CONCISE REPORT

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

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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-sclero derma-70 and 43.6% for anticientromere antibodies (ACA). The first digital ulcer in the anti-sclero derma-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 enrolls 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 literature3 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, anticientromere 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...
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, 45.6% (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 and 1.4% (34/2439) for anti-scleroderma-70 plus anti-U3 ribonucleoprotein. The frequencies for anti-RNA polymerase 3, 9.7% (120/1243), anti-U1 ribonucleoprotein, 1.4% (34/2439), anti-U3 ribonucleoprotein and 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).
Clinical and epidemiological research

Disease manifestations by antibody status

Table 2 Disease manifestations by antibody status

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Lung fibrosis, n/N (%) (95% CI)</th>
<th>Kidney manifestations, n/N (%) (95% CI)</th>
<th>Gastrointestinal manifestations, n/N (%) (95% CI)</th>
<th>Heart manifestations, n/N (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA (N=2085)</td>
<td>873/2085 (41.9) (39.7 to 44.0)</td>
<td>105/2085 (5.0) (4.1 to 6.1)</td>
<td>1182/2085 (57.2) (56.4 to 58.3)</td>
<td>220/2085 (10.6) (9.3 to 12.0)</td>
</tr>
<tr>
<td>Anti-Scl-70 (N=854)</td>
<td>531/854 (62.4) (58.8 to 65.4)</td>
<td>43/854 (5.0) (3.7 to 6.7)</td>
<td>488/854 (58.3) (56.4 to 60.9)</td>
<td>105/854 (12.3) (10.2 to 14.7)</td>
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<td>Anti-RNA Pol 3 (N=86)</td>
<td>133/854 (15.6) (13.2 to 18.2)</td>
<td>7/854 (0.8) (0.3 to 1.3)</td>
<td>51/854 (59.3) (47.9 to 70.8)</td>
<td>6/854 (7.3) (2.6 to 14.6)</td>
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<td>ACA (N=775)</td>
<td>173/775 (22.3) (19.4 to 25.4)</td>
<td>12/854 (1.4) (0.6 to 2.4)</td>
<td>440/775 (56.8) (53.2 to 60.3)</td>
<td>47/775 (6.1) (4.5 to 8.0)</td>
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<td>Anti-U1 RNP (N=120)</td>
<td>120/775 (15.5) (13.0 to 18.2)</td>
<td>10/120 (8.3) (4.1 to 14.8)</td>
<td>63/120 (52.5) (43.2 to 61.7)</td>
<td>16/120 (13.3) (7.8 to 20.7)</td>
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<tr>
<td>Anti-U3 RNP (N=39)</td>
<td>36/86 (41.9) (31.3 to 53.0)</td>
<td>7/86 (8.1) (3.3 to 16.1)</td>
<td>3/39 (7.7) (1.6 to 20.9)</td>
<td>3/39 (7.7) (1.6 to 20.9)</td>
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<td>PAH (N=854)</td>
<td>531/854 (62.2) (58.8 to 65.4)</td>
<td>43/854 (5.0) (3.7 to 6.7)</td>
<td>488/854 (58.3) (56.4 to 60.9)</td>
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</table>

The denominator N varies according to the number of available observations.

The proportion of patients reported here as anti-U3 ribonucleoprotein positive was low (4.9%), a finding similar to that observed in previous studies. Therefore potential variations between different analysis methods should be considered when interpreting the data.

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, PAH and anti-U1 ribonucleoprotein positivity was not always recorded.

Alien and endothelial fibrosis were identified by several investigators, including in previous studies. There were no differences in the proportion of patients with PAH between those with and without these antibodies. Anti-U1 ribonucleoprotein positivity was low (4.9%), and anti-U3 ribonucleoprotein was not detected.

