CONCISE REPORT

Demographic, clinical and antibody characteristics of patients with digital ulcers in systemic sclerosis: data from the DUO Registry

Christopher P Denton,[1] Thomas Krieg,[2] Loic Guillevin,[3] Barbara Schwierin,[4] Daniel Rosenberg,[4] Mariabeth Silkey,[4] Maurice Zultak,[4] Marco Matucci-Cerinic,[5] on behalf of the DUO Registry investigators*

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[1]Centre for Rheumatology and Connective Tissue Diseases, Royal Free Hospital, London, UK
[2]Department of Dermatology, University of Cologne, Cologne, Germany
[3]Department of Internal Medicine, Paris Descartes University, Paris, France
[4]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland
[5]Department of Medicine, University of Florence, Florence, Italy

Correspondence to
Christopher P Denton, Centre for Rheumatology and Connective Tissue Diseases, Department of Inflammation, Division of Medicine, UCL Medical School, Royal Free Campus, Rowland Hill Street, London NW3 2PF, UK; cdenton@medsch.ucl.ac.uk

*The complete list of DUO Registry investigators is provided as online supplement Appendix 1

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ABSTRACT

Objectives The Digital Ulcers Outcome (DUO) Registry was designed to describe the clinical and antibody characteristics, disease course and outcomes of patients with digital ulcers associated with systemic sclerosis (SSc).

Methods The DUO Registry is a European, prospective, multicentre, observational, registry of SSc patients with ongoing digital ulcer disease, irrespective of treatment regimen. Data collected included demographics, SSc duration, SSc subset, internal organ manifestations, autoantibodies, previous and ongoing interventions and complications related to digital ulcers.

Results Up to 19 November 2010 a total of 2439 patients had enrolled into the registry. Most were classified as either limited cutaneous SSc (lcSSc; 52.2%) or diffuse cutaneous SSc (dcSSc; 36.9%). Digital ulcers developed earlier in patients with dcSSc compared with lcSSc. Almost all patients (95.7%) tested positive for antinuclear antibodies, 45.2% for anti-scleroderma-70 and 43.6% for anticentromere antibodies (ACA). The first digital ulcer in the anti-scleroderma-70-positive patient cohort occurred approximately 5 years earlier than the ACA-positive patient group.

Conclusions This study provides data from a large cohort of SSc patients with a history of digital ulcers. The early occurrence and high frequency of digital ulcer complications are especially seen in patients with dcSSc and/or anti-scleroderma-70 antibodies.

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterised by microvascular damage and excessive fibrosis of the skin and various internal organs. Limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) subsets are also associated with the presence of a number of autoantibodies, the expression of which can be useful in the diagnosis, prognosis and SSc disease management.[1]

The European Medicines Agency (EMA) requested the establishment of a prospective registry of patients with ongoing digital ulcers associated with SSc as a licensing requirement for bosentan in this indication. The Digital Ulcers Outcome (DUO) Registry enrols patients with digital ulcer disease regardless of their treatment status; however, a large proportion are receiving bosentan. This study provides valuable insights into this patient group and here we describe the clinical and autoantibody characteristics of these patients at enrolment.

METHODS

The DUO Registry was initiated in April 2008 as an EMA postapproval commitment (after approval of a new indication for bosentan 'to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease').[2] Participating centres received approval from relevant national and local ethics committees, data protection and health authorities. In line with an observational study design, physicians were asked to enter all consenting consecutive patients with ongoing digital ulcers associated with SSc, irrespective of treatment regimen. Patients received standard medical care and follow-up as determined by their physician. Data definitions were informed by literature[3] and scientific committee consensus. Data collection included demographics, SSc disease duration, underlying disease classification (lcSSc, dcSSc, overlap SSc/mixed connective tissue disease and other), internal organ manifestations, autoantibodies, history of interventions/complications related to digital ulcers, ongoing complications related to digital ulcers, and ongoing medications and functional assessment based on a disease-specific questionnaire. The presence of antinuclear antibodies, anti-scleroderma-70 antibodies, anticentromere antibodies (ACA), anti-RNA polymerase 3, anti-U1 ribonucleoprotein and anti-U3 ribonucleoprotein were recorded. All serology tests and other data collection parameters were collected if performed. Quality assurance comprised automatic online quality checks and annual source data verification on 10% of the patients.

Data analysis

Enrolment data for the antibody subsets were analysed cross-sectionally for differences by group. SAS statistical software was used for analysing the data. Descriptive statistics (mean, median, SD, 95% CI, minimum, maximum) are provided for numerical variables. Categorical variables are summarised by counts and percentages and 95% CI.

RESULTS

As of 19 November 2010, a total of 2439 patients had been enrolled into the DUO Registry from 271

