point verbal rating scale (none, slight, moderate, lots, complete) | Pregnant or lactating women; Painful ulcers resistant to analgesic treatment over past 6 months or more allergy or other contraindication to ibuprofen; Use of unscheduled additional pain medication for 3 days prior to study admission |
| **Gottrup, 2008**[**23**](#_ENREF_23) | RCT; parallel arms | 122 (NR) | 2005 to 200647 days | From 13 centers from 6 countries (but the centers are not defined) | 6 European countries, Great Britain, Lithuania, Denmark, Germany, Czech Republic, Finland | Yes run-inNo compliance | no CVUAge: <19Ulcer duration: <8 weeksclinical infectionABI: < 0.8Comorbids excludedDiabetes excludedSystemic antimicrobials excludedPain: (1) Less than 'Moderate', on a 5 point Verbal Rating Score and also, (2) ulcers not resistant to analgesic treatment over the past 6 months or more | 1) Wound size of <1.6cm in any direction and maximum area of 50cm2, (2) Pregnant or lactating women (3) Local (and also clinical) infection or bacterial imbalance within or surrounding the ulcer area 1) Allergy or other contraindication to ibuprofen or related analgesics (non-steroidal anti-inflammatory agents), (2) History of asthma, rhinitis or urticaria, (3) previous participation in this study 1) use of unscheduled additional pain medication for 3 days before the study admission (except for regular concomitant pain medication), (2) Treatment with other immunosuppressant or cancer chemotherapeutic agents within 1 month before inclusion (1) Concomitant participation in other studies |
| **Greguric, 1994**[**48**](#_ENREF_48) | RCT; parallel arms | 110 (NR) | 1993 to 1993  | hospital inpatient outpatient | Croatia | No run-inYes compliance | no CVUAge: <18ABI: < 0.9Comorbids excluded | treatment with immunodepressants, malignant ulcers, chemotx, immune def, other condition affecting wound healing Pregnancy, sensitivity to any of the tx materials; Ulcers resulting from other disease ulcers <2.5 or >5 cm |
| **Guest, 2003**[**64**](#_ENREF_64) | RCT; parallel arms | 76 (206) | NR | Primary care | UK | Yes run-inNo compliance | ABI: < 0.8Comorbids excludedDiabetes excluded | Patients unfit for surgery |
| **Hansson, 1998**[**37**](#_ENREF_37) | RCT; parallel arms | 153 (NR) | Year NR12 weeks | derm clinic | Sweden, Denmark, the Netherlands, and the UK | No run-inYes compliance | clinical infectionABI: < 0.8Comorbids excludedDiabetes excluded | known sensitivity to products in trial, treatment with systemic antimicrobials patients undergoing investigation of thyroid |
| **Harding, 2005**[**33**](#_ENREF_33) | RCT; parallel arms | 194 (259) | Year NR14 weeks | wound center | Belgium, UK, Germany and Poland | Yes run-inNo compliance | Age: < 30 & > 85Ulcer duration: < 6 weeksclinical infectionABI: < 0.8 | Previous treatments with cell derived or growth factor derived therapies within 1 month prior to screening or planned during the study History of allergy to materials used within the study DVT at the time of the screening |
| **Harding, 2011**[**20**](#_ENREF_20) | RCT; parallel arms | 281 (NR) | 2010 to 20108 weeks | pop source NR | UK, Germany, France, Denmark, and Poland | NR run-inNo compliance | Age: <18Ulcer duration: >96 weeksclinical infectionABI: < 0.8Systemic antimicrobials excluded | Recent DVT within last 3 months Recent venous surgery within last 3 months Progressive neoplastic lesion treated by radiotherapy or chemotherapy |
| **Harlander-Locke, 2011**[**74**](#_ENREF_74) | Case series | 72 (433) | 2007 to 201112 months | wound center |  | No run-inNo compliance | no CVU | Failed non-interventional venous ulcer treatment for a minimum of 5 weeks |
| **Holloway, 1989**[**42**](#_ENREF_42) | RCT; parallel arms | 75 (NR) | Year NR24 weeks | outpatient, but not otherwise specified | US | No run-inYes compliance | no CVUUlcer duration: <12 weeksComorbids excluded | ulcer < 2cm in max diam (was relaxed later in trial) Proven/suspected non-venous cause of ulcer, inability to comply with treatment regimen, iodine allergy, clinically significant arterial disease |