The proportion of patients with PAH and anti-U1 ribonucleoprotein was low (4.9%). The proportion of patients with PAH and anti-U1 ribonucleoprotein was low (4.9%)

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Table 3

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<tr>
<th>previous ulcer complications and interventions by antibody status</th>
<th>Anti-U3 RNP (N = 39)</th>
<th>Anti-U3 RNP (N = 120)</th>
<th>Anti-RNA Pol 3 (N = 86)</th>
<th>Anti-Scl-70 (N = 1854)</th>
<th>Anti-RNA Pol 3 (N = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous soft tissue infection requiring systemic antibiotics</td>
<td>62/113 (54.9) (45.2 to 64.2)</td>
<td>86/796 (10.8) (8.7 to 13.2)</td>
<td>30/82 (37.5) (26.9 to 49.0)</td>
<td>169/1965 (8.6) (7.4 to 9.9)</td>
<td>4/38 (10.5) (2.9 to 24.8)</td>
</tr>
<tr>
<td>Previous hospitalisation for digital ulcer</td>
<td>17/36 (47.2) (33.0 to 61.9)</td>
<td>411/707 (58.1) (54.4 to 61.8)</td>
<td>9/115 (7.8) (3.6 to 14.3)</td>
<td>15/289 (5.3) (3.1 to 8.7)</td>
<td>4/38 (10.5) (2.9 to 24.8)</td>
</tr>
<tr>
<td>Previous upper limb sympathectomy</td>
<td>74/1922 (3.9) (3.0 to 4.8)</td>
<td>340/805 (42.2) (38.8 to 45.7)</td>
<td>15/289 (5.3) (3.1 to 8.7)</td>
<td>70/1620 (4.4) (3.5 to 5.5)</td>
<td>4/38 (10.5) (2.9 to 24.8)</td>
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<td>Previous debridement</td>
<td>189/1644 (11.5) (10.0 to 13.1)</td>
<td>49/491 (10.0) (8.2 to 13.1)</td>
<td>8/71 (11.3) (5.0 to 21.0)</td>
<td>90/608 (14.8) (12.1 to 17.9)</td>
<td>3/33 (9.1) (1.9 to 24.3)</td>
</tr>
<tr>
<td>Previous surgical amputation</td>
<td>158/1661 (9.5) (8.1 to 11.0)</td>
<td>51/642 (7.9) (6.0 to 10.3)</td>
<td>6/72 (8.3) (3.1 to 17.3)</td>
<td>90/618 (14.6) (11.9 to 17.6)</td>
<td>4/34 (11.8) (3.3 to 27.5)</td>
</tr>
<tr>
<td>Previous use of parenteral prostanoids</td>
<td>118/1145 (10.3) (7.9 to 13.2)</td>
<td>36/361 (10.0) (7.6 to 12.7)</td>
<td>6/72 (8.3) (3.1 to 17.3)</td>
<td>90/618 (14.6) (11.9 to 17.6)</td>
<td>4/34 (11.8) (3.3 to 27.5)</td>
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</table>

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, MM, MM; manuscript preparation: CPD, TK, 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.

Acknowledgements

The authors gratefully acknowledge all investigators involved in this registry. The authors would like to thank Lisa Thomas, Elements Communications Ltd, for providing editorial assistance, funded by Actelion Pharmaceuticals Ltd.

Funding

This registry was sponsored by Actelion Pharmaceuticals Ltd. The registry sponsor was involved in the registry design, and in the collection, analysis and interpretation of data.

Competing interests

BS, DR, MS and MZ are employees of Actelion Pharmaceuticals Ltd, the manufacturers of bosentan. The non-Actelion employees who are authors of this manuscript have received consultancy fees or research grant funding from Actelion Pharmaceuticals Ltd.

Provenance and peer review

Not commissioned; externally peer reviewed.

Correction notice

This article has been corrected since it was published Online First. The author list has been amended.

REFERENCES

The authors gratefully acknowledge all investigators involved in this registry.

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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 Richet
BREST; B Sassolas, L Miserly, 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 Wouitasik, H Charlanne, M Lambert, N Jourdain, PY Hatron, S Morel
LIMOGES; A Spars, A Couraud, V Deffel-Hantz
LIMOGES; AL Fauchais, E Vidal, G Goudran, H Bezanahary, N Bousely, 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 Kostrzewa, 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
STRAISBOURG; C Sordet, E Chatelus, H Chiffot, J Sibilla
TOULOUSE; B Couret, G Mouli, L Sailler
TOULOUSE; D Addou
TOULOUSE; F Gaches
TOURS; E Diot
VALENCE; F SKOWRON
VALENCE; T ZENONE
VALENCIENNES; T QUEMENEUR, X KYNDT
VANDOEUVRE-LES-NANCY; D WAHL, S ZUILY, T MOLINE, V BRAVETTI