Table 1 Demographics and clinical features by antibody status

	ANA* (N=2085)	Anti-Scl-70 (N=854)	Anti-RNA Pol 3 (N=86)	ACA (N=775)	Anti-U1 RNP (N=120)	Anti-U3 RNP (N=39)
Tested positive/tests performed (%)	2085/2179 (95.7)	854/1888 (45.2)	86/867 (9.9)	775/1778 (43.6)	120/1243 (9.7)	39/799 (4.9)
Female, n/N (%)	1719/2085 (82.4)	676/854 (79.2)	70/86 (81.4)	677/775 (87.4)	91/120 (75.8)	31/39 (29.5)
dcSSc, n/N (%) (95% CI)	776/2070 (37.5) (35.4 to 39.6)	557/848 (65.7) (62.4 to 68.9)	37/85 (43.5) (32.8 to 54.7)	91/770 (11.8) (9.6 to 14.3)	34/119 (28.6) (20.7 to 37.6)	10/38 (26.3) (13.4 to 43.1)
lcSSc, n/N (%) (95% CI)	1071/2070 (51.7) (49.6 to 53.9)	249/848 (29.4) (26.3 to 32.6)	28/85 (32.9) (23.1 to 44.0)	638/770 (82.9) (80.0 to 85.5)	38/119 (31.9) (23.7 to 41.1)	15/38 (39.5) (24.0 to 56.6)
Overlap SSc/mCTD, n/N (%) (95% CI)	149/2070 (7.2) (6.1 to 8.6)	17/848 (2.0) (1.2 to 3.2)	14/85 (16.5) (9.3 to 26.1)	23/770 (3.0) (1.9 to 4.5)	40/119 (33.6) (25.2 to 42.8)	12/38 (31.6) (17.5 to 48.7)
Age at enrolment, years, mean (95% CI)	54.4 (53.8 to 55.0)	52.4 (51.4 to 53.3)	51.3 (48.4 to 54.2)	58.1 (57.2 to 59.1)	49.9 (47.4 to 52.5)	48.5 (44.0 to 53.0)
Age at RP onset, years, mean (95% CI)	39.7 (39.0 to 40.5)	38.5 (37.5 to 39.6)	37.6 (34.7 to 40.6)	41.1 (39.9 to 42.3)	35.7 (32.9 to 38.6)	33.7 (28.5 to 38.9)
Age at first digital ulcer, years, mean (95% CI)	46.6 (45.9 to 47.4)	44.7 (43.6 to 45.7)	44.1 (41.1 to 47.2)	50.1 (48.9 to 51.3)	42.6 (39.6 to 45.5)	38.8 (33.6 to 44.0)
Time from onset of RP to first digital ulcer, years, mean (95% CI)	6.6 (6.2 to 7.0)	6.0 (5.4 to 6.6)	6.1 (4.4 to 7.8)	8.1 (7.3 to 9.0)	6.5 (4.9 to 8.0)	6.9 (3.5 to 10.4)
Time from first non-RP to first digital ulcer manifestation, years, mean (95% CI)	3.6 (3.3 to 3.9)	3.2 (2.9 to 3.6)	3.6 (2.5 to 4.8)	3.9 (3.4 to 4.5)	3.8 (2.7 to 4.9)	4.6 (1.9 to 7.4)

The denominator N varies according to the number of available observations.
*Antibody subsets are not mutually exclusive: one patient can have several antibodies and therefore contribute to several groups.
ACA, anticentromere antibodies; ANA, antinuclear antibodies; anti-Scl-70, anti-scleroderma-70 antibodies; anti-RNA Pol 3, anti-RNA polymerase 3; anti-U1 RNP, anti-U1 ribonucleoprotein; anti-U3 RNP, anti-U3 ribonucleoprotein; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; mCTD, mixed connective tissue disease; RP, Raynaud's phenomenon; SSc, systemic sclerosis.

participating centres in 18 European countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland and UK).

Study cohort characteristics

The mean age of the patients enrolled was 54.6 years (SD 14.1) and the majority were women. Age at first Raynaud's phenomenon was on average 39.8 years and age at first digital ulcer was 46.7 years. At the time of enrolment, 60.0% (1426/2377) had at least one digital ulcer (data were missing for 62 patients). All patients who had no current digital ulcers at enrolment had a history of digital ulcer disease. Overall, 52.2% of the patients were classified as lcSSc, 36.9% as dcSSc, 6.8% as overlap SSc/mixed connective tissue disease, and 4.1% had other diseases (eg, systemic lupus erythematosus, dermatomyositis, vasculitis or SSc not further specified) (data were missing for 44 patients).

At enrolment, gastrointestinal tract manifestations had occurred in more than half of the patients (55.7%). Also common were lung fibrosis (41.3%), pulmonary arterial hypertension (PAH) (15.0%) and heart manifestations (10.7%). Almost half of all patients (47.4%) were receiving treatment with bosentan or another ERA (endothelin receptor antagonist), with a similar proportion receiving calcium antagonists and approximately one third receiving prostanoids (see supplementary table S1, available online only).

Antibody distribution

Almost all, 95.7%, (2085/2179) of patients tested were positive for antinuclear antibodies, 45.2% (854/1888) for anti-scleroderma-70 antibodies, 43.6% (775/1778) for ACA, 9.9% (86/867) for anti-RNA polymerase 3, 9.7% (120/1243) for anti-U1 ribonucleoprotein and 4.9% (39/799) for anti-U3 ribonucleoprotein. Few patients had a combination of antibodies. The combination with the highest occurrence was anti-scleroderma-70 plus ACA, 2.3% (56/2439), followed by anti-scleroderma-70 plus anti-U1 ribonucleoprotein, 1.8% (43/2439), anti-scleroderma-70 plus anti-RNA polymerase 3, 1.5% (36/2439), ACA plus anti-U1 ribonucleoprotein, 1.4% (34/2439), ACA plus anti-RNA polymerase 3, 1.4% (34/2439) and anti-U1 ribonucleoprotein plus anti-U3 ribonucleoprotein, 1.3% (31/2439).

SSc disease characteristics by antibody status

Patients positive for ACA were predominantly classified as lcSSc (82.9%; table 1). From the patients positive for anti-scleroderma-70 antibodies, a high proportion were classified as dcSSc (66.6%) and a lower proportion were classified as lcSSc (29.4%). Lung fibrosis was most frequent in the anti-scleroderma-70 subset (62.2%) compared with other antibody subsets (22.3–41.9%). Gastrointestinal manifestations showed a similar high proportion in all antibody subgroups, except for patients who were anti-U3 ribonucleoprotein positive. The frequencies of PAH and kidney manifestations were generally similar across the antibody subsets, although the proportion among patients with anti-U3 ribonucleoprotein was slightly higher; heart manifestations were highest in patients with anti-scleroderma-70 and anti-U1 ribonucleoprotein and lowest in patients with ACA (table 2). The proportion of patients with previous digital ulcer complications and interventions was broadly similar in the anti-scleroderma-70 subgroup and the ACA subgroup; the most marked exception was for surgical amputation, which occurred almost twice as frequently in patients with ACA (14.6%) compared with anti-scleroderma-70-positive patients (7.9%) (table 3).