| **Huovinen, 1994**[**57**](#_ENREF_57) | RCT; parallel arms | NR | Year NR16 weeks | pop source NR | Finland | No complianceNo washout | Age: < 18 years | body weight < 50 kg, allergies to antimicrobial agents used; current warfarin or theophylline treatment; antimicrobial treatment within 2 weeks of study |
| **Krishnamoorthy, 2003**[**47**](#_ENREF_47) | RCT; parallel arms | 53 (63) | Year NR12 weeks | Undefined health centers | Can UK | Yes run-inYes compliance | no CVUAge: <18Ulcer duration: > 8 weeks & > 240 weeksclinical infectionABI: < 0.7Comorbids excluded | ulcer area <3 or >25 cm2 Severe leg edema, impaired mobility, other cause of ulcer lack of either venous reflux, h/o DVT, or clinical appearance of post-DVT limb ulcer healed >50% during 14-day run-in period with treatment with compression |
| **Kucharzewski, 2003**[**46**](#_ENREF_46) | non randomized; parallel arms | 54 (NR) | Year NR  | people who 'applied for consultation by surgery doctor' | Poland | No run-inNo compliance | no CVUABI: < 0.8Diabetes excluded |  |
| **Labas, 2009**[**76**](#_ENREF_76) | Case series | 56 (NR) | 1991 to 2002NR | pop source NR | Slovak Republic | No run-inNo compliance | no CVU | Responded to sclerotherapy of the superficial system combined with compression within 6 months |
| **Lammoglia-Ordiales, 2011**[**56**](#_ENREF_56) | RCT; parallel arms | 41 (NR) | 2007 to 2009  | wound center | Mexico | No run-inNo compliance | Age: <18clinical infectionABI: < 0.8Diabetes excluded | Patients who were immunosupressed or had arterial disease |
| **Lane, 2003**[**77**](#_ENREF_77) | cohort | 41 (NR) | 1987 to 199111.9 years | pop source NR | Australia | NR run-inNo compliance | Age: <18 yearsUlcer duration: <4 weeksABI: < 0.7 | chronic insufficiency not cause by deep venous disease; symptoms of venous insufficiency of less than 2 years; not medically fit for surgery; history of thrombophlebitis, DVT or pregnancy within the previous year |
| **Lawrence, 2011**[**14**](#_ENREF_14) | Case aeries | 45 (208) | 2007 to 201012.85 months | wound center |  | No run-inNo compliance | no CVU | <3 months of treatment at wound center; no incompetent perforating veins |
| **Limova, 2003**[**35**](#_ENREF_35) | RCT; parallel arms | 20 (NR) | 1997 to 19996 weeks | wound center | US | No run-inNo compliance | Age: < 21Ulcer duration: <4 weeksclinical infectionABI: < 0.8 | Uncontrolled diabetes mellitus Allergy to materials used in the study |
| **Maggio, 2011**[**21**](#_ENREF_21) | RCT; parallel arms | 52 (NR) | Year NR70 days | pop source NR | Italy | No run-inNo compliance | Age: <18 & >70ABI: < 0.8Diabetes excluded | Treatment with immunosuppressive agents Treatment with cytotoxic agents History of bleeding disorders History of delayed wound healing |
| **Masuda, 1994**[**72**](#_ENREF_72) | cohort | 48 (81) | 1968 to 199021 years | hospital inpatient |  | NR run-inNo compliance |  | less than 4 years of follow-up |
| **Michaels, 2009**[**22**](#_ENREF_22) | RCT; parallel arms | 213 (304) | 2005 to 200712 months | derm clinic Primary care | UK | NR run-inYes compliance | no CVUUlcer duration: < 6 weeksABI: < 0.8Comorbids excluded Diabetes excludedSystemic antimicrobials excluded | refusal to give informed consent pregnancy sensitivity or specific contraindications to the use of silver leg ulcers with a maximum diameter of less than 1 cm, atypical ulcers including those with suspicion of malignancy |
| **Moffatt, 1992**[**49**](#_ENREF_49) | RCT; parallel arms | 60 (NR) | Year NR12 weeks | wound center | UK | No run-inNo compliance | no CVUUlcer duration: <12 weeksABI: < 0.8 | previously treated and healed within 24 weeks or decreased in size decreased by 20% or more after 12 weeks known allergy or other contraindication to the product |
| **Mostow, 2005**[**32**](#_ENREF_32) | RCT; crossover if desired | 120 (NR) | Year NR  | derm clinic wound center vascular clinic | United States, United Kingdom and Canada | NR run-inYes compliance | no CVUAge: <18Ulcer duration: <4 weeksclinical infectionABI: < 0.8Comorbids excludedDiabetes excludedSystemic antimicrobials excluded | Previous organ transplantation; Patients with Malnutrition and sickle cell disease; History of radiotherapy to the ulcer site; Patients with exposed bone, fascia and tendon |