GR – GREECE
ALEXANDROUPOLIS; N GALANOPoulos
ATHENS; D VASILIOPOULOS
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 ELEZOGLIOU

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

IT – ITALY
ANCONA; A GABRIELLI
BARI; G LAPADULA
BARI; L SERAFINO, N TERUZZI
BENEVENTO; S BELLISSIMO, S STISI
BOLOGNA; N MALAVOLTA
BRECIA; P AIRO
CAGLIO; A VACCIA
CATANIA; E BATTAGLIA
CATANIA; R FOTI
CATANZARO; S MAZZUCA
FERRARA; A BORTOLOZZI, 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 CEPIAN
LEGNA; A MAZZONE, P FAGGIOLI
MILAN; A SEVERINO, R SCORZA
MILAN; L BELLOLI, N UGHI
MILAN; M ANTIVALE
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 TRIOLI
PASSIRANA DI RHIO; S GATTI
PAVIA; CM MONT ECUCO
PIZA; M DOVERI
POTENZA; A NIGRO, I OLVIERI
REGGIO EMILIA; G BAJOCCHI
NL – THE NETHERLANDS
ALKMAAR; J D MOOLENBURGH
AMERSFOORT; AHM HEURKENS
AMSTERDAM; A VOISKUL
AMSTERDAM; AE HAK, ESK STROES, J REMANS
AMSTERDAM; V GERDES
APeldoorn; JM VAN WOERKOM
ARnhem; AIL DE LONG, HAH KAASJAGER, H VISser, M JANSSen
BRida; C VAN GULDener, F VAN NEER, P Vos
DELT; AJ Peters
DEN Haag; H HULSMANS, K RONDAY, R GOEKOOp
DEN Haag; J EWAlS, R VALENTIUN
DEN Haag; M De BoIs
DEN Haag; ML WEstEDT
DEVENTER; D SIEWERTSZ VAN REESMA
EDe; E KNIVJU-DUTmer, JN STOLK
EINDhoven; H WIllEMS
EMMElooord; DG Kuiper-Geertsma, P BAudaoIn
EMMEN; P FRETTER, R WESTRA
Goes; PBJ SonnAVille
Groningen; A Smit, H Bootsma, L Brouwer, M BUL, N MOLDERS
HARDenberg; C LeBrun
HARDERWIJK; MJ VAN DER VeEn
HHeereneeEn; M NOORDZIJ
HHeerlen; H HObEN, RMB LANDEWE, W VERCOUtERE
HILversum; ZN JAHANGIER De VeEn
HOOGveEn; TR ZUIstra
Leeuwarden; F UBEls, G BRuYN, P JANSEN
Leiden; A SCHUERwegH, TWJ HuIZINGa
MAASTRICHT; P PAASSEN, T HurKENS
NiEUwegEIN; M GeURts
NiMeGEN; F VAN DeN HooGEN
NiMeGEN; M VoNK
RoermOnd; PJC Jacobs
Roosendaal; JHLM GroenendarL, P SEYS
Rotterdam; D VAN zEBEn, H VAN PAaSSEN, J GroenendarL
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
Tromsø; G Bakland, HK Aksaksen, M Seip, S Kalstad, W Koldingsnes
Trondheim; B Grandaent, 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; J 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 Ogunbami
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**

<table>
<thead>
<tr>
<th>Medications/therapies (use for any reason)</th>
<th>Number of patients, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioid analgesics and NSAIDs</td>
<td>714 (29.3)</td>
</tr>
<tr>
<td>Opioids</td>
<td>238 (9.8)</td>
</tr>
<tr>
<td>Corticoids</td>
<td>792 (32.5)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>438 (18.0)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>717 (29.4)</td>
</tr>
<tr>
<td>Systemic antibiotics</td>
<td>344 (14.1)</td>
</tr>
<tr>
<td>ERA**</td>
<td>1157 (47.4)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1058 (43.4)</td>
</tr>
<tr>
<td>Prostacyclins</td>
<td>828 (33.9)</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitors</td>
<td>124 (5.1)</td>
</tr>
<tr>
<td>Other medications</td>
<td>1616 (66.3)</td>
</tr>
<tr>
<td>Topical DU treatments</td>
<td>520 (21.3)</td>
</tr>
</tbody>
</table>

*Denominator = all patients = 2439; **ERA= bosentan or other ERA; DU, digital ulcer; ERA, endothelin receptor antagonist