Table 2 Disease manifestations by antibody status

	ANA (N=2085)	Anti-Scl-70 (N=854)	Anti-RNA Pol 3 (N=86)	ACA (N=775)	Anti-U1 RNP (N=120)	Anti-U3 RNP (N=39)
Lung fibrosis, n/N (%) (95% CI)	873/2085 (41.9) (39.7 to 44.0)	531/854 (62.2) (58.8 to 65.4)	36/86 (41.9) (31.3 to 53.0)	173/775 (22.3) (19.4 to 25.4)	50/120 (41.7) (32.7 to 51.0)	16/39 (41.0) (25.6 to 57.9)
PAH, n/N (%) (95% CI)	307/2085 (14.7) (13.2 to 16.3)	133/854 (15.6) (13.2 to 18.2)	12/86 (14.0) (7.4 to 23.1)	120/775 (15.5) (13.0 to 18.2)	19/120 (15.8) (9.8 to 23.6)	9/39 (23.1) (11.1 to 39.3)
Kidney manifestations, n/N (%) (95% CI)	105/2085 (5.0) (4.1 to 6.1)	43/854 (5.0) (3.7 to 6.7)	7/86 (8.1) (3.3 to 16.1)	26/775 (3.4) (2.2 to 4.9)	10/120 (8.3) (4.1 to 14.8)	5/39 (12.8) (4.3 to 27.4)
Gastrointestinal manifestations, n/N (%) (95% CI)	1192/2085 (57.2) (55.0 to 59.3)	498/854 (58.3) (56.4 to 63.9)	51/86 (59.3) (47.9 to 70.8)	440/775 (56.8) (53.2 to 60.3)	63/120 (52.5) (43.2 to 61.7)	15/39 (38.5) (23.4 to 55.4)
Heart manifestations, n/N (%) (95% CI)	220/2085 (10.6) (9.3 to 12.0)	105/854 (12.3) (10.2 to 14.7)	6/86 (7.0) (2.6 to 14.6)	47/775 (6.1) (4.5 to 8.0)	16/120 (13.3) (7.8 to 20.7)	3/39 (7.7) (1.6 to 20.9)

The denominator N varies according to the number of available observations.
*Antibody subsets are not mutually exclusive: one patient can have several antibodies and therefore contribute to several groups.
ACA, anticentromere antibodies; ANA, antinuclear antibodies; anti-Scl-70, anti-scleroderma-70 antibodies; anti-RNA Pol 3, anti-RNA polymerase 3; anti-U1 RNP, anti-U1 ribonucleoprotein; anti-U3 RNP, anti-U3 ribonucleoprotein; PAH, pulmonary arterial hypertension.

Onset of disease manifestations by antibody status

In anti-scleroderma-70-positive patients, the first digital ulcer occurred at a mean age of 44.7 years (95% CI 43.6 to 45.7), whereas in ACA-positive patients, the first digital ulcer occurred approximately 6 years later, at 50.1 years (95% CI 48.9 to 52.3).

Compared with ACA-positive patients, anti-scleroderma-70 -positive patients were younger at the onset of first Raynaud's phenomenon symptoms (anti-scleroderma-70: 38.5 years (95% CI 37.5 to 39.6); ACA: 41.1 years (95% CI 39.9 to 42.3)) and had shorter time periods from the onset of Raynaud's phenomenon to the first digital ulcer (anti-scleroderma-70: 6.0 years (95% CI 5.4 to 6.6); ACA: 8.1 years (95% CI 7.3 to 9.0)) (table 1).

DISCUSSION

The findings of the DUO Registry regarding the burden of disease in SSc patients with digital ulcers confirm the findings of other large cohort studies.[4 5] Organ manifestations are common, with gastrointestinal manifestations being the most frequently reported, followed by lung fibrosis, PAH and heart manifestations.

Complications associated with digital ulcers, such as infection requiring systemic antibiotics, gangrene and amputation occurred frequently in all major SSc subsets. Anti-scleroderma-70-positive patients were younger at the onset of the first digital ulcer and had approximately double the rate of lung fibrosis compared with ACA-positive patients, these data are in line with findings from the European League Against Rheumatism Scleroderma Trials and Research.[4] Furthermore, heart manifestations were also more common in the anti-scleroderma-70-positive group. Taken together, these findings confirm the association between anti-scleroderma-70 and more severe disease seen in other studies.[1]

The data show that anti-scleroderma-70-positive patients have fewer surgical amputations than ACA-positive patients but more autoamputation. As patients with this antibody have more SSc disease manifestations, the physician may be more reluctant to perform surgical interventions with the patient being more likely to be left to autoamputation; whereas ACA-positive patients may have a phenotype that leads to a decision to amputate surgically.

The proportion of anti-U1 ribonucleoprotein in patients with SSc, at approximately 30% in both lcSSc and dcSSc, was much higher than the previously reported figures.[1] In contrast to other studies, the presence of anti-U1 ribonucleoprotein did not appear to have a greater association with PAH or with gastrointestinal manifestations than other autoantibodies.[1]

The proportion of patients reported here as anti-U3 ribonucleoprotein positive was low (4.9%), a finding similar to that reported in other studies.[1] In addition, the complications associated with anti-U3 ribonucleoprotein positivity were similar as in previous studies.[6–10]

There are a number of limitations in this study. The DUO Registry is an observational study and not all data fields were completed for every patient; for example, the number of digital ulcers at enrolment was missing for 62 patients and few patients were tested for anti-RNA polymerase 3 or for anti-U3 ribonucleoprotein antibodies. Central testing was not performed and therefore potential variations between different analysis methods should be considered when interpreting the data.