| **Nash, 1991**[**73**](#_ENREF_73) | NR | 90 (NR) | 1979 to 19863 years | pop source NR | NR | NR run-inNo compliance | no CVU |  |
| **Nelson, 2007**[**29**](#_ENREF_29) | RCT; factorial | 245 (525) | Year NR24 weeks | wound center | UK | No run-inYes compliance | no CVUAge: <18Ulcer duration: <8 weeksclinical infectionABI: < 0.8Comorbids excludedDiabetes excluded | ulcer < 1 cm in length; Significant arterial disease; Pregnant or lactating women; Unable or unwilling to provide written, informed consent; Premenopausal women not using contraceptives; Sensitivity to methylxanthines or caffeine containing drinks; Taking warfarin, steroids, oxpentifylline, oxerutins, or naftidrofuryl; Life expectancy <6 months, immobile patients, immunosuppression |
| **O'Hare, 2010**[**58**](#_ENREF_58) | RCT; parallel arms | 40 (315) | 2005 to 200724 weeks | Leg ulcer clinic | UK | No run-inNo compliance | ABI: < 0.8Comorbids excludedDiabetes excluded | <1s retrograde flow on venous duplex imaging in GSV, SSV, AASV or other large superficial vein with significant proximal deep venous connection; Previous deep vein thrombosis or pulmonary embolism; Treatment with warfarin; Immobility and unable to give informed consent |
| **Omar, 2004**[**34**](#_ENREF_34) | RCT; parallel arms | 18 (NR) | Year NR12 weeks | pop source NR | UK | No run-inNo compliance | no CVUUlcer duration: <12 weeksABI: < 0.9 | lack of superficial reflux presence of deep venous reflux DVT non-venous causes of ulceration, area <3 or >25 cm2 |
| **Ormiston MC, 1983**[**55**](#_ENREF_55) | RCT; parallel arms |  (NR) | Year NR24 weeks | pop source NR | NR | NR run-inNo compliance | no CVUAge: <21Ulcer duration: <13 weeksDiabetes excluded | Ulcer diameter< 2cm; patients unable to change their own dressings non-venous cause, metabolic disease, psychiatric disease, malignancy patients with travel problems, iodine sensitivity multiple ulcers, pregnancy |
| **Ormiston, 1985**[**44**](#_ENREF_44) | RCT; Parallel but allowed optional cross-over | 61 (NR) | Year NR24 weeks | Outpatients (center not identified) | UK | No run-inNo compliance | Ulcer duration: <12 weeksABI: < 0.7 | Non-venous etiology ulcers When poor compliance was anticipated (because of distance or other limitations) unable to change dressing and did not have relative/friend to change dressing |
| **Pang, 2010**[**70**](#_ENREF_70) | Case series | 83 (NR) | 2005 to 200916 months | vascular clinic | UK | No run-inNo compliance | ABI: < 0.8 | patients that do not have CEAP 5-6; post thrombotic DVR and/or obstruction |
| **Pessenhofer, 1989**[**41**](#_ENREF_41) | RCT; parallel arms | 48 (NR) | Year NR281 days | derm clinic | NR | NR run-inNo compliance |  | Hospitalization |
| **Rojas, 2009**[**63**](#_ENREF_63) | non randomized; parallel arms | 67 (72) | 2006 to 2008NR | hospital inpatient | Mexico | No run-inNo compliance | no CVUABI: < 0.8 | Pulses at all levels |
| **Schulze, 2001**[**36**](#_ENREF_36) | RCT; Randomised Stratified controlled open-label study | 113 (NR) | Year NR4 weeks | wound center | Germany, UK | No run-inNo compliance | no CVUABI: < 0.8 | Patients who were part of another research study within the previous 30 days |
| **Scurr JH, 1993**[**54**](#_ENREF_54) | RCT; parallel arms |  (NR) | Year NR6 weeks | pop source NR | UK | NR run-inNo compliance | no CVUABI: < 0.9Comorbids excludedDiabetes excluded | ulcer of unclear etiology |
| **Scurr JH, 1994**[**53**](#_ENREF_53) | RCT; parallel arms | 40 (NR) | to Year NR6 weeks | wound center | UK | No run-inYes compliance | Diabetes excludedSystemic antimicrobials excluded | chemotherapy or radiation treatment peripheral arterial disease |
| **Sigala, 2007**[**78**](#_ENREF_78) | cohort | 62 (NR) | 2001 to 20051 year | vascular clinic | Germany | No run-inNo compliance | Ulcer duration: >12 weeksclinical infection excludedABI: < 0.8comorbids excludeddiabetes excluded | Malignancy; no venous perforator insufficiency; no CEAP stage 6 |