In addition, at enrolment, differential recall bias for data recorded in the past may confound interpretation.

Almost half of all patients were being treated with bosentan. This is likely to be a reflection of the fact that the DUO Registry

Table 3 Previous digital ulcer complications and interventions by antibody status

	ANA* (N=2085)	Anti-Scl-70 (N=854)	Anti-RNA Pol 3 N=86	ACA (N=775)	Anti-U1 RNP (N=120)	Anti-U3 RNP (N=39)
Previous digital ulcer complications						
Previous critical digital ischaemia, n/N* (%) (95% CI)	459/867 (52.9) (49.6 to 56.3)	174/340 (51.2) (45.7 to 56.6)	13/19 (68.4) (43.4 to 87.4)	178/321 (55.5) (49.8 to 61.0)	25/47 (53.2) (38.1 to 67.9)	12/17 (70.6) (44.0 to 89.7)
Previous gangrene, n/N* (%) (95% CI)	442/1960 (22.6) (20.7 to 24.5)	171/792 (21.6) (18.8 to 24.6)	14/83 (16.9) (9.5 to 26.7)	181/739 (24.5) (21.4 to 27.8)	28/114 (24.6) (17.0 to 33.5)	11/38 (28.9) (15.4 to 45.9)
Previous autoamputation, n/N* (%) (95% CI)	169/1965 (8.6) (7.4 to 9.9)	86/796 (10.8) (8.7 to 13.2)	4/82 (4.9) (1.3 to 12.0)	51/740 (6.9) (5.2 to 9.0)	9/115 (7.8) (3.6 to 14.3)	4/38 (10.5) (2.9 to 24.8)
Previous soft tissue infection requiring systemic antibiotics, total, n/N* (%)	601/1876 (32.0) (29.9 to 34.2)	243/768 (31.6) (28.4 to 35.1)	18/78 (23.1) (14.3 to 34.0)	257/712 (36.1) (32.6 to 39.7)	30/109 (27.5) (19.4 to 36.9)	14/35 (40.0) (23.9 to 57.9)
Previous osteomyelitis, n/N* (%) (95% CI)	69/1952 (3.5) (2.8 to 4.5)	31/793 (3.9) (2.7 to 5.5)	1/82 (1.2) (0.03 to 6.6)	33/735 (4.5) (3.1 to 6.3)	6/114 (5.3) (2.0 to 11.1)	5/37 (13.5) (4.5 to 28.8)
Previous digital ulcer interventions						
Previous hospitalisation for digital ulcer, n/N* (%) (95% CI)	870/1974 (44.1) (41.9 to 46.3)	340/805 (42.2) (38.8 to 45.7)	30/80 (37.5) (26.9 to 49.0)	356/743 (47.9) (44.3 to 51.6)	53/111(47.7) (38.2 to 57.4)	16/35 (45.7) (28.8 to 63.4)
Previous upper limb sympathectomy, n/N* (%) (95% CI)	74/1922 (3.9) (3.0 to 4.8)	21/768 (2.7) (1.7 to 4.2)	3/82 (3.7) (0.8 to 10.3)	43/720 (6.0) (4.4 to 8.0)	4/113 (3.5) (1.0 to 8.8)	1/36 (2.8) (0.1 to 14.5)
Previous digital sympathectomy, n/N* (%) (95% CI)	40/1921 (2.1) (1.5 to 2.8)	15/767 (2.0) (1.1 to 3.2)	3/82 (3.7) (0.8 to 10.3)	22/721 (3.1) (1.9 to 4.6)	2/113 (1.8) (0.2 to 6.3)	1/36 (2.8) (0.1 to 14.5)
Previous arterial reconstruction, n/N* (%) (95% CI)	20/1918 (1.0) (0.6 to 1.6)	6/767 (0.8) (0.3 to 1.7)	2/82 (2.4) (0.3 to 8.5)	12/716 (1.7) (0.9 to 2.9)	2/113 (1.8) (0.2 to 6.3)	1/36 (3.0) (0.1 to 15.8)
Previous arthrodesis, n/N* (%) (95% CI)	31/1642 (1.9) (1.3 to 2.7)	12/638 (1.9) (1.0 to 3.3)	1/70 (1.4) (0.04 to 7.7)	10/607 (1.6) (0.8 to 3.0)	2/99 (2.0) (0.3 to 7.1)	1/33 (3.0) (0.1 to 15.8)
Previous debridement, n/N* (%) (95% CI)	189/1644 (11.5) (10.0 to 13.1)	49/491 (10.0) (8.2 to 13.1)	8/71 (11.3) (5.0 to 21.0)	90/608 (14.8) (12.1 to 17.9)	10/97 (10.3) (5.1 to 18.1)	3/33 (9.1) (1.9 to 24.3)
Previous surgical amputation, n/N* (%) (95% CI)	158/1661 (9.5) (8.1 to 11.0)	51/642 (7.9) (6.0 to 10.3)	6/72 (8.3) (3.1 to 17.3)	90/618 (14.6) (11.9 to 17.6)	10/103 (9.7) (4.8 to 17.1)	4/34 (11.8) (3.3 to 27.5)
Previous use of parenteral prostanoids, n/N* (%) 95% CI)	1112/1907 (58.3) (56.1 to 60.5)	462/775 (59.6) (56.1 to 63.1)	37/81 (45.7) (34.6 to 57.1)	411/707 (58.1) (54.4 to 61.8)	62/113 (54.9) (45.2 to 64.2)	15/36 (41.7) (25.5 to 59.2)

The denominator N varies according to the number of available observations.
*Antibody subsets are not mutually exclusive: one patient can have several antibodies and therefore contribute to several groups.
ACA, anticentromere antibodies; ANA, antinuclear antibodies; anti-Scl-70, anti-scleroderma-70 antibodies; anti-RNA Pol 3, anti-RNA polymerase 3; anti-U1 RNP, anti-U1 ribonucleoprotein; anti-U3 RNP, anti-U3 ribonucleoprotein.

was initiated following EMA approval of bosentan,[2] and it is possible that patient entry into the registry was biased towards patients receiving bosentan. Therefore, there are limitations in the application of these data to the wider SSc population. Nevertheless, this study provides, and will continue to provide, valuable prospectively collected data from a large cohort of over 2000 SSc patients. The strengths include the prospective nature of data collection and the strong framework of research governance compared with that of previous studies. The multinational and multicentre nature of this registry offers the potential for comparison of different patient populations and healthcare systems.

CONCLUSION

This report provides the first analysis of data from the large, multinational DUO Registry confirming the high clinical burden of digital ulcers in patients with SSc across antibody subsets, with early occurrence and high frequency in patients with dcSSc. The feasibility and utility of the DUO Registry is confirmed by the findings of this study.

Contributors Registry design: CPD, TK, LG, BS, DR, MS, MZ, MMC; data acquisition: CPD, TK, LG, MMC; manuscript preparation: CPD, TK, LG, BS, DR, MS, MZ, MMC; statistical analysis: MS, DR. All authors were involved in the drafting and reviewing of the manuscript and approved the final version.

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AT – AUSTRIA
AMSTETTEN; M STETTER
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VIENNA; M HIRSCHL
VIENNA; P MESARIC
VIENNA; R FELDMANN
VIENNA; K SEMMELWEIS
WELS; M HUNDSTORFER, V REINHART

CH – SWITZERLAND
ZURICH; B MAURER, D VERNER, O DISTLER, R SCHMIDT-BOSSHARD

CZ – CZECH REPUBLIC
BRNO; J BOHMOVA, L PROCHAZKOVA, P NEMEC
BRNO; Z FOJTIK
HRADEC KRALOVE; T SOUKUP
JESENIK; A SMRZOVA
PLZEN; D SUCHY
PRAGUE; I ZEMANOVA
PRAGUE; R BECVAR

DE – GERMANY
AACHEN; A GAWLIK, M KOCH, T RAUEN
AACHEN; B VOSS
AACHEN; R KURTHEN
AUGSBURG; A UNHOLZER, H STARZ, J WELZEL, K PLAUMANN
BAD AIBLING; B MERK, HH BLOCHING
BAD BRAMSTEDT; F MOOSIG, P FREY, S KAHL
BAD ENDBACH; H SCHLEENBECKER, ,K STORCK-MUELLER
BAD KREUZNACH; A SCHWARTING, A HAZENBILLER, V NICHELMANN
BAD KREUZNACH; W FLAIG
BAD NAUHEIM; C RUMBAUR, I BOESENBERG, T SCHMEISER
BAD STAFFELSTEIN; J MARX, L MAYER
BASSUM; T STEIN
BAYREUTH; W OCHS
BERLIN; C RASCHE, M WORM
BERLIN; G RIEMEKASTEN, K DEUSCHLE, M BECKER
BERLIN; HJ KLEINER
BERLIN; K SCHULZE

BOCHUM; C TIGGERS, J PETERS, J KIRSCHKE
BONN; C SCHAEFER, M MONSHAUSEN, T MENGDEN
BONN; F SADEGHLAR, M SEIDEL
BREMEN; C HILLEBRECHT, J ANDRESEN, R REEMTSEN
DARMSTADT; F STOECKL, S SPERLING
DARMSTADT; M PODDA, N WAGNER
DORTMUND; J GUENZEL
DRESDEN; I WUERZBURG, K LUETHKE
DRESDEN; M ENDERLEIN, M KAYSER
DUESSELDORF; A GERBER, M HAUST, NP HOFF, R MOTA, S AKANAY-DIESEL
DUESSELDORF; K JAHNKE, S METTLER, S TOELLER, S ZWENGER
EBENSFELD; E KLEIN, K HAHN
ERIANGEN; C BEYER, J DISTLER
ERLANGEN; A KATZEMICH, C ERFURT-BERGE, M STICHERLING
ERLANGEN; F SCHUCH, P RAPP
ESSEN; A MITCHELL, C FREUNDLIEB, U RUSHENTSOVA
FRANKFURT; A HIMSEL, U HENKEMEIER
FRANKFURT; P EILBACHER
FRIEDRICHSRODA; C ULLRICH-GUENTHER, S NEUL
GERA; M OELSNER
GOETTINGEN; G HERMANNS
GREIFSWALD; M FIENE
HAMBURG; A GAUSE
HAMBURG; C MENSING, D KLINGS, H MENSING, J MESSALL, R ZUPER
HAMBURG; D MAY
HAMBURG; L BRUCKNER, N SHEIKH
HAMBURG; P ARIES, S KIRCHBERG
HELDELBERG; A FUNKERT, N BLANK, S LUPASCHKO,
HEMAU; M SCHWUERZER-VOIT
HOFHEIM; L MEIER, U HERR, U MEIER
HOHENFELDE; G NEEK, H WERNITZSCH
HOMBURG; C PFOEHLER
HOMBURG; G ASSMANN, J VOSSWINKEL
KARLSBAD; B KROG, E WOLLERSDORFER
KIEL; J OLTMANN-SCHROEDER, R ZEUNER, S UHLIG, S BARTH
KIEL; R HUEGEL, R GLAESER
KOELN; B RABE, J SCHUSTER, J SCHOLZ, K KREMER, M ROBAKIDZE-TORBAHN, P MOINZADEH
LEIPZIG; M MITTAG
LUEBECK; A DOHSE, A MUHLACK, L SCHULTZ, S SCHULT, Y FRAMBACH
MAINZ; A KETTENBACH, I FELL, K SCHWEDA, K STEINBRINK, M PODOBINSKA
MARKTREDWITZ; W HARMUTH
MONCHENGLADBACH; C NIELEN
MUENCHEN; A KACZMARCZYK, C KELLNER, J VON OELHAFEN, PB VON BILDERING, S KUNZE
MUENCHEN; A NIEDERMEIER, G MESSER, M SARDY, V BEKOU
MUENCHEN; B BELLONI, B HUETTIG, M ZIAI, R HEIN
MUENSTER; A HALLECKER, M GAUBITZ
MUENSTER; C HALLERMANN, K SCHMIDT
MUENSTER; I HERRGOTT
NEUBURG A.D. DONAU; B HILDEBRANDT
NEUSS; E EIDEN, I GUERTLER
PADERBORN; E GERNOT SCHEIBL, H BRAND
PARCHING; U KAEDING
PASSAU; E WEISS, N REISCHEL, S KERN
PLAUEN; C BAUMANN
PLOCHINGEN; B HELLMICH, C LOEFFLER, J PFLUGFELDER, P KARAENKE
RECKLINGHAUSEN; J RUCHENBURG, J BLUME, M ZABEL, N DEPPERMANN, S CHROMIK
REGENSBURG; C METZLER