| **Smith, 1992**[**50**](#_ENREF_50) | RCT; parallel arms | 200 (529) | 1987 to 19884 months | community | UK | No run-inNo compliance | no CVUABI: < 0.75Comorbids excludedDiabetes excluded | ulcer diameter <2cm; infection requiring immediate antibiotics; lymphedema, history of iodine allergy, neurologic disease |
| **Sottiurai, 1991**[**67**](#_ENREF_67) | NRNA | 46 (NR) | 1981 to 198773 months | pop source NR | US | NR run-in |  | No recurrent leg ulcer refractory to non-surgical treatment, no incompetent perforator and deep venous valve demonstrated by venography, not compliant to pre-and post-treatment protocol |
| **Taradaj, 2011**[**75**](#_ENREF_75) | Case series from a RCT | 305 (NR) | 1999 to 20082 years | vascular clinic | Poland | No run-inNo compliance | no CVUABI: < 1comorbids excludeddiabetes excludedcorticosteroids excluded | patients with metal implants; pregnancy |
| **Teepe, 1993**[**40**](#_ENREF_40) | RCT; parallel arms | 43 (NR) | 1989 to 19916 weeks | derm clinic | Belgium | Yes run-inNR compliance | no CVUUlcer duration: <12 weeks |  |
| **van Gent, 2006**[**65**](#_ENREF_65) | RCT; parallel arms | 170 (NR) | 1997 to 200136 months | pop source NR | The Netherlands | NR run-inNo compliance | no CVUABI: < 0.8 | Total or partial occlusion of the deep venous system; Former subfascial ligation of perforating veins; Severe neurologic or muscular pathology; Immobility |
| **Vanscheidt, 2007**[**26**](#_ENREF_26) | RCT; parallel arms | 225 (NR) | NR182 days | pop source NR | Germany, Czech Republic, Hungary | Yes run-inNo compliance | Age: <18 & >90Ulcer duration: <12 weeksABI: < 0.8Comorbids excludedDiabetes excluded | Venous leg ulcers above the knee joint or on distal metatarsal part of foot; venous ulcers <2 cm2 or > 50cm2; Pregnant or lactating women Venous surgery or sclerotherapy in preceding 3 months; know hypersensitivity to bovine proteins or other constituents of Bioseed; Phlebitis or deep leg vein thrombosis in preceding 3 months; unable to get or apply compression therapy |
| **Vowden, 2006**[**30**](#_ENREF_30) | RCT; parallel arms | 123 (NR) | 2003 to 200412 weeks | pop source NR | pan-Europe | No run-inNo compliance |  Ulcer duration: <26 weeksclinical infectionABI: < 0.8Comorbids excludedDiabetes excluded | ulcer size between <5 and >25 cm2 patient had to have received at least 1 month of compression therapy without ulcer improvement before study entry highly exuding wounds, recent vascular surgery or overt evidence of arterial disease, severe immobility those undergoing concomitant topical therapy |
| **Vowden, 2007**[**25**](#_ENREF_25) | RCT; parallel arms | 83 (101) | NR12 weeks | pop source NR | NR | Yes run-inNo compliance | Age: <18Ulcer duration: <24 weeksclinical infectionABI: < 0.8Comorbids excludedDiabetes excluded | Ulcer area <8cm2 or >36cm2 Confinement to bed or wheelchair; Physical and/or mental conditions making compliance difficult; Known allergy/hypersensitivity to product components |
| **Weiss RA, 1996**[**52**](#_ENREF_52) | RCT; parallel arms | 18 (NR) | NR16 weeks | pop source NR | US | NR run-inYes compliance | no CVUUlcer duration: <9 weeks | <1 or >4 cm2 in size |
| **Wolters, 1997**[**79**](#_ENREF_79) | cohort | 74 (NR) | 1992 to 19951 year | vascular clinic | Germany | NR run-inNo compliance |  | no singular insufficiency of perforating veins |
| **Zamboni, 2003**[**61**](#_ENREF_61)  | RCT; parallel arms | 45 (80) | 3 years | pop source NR | Italy | Yes run-inNR compliance | Age: >80ABI: < 0.9Diabetes excludedsystemic antimicrobials excluded | Ulcer size<2cm2 & >12cm2; Patients unable to walk; secondary or congenital venous disease; (History of DVT &/duplex evidence of deep venous reflux or obstruction; congenital angiodysplasia) |

Abbreviations: AASV = antibody associated systemic vasculitis; ABI = Ankle Brachial Index; CVI = chronic venous insufficiency; CVU = cardiovascular unit; Derm clinic = dermatological clinic; Diam = diameter; DM = diabetes mellitus; DVR = double valve replacement; DVT = deep vein thrombosis; GSV = great saphenous vein; Immune def = immune deficient; NR = not reported; RCT = randomized controlled trial; SSV = short saphenous vein; kg = kilogram; CEAP = clinical severity, etiology or cause, anatomy, pathophysiology; IMM = immunosuppressants