REGENSBURG; E KRUPP, H RUMPEL
REGENSBURG; J-O KRAUSE
ROSTOCK; C KNEITZ, I FEDEROW, K SCHNEIDER, M SEMMLER, S HAPKE
SCHLANGENBAD; A BARND
STADTBERGEN; M LINKE
STRAUBING; E KAMPE-JUZAK, K KNOEBEL
STRAUBING; K NIEFANGER
STUTTGART; HU WILHELM
TETTNANG; B LAUTERWEIN
TUEBINGEN; G FIERLBECK, S SCHANZ
ULM; C PFEIFFER, R HASSEL
WANGEN/ALLGAU; H WAHN, K SCHILDT
WEDEL; A VON ELLING, D BORO, J EBEL, K AHMADI
WEIDEN; D MORITZ, S DIETL
WETTSTETTEN; J DYBALLA
WIESBADEN; B ALSHEIMER, N SCHUETZ
WINSEN; T SCHUART
WURZBURG; C MUEGLICH, HP TONY, P MARINA
WURZBURG; F DEININGER, F HARTMANN

DK – DENMARK
ARHUS C; AB OLSEN, KH SONDERGAARD
ARHUS C; Y NADERI
KOBENHAVN NV; LV IVERSEN, T KARLSMARK
ODENSE C; JB KNUDSEN

ES – SPAIN
A CORUNA; JG GIL, JCF LOPEZ, JAP TASENDE, MF GONZALES, AA SANDOVAL
AVILA; M DEL CARMEN TORRES MARTIN, M CORTEGUERA
AVILES; BA BARCA, IC MONTES, RG DE LA TORRE
BARAKALDO; M VICTORIA EGURBIDE
BARCELONA; A PROS, J MUNOZ
BARCELONA; CP SIMEON
BARCELONA; G ESPINOSA, G ESPINPOSA, MAP RODRIGUEZ
BARCELONA; I CASTELLVI
BARCELONA; JM MASCARO
CIUDAD REAL; D BELLIDO, VS MANZANEDO, M P HUERTAS, MDM SANCHEZ, MSS TRENADO, PV GARCIA
CORDOBA; F GINES MARTINEZ, M ANGELES AQUIRRE,
FERROL; AH DEL RIO, JLG VAZQUEZ, JV COLEMAN, MR LOPEZ, PS SANCHEZ
GIJON; EMF AIZPURU, FJN MATEO
GRANADA; JL CALLEJAS, N ORTEGO
HOSPITALET; I CASTELLVI, MP SANTO
HOSPITALET; M RUBIO
HUELVA; I MARTIN
LEGANES; A CRUZ, M CRESPO, PC RAMOS
LUGO; A S-A FERNANDEZ, JAM FILLOY, TRV RODRIGUEZ
MADRID; AR MARHUENDA, JJR BLANCO, MGB HERNAN
MADRID; AZ MENDOZA, C DE LA PUENTE
MADRID; EV RABANEDA, RG DE VICUNA
MADRID; M DEL MAR RIPOLL MACIAS
MADRID; PG DEL LA PENA LEFEBVRE
MALAGA; E DE RAMON, MT CAMPS
MOSTOLES; C FERNANDEZ, R MIGUELEZ, J USON, EG DELGADO,V VILLAVERDE
PONTEVEDRA; F MACEIRAS, J CRUZ, JA MOSQUERA
SANTIAGO; A MERA, EP PAMPIN, JS BLANCO, JR MANEIRO, JJ DIAZ, L LOSADA, M CAAMANO, S FERNANDEZ, SA INSUA
SEGOIVA; CU LAURIN

SEVILLA; J SANCHEZ
TALAVERA DE LA REINA; NC FERNANDEZ, ND BECERRA
TOLEDO; A GARCIA, GM NICOLAS
VALDEMORO; M DEL CARMEN ORTEGA DE LA O
VALENCIA; A RUEDA, J CALVO
VALENCIA; J ROMAN IVORRA, JJ ALEGRE SANCHO
VALLADOLID; J BARBADO
VIGO; J MONTES
ZARAGOZA; L SAEZ

FI – FINLAND
HELSINKI; A KAARTO
TAMPERE; H MAKINEN

FR – FRANCE
ALBI; S MADAULE
AMIENS; A DADBAN, C LOK
BESANCON; D FERRANDIZ, MP MOITON, N MAGY-BERTRAND
BORDEAUX; A TAIEB, C DROITCOURT, E BELIN, S BALQUIERE, S PREY
BORDEAUX; C BOULON, J CONSTANS
BORDEAUX; C RICHEZ
BREST; B SASSOLAS, L MISERY, M GRECO
DIJON; E COLLET
DIJON; S BERTHIER, V LEGUY-SEGUIN
LA TRONCHE; B IMBERT, P CARPENTIER, S BLAISE
LE MANS; H MAILLARD, N BENETON
LILLE; D LAUNAY, E HACHULLA, G WOIJTASIK, H CHARLANNE, M LAMBERT, N JOURDAIN, PY HATRON, S MORELL
LIMOGES; A SPARS, A COURAUD, V DOEFFEL-HANTZ
LIMOGES; AL FAUCHAIS, E VIDAL, G GOUDRAN, H BEZANAHARY, N BOUSSELY, P MANEA, S DUMONTEIL, V LOUSTAUD-RATTI
LYON; A HOT, B COPPERE, H DESMURS-CLAVEL, J NINET, MH GIRARD-MADOUX
MARSEILLE; B GRANEL
MONTPELLIER; A KEYNOTE, A KHAU VAN KIEN, P RULLIER
MONTPELLIER; A LE QUELLEC, S RIVIERE
MONTPELLIER; D BESSIS
MONTPELLIER; JD COHEN
NANCY; C FARCAS
NANCY; F GRANEL-BROCARD
NANTES; C AGARD
NANTES; C DURANT
NICE; JG FUZIBET, V QUEYREL
PARIS; A BEREZNE, L GUILLEVIN, L MOUTHON
PARIS; C FRANCES
PARIS; C TOLEDANO, J CABANE, K TIEV
PARIS; D FARGE, H KESHTMAND
PARIS; I LAZARETH, P PRIOLLET, U MICHON-PASTUREL
PARIS; J WIPFF, N ASSOUS
PERPIGNAN; O CARTRY
PESSAC; E KOSTRZWEWA, MS DOUTRE
PONTOISE; L BLUM
REIMS; Z REGUIAI
RENNES; A LETREMY, A PERLAT, C CAZALETS-LACOSTE, O DECAUX, P JEGO
ROUEN; AB DUVAL-MODESTE, O DEBOVES
STRASBOURG; C SORDET, E CHATELUS, H CHIFFOT, J SIBILLIA
TOULOUSE; B COURET, G MOULIS, L SAILLER
TOULOUSE; D ADOUE
TOULOUSE; F GACHES
TOURS; E DIOT

VALENCE; F SKOWRON
VALENCE; T ZENONE
VALENCIENNES; T QUEMENEUR, X KYNDT
VANDOEURVRE-LES-NANCY; D WAHL, S ZUILY, T MOLINE, V BRAVETTI

GR – GREECE
ALEXANDROUPOLIS; N GALANOPOULOS
ATHENS; D VASILOPOULOS
ATHENS; P VLACHOYANNOPOULOS
HERAKLEIO/CRETA; I KRITIKOS
IOANNINA; N TSIFETAKI
LARISSA; A KOUTROUMBAS
THESSALONIKI; A GARYFALLOS
THESSALONIKI; P ATHANASSIOU
THESSALONIKI; S ASLANIDIS
THESSALONIKI; S KAMALI
THESSALONIKI; T DIMITROULAS
THESSALONIKI; V GALANOPOULO
VOULA; A ELEZOGLOU

IE – IRELAND
DUBLIN; A GRIER, M MURRAY, M O'ROURKE

IT – ITALY
ANCONA; A GABRIELLI
BARI; G LAPADULA
BARI; L SERAFINO, N TERLIZZI
BENEVENTO; S BELLISSIMO, S STISI
BOLOGNA; N MALAVOLTA
BRESCIA; P AIRO
CAGLIARI; A VACCA
CATANIA; E BATTAGLIA
CATANIA; R FOTI
CATANZARO; S MAZZUCA
FERRARA; A BORTOLUZZI, F TROTTA
FIRENZE; F GALLUCCIO
FOGGIA; A MARUCCI, F CANTATORE
FOGGIA; R BUCCI
GENOVA; F PUPPO
JESI; R DE ANGELI, W GRASSI
L'AQUILA; P CIPRIANI
LEGNANO; A MAZZONE, P FAGGIOLI
MILAN; A SEVERINO, R SCORZA
MILAN; L BELLOLI, N UGHI
MILAN; M ANTIVALLE
MILAN; N DEL PAPA, W MAGLIONE
MILAN; S ZENI
MODENA; C FERRI, M COLACI
MORMANNO; G VARCASIA
NAPOLI; G CUOMO
PADUA; F COZZI
PALERMO; G TRIOLO
PASSIRANA DI RHO; S GATTI
PAVIA; CM MONTECUCCO
PISA; M DOVERI
POTENZA; A NIGRO, I OLIVIERI
REGGIO EMILIA; G BAJOCCHI

ROMA; E ROSATO, F SALSANO
ROMA; F FAUSTINI, G FERRACCIOLI
ROMA; L COLONNA
ROMA; S PALLOTTA
ROMA; V RICCIERI
ROME; A MUSSI
SIENA; F BELLISAI, M GALEAZZI
TURIN; E FUSARO
TURIN; M SARACCO, R PELLERITO
UDINE; P MASOLINI, S DE VITA, S LOMBARDI
VERONA; C LUNARDI

NL – THE NETHERLANDS
ALKMAAR; J D MOOLENBURGH
AMERSFOORT; AHM HEURKENS
AMSTERDAM; A VOSKUYL
AMSTERDAM; AE HAK, ESK STROES, J REMANS
AMSTERDAM; V GERDES
APELDOORN; JM VAN WOERKOM
ARNHEM; AJL DE LONG, HAH KAASJAGER, H VISSER, M JANSSEN
BRIDA; C VAN GULDENER, F VAN NEER, P VOS
DELFT; AJ PETERS
DEN HAAG; H HULSMANS, K RONDAY, R GOEKOOP
DEN HAAG; J EWALS, R VALENTIJN
DEN HAAG; M DE BOIS
DEN HAAG; ML WESTEDT
DEVENTER; D SIEWERTSZ VAN REESEMA
EDE; E KNIFJJ-DUTMER, JN STOLK
EINDHOVEN; H WILLEMS
EMMELOORD; DG KUIPER-GEERTSMA, P BAUDAOIN
EMMEN; P FRETTER, R WESTRA
GOES; PBJ SONNAVILLE
GRONINGEN; A SMIT, H BOOTSMA, L BROUWER, M BIJL, N MOLDERS
HARDENBERG; C LEBRUN
HARDERWIJK; MJ VAN DER VEEN
HEERENVEEN; M NOORDZIJ
HEERLEN; H HOUBEN, RMB LANDEWE, W VERCOUTERE
HILVERSUM; ZN JAHANGIER DE VEEN
HOOGEVEEN; TR ZIJLSTRA
LEEUWARDEN; F UBELS, G BRUYN, P JANSEN
LEIDEN; A SCHUERWEGH, TWJ HUIZINGA
MAASTRICHT; P PAASSEN, T HURKENS
NIEUWEGEIN; M GEURTS
NIJMEGEN; F VAN DEN HOOGEN
NIJMEGEN; M VONK
ROERMOND; PJC JACOBS
ROOSENDAAL; JHLM GROENENDAEL, P SEYS
ROTTERDAM; D VAN ZEBEN, H VAN PAASSEN, J GROENENDAEL
ROTTERDAM; KH HAN, M WLARVENS
ROTTERDAM; M VAN HAGEN, P VAN DAELE, R DOLHAIN
SCHIEDAM; AH GERARDS, P VAN DER LUBBE
TILBURG; M DE KANTER, WH MULLER
UTRECHT; E TON
VLISSINGEN; M VAN KRUGTEN
WINSCHOTEN; I VAN GAMEREN
WINTERSWIJK; P LANTING
WOERDEN; C DEN HENGST

NO – NORWAY
BERGEN; CG GJESSDAL, SL HJERTAKER, TM MADLAND
KRISTIANSAND; A BENDVOLD, H BITTER
OSLO; AM HOFFMANN-VOLD, O MIDTVEDT
TROMSO; G BAKLAND, HK ASLKAKSEN, M SEIP, S KALSTAD, W KOLDINGSNES
TRONDHEIM; B GRANDAUENT, BY NORDVAG, EK STRAN, J SKOMSVOLL, M ANDERSEN, RS THOMSEN, T PEDERSEN, V BAKKEHEIM

PT – PORTUGAL
ALMADA; A CORDEIRO
AMADORA; J ALVES, S OLIVEIRA
LISBOA; P COELHO
LISBON; C RESENDE, C PONTE
PORTO; I ALMEIDA, I SILVA
SANTAREM; C SANTOS, I CAMARA, J COSTA

SE – SWEDEN
FALUN; H HELLSTROM
HELSINGBORG; A MOHAMMAD
KARLSKRONA; I LIND, K LIND, T BRACIN
KARLSTAD; E LILJEQUIST, T VINGREN
KRISTIANSTAD; A OSTENSON
LINKOPING; E HERMANSSON
OSKARSTROM; C THORSSON, M SODERLIN
STOCKHOLM; A NORDIN, E WALDHEIM, K VENGEMYR, K ALBERTSSON, ML KARLSSON, Y RYDVALD
VASTERAS; M RIZK

SI – SLOVENIA
LJUBLJANA; AS DOLNICAR

SK – SLOVAKIA
PIESTANY; J LUKAC

UK – UNITED KINGDOM
BATH; J JAMES, N MCHUGH, S COLE, S BROWN
BELFAST; A HAMILTON
BIRMINGHAM; A FAIZAL
CAMBRIDGE; F HALL, K MURPHY, S SKINGLE
FIFE; H HARRIS
GLASGOW; F MADHOK, R HAMPSON
HULL; E BAGULEY, O OGUNBAMBI
LIVERPOOL; J LAMB, M ANDERSON, R MOOTS
LONDON; B WHITE-ALAO, C MORRISON, J DOBSON, P GORDON, R SALERNO
LONDON; C DENTON, L PARKER, R OCHIEL, R VINCENT, S ZIMBA, T NGCOZANA, Y XU
LONDON; D D'CRUZ, LM CHOONG
MANCHESTER; A HERRICK, E WRAGG, J MANNING, T MOORE
ROMFORD; C KELSEY, K CHAKRAVARTY
SOUTHPORT; H SKYES
WORCESTER; P ATHIVEER

Supplementary table

Table S1: Ongoing medications/therapies at enrolment

Medications/therapies (use for any reason)	Number of patients, n (%)*
Non-opioid analgesics and NSAIDs	714 (29.3)
Opioids	238 (9.8)
Corticoids	792 (32.5)
Anticoagulants	438 (18.0)
Immunosuppressants	717 (29.4)
Systemic antibiotics	344 (14.1)
ERA**	1157 (47.4)
Calcium channel blockers	1058 (43.4)
Prostacyclins	828 (33.9)
Phosphodiesterase-5 inhibitors	124 (5.1)
Other medications	1616 (66.3)
Topical DU treatments	520 (21.3)
*Denominator = all patients = 2439; **ERA= bosentan or other ERA; DU, digital ulcer; ERA, endothelin receptor antagonist	