

**NIHR Innovation Observatory  
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## **Nintedanib for Systemic Sclerosis Associated Interstitial Lung Disease**

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### **LAY SUMMARY**

Systemic Sclerosis (Scleroderma or SSc) is an uncommon condition that results in hard, thickened areas of skin and sometimes problems with the internal organs and blood vessels. This condition is caused by the immune system attacking the areas under the skin and around internal organs and blood vessels called connective tissue. This causes scarring and thickening in these areas. SSc affects the lungs of about half of the people with the condition. Inflammation and scarring of the lung tissue is called interstitial lung disease (ILD). The most common presenting symptom of ILD is difficult breathing on exertion. Other indicators of ILD may include non-productive cough, fatigue and chest pain. Many patients with SSc become less physically active because of musculoskeletal complaints or the fatiguing nature of the illness. Lung involvement in all its forms in patients with SSc has emerged to be the leading cause of death and disability.

Nintedanib (OFEV®) is a medicine that is being developed for the treatment of Systemic Sclerosis associated interstitial lung disease (SSc-ILD). It acts by targeting the specific mechanisms by which scarring of the lungs occur, reducing progression of the disease. It is given by mouth as capsules. Nintedanib (as OFEV) is already available in the EU for the treatment of idiopathic pulmonary fibrosis (IPF). Because SSc-ILD and IPF share similarities in how the underlying lung scarring, or fibrosis, forms in people with the disease, the development of nintedanib for the treatment of SSc-ILD may address unmet needs. If licensed, nintedanib may offer an additional treatment option (the first licensed) for patients with SSc-ILD.

*This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD).

## TECHNOLOGY

### DESCRIPTION

Nintedanib (Ofev; BIBF 1120) is a small molecule tyrosine kinase inhibitor (TKI) developed for the treatment of idiopathic pulmonary fibrosis (IPF). SSc-ILD and IPF share similarities in terms of the formation of lung scarring, or fibrosis.<sup>1</sup> SSc-ILD is a pulmonary fibrosing disorder characterised by systemic inflammation and progressive scarring of the lungs that leads to respiratory failure.<sup>2</sup> Nintedanib targets growth factor receptors, which have been shown to be involved in the mechanisms by which pulmonary fibrosis occurs. Most importantly, nintedanib inhibits platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR). By blocking the signalling pathways that are involved in fibrotic processes, it is believed that nintedanib has the potential to reduce disease progression in lungs diseases such as IPF by slowing the decline of lung function.<sup>3</sup>

In the phase III clinical trial (NCT02597933), nintedanib is given as 150 mg capsules twice daily over 52 weeks up to a maximum of 100 weeks in people with in people with SSc-ILD.<sup>4,5</sup>

Nintedanib is also in phase III development for the treatment of Mesothelioma<sup>6,7</sup> and Progressive fibrosing ILD (PF-ILD).<sup>8,9</sup>

Nintedanib (Ofev) is licensed in the EU for the treatment of adults with idiopathic pulmonary fibrosis (IPF). The most common side effects with Nintedanib (Ofev) (which may affect more than 1 in 10 people) are diarrhoea, nausea, abdominal pain and raised levels of liver enzymes in the blood. Vomiting, decreased appetite and weight loss are also common.<sup>10</sup>

## INNOVATION and/or ADVANTAGES

Nintedanib is approved for the treatment of IPF, which is a rare lung disease, and has been shown to slow disease progression as measured by annual rate of decline in lung function. Because SSc-ILD and IPF share similarities in how the underlying lung scarring, or fibrosis, forms in people with the disease, nintedanib is being evaluated if it can have a beneficial impact on lung fibrosis associated with SSc. This may address the unmet needs of people affected by rare diseases and serious respiratory conditions, including fibrotic lung diseases.<sup>1</sup> Therefore, if licensed, nintedanib may offer an additional treatment option (the first licensed) for patients with SSc-ILD.

## DEVELOPER

Boehringer Ingelheim Ltd

## AVAILABILITY, LAUNCH or MARKETING

Nintedanib was granted Orphan Drug Designation for IPF and SSc in the EU in 2013 and 2016 respectively.<sup>11</sup>

Nintedanib is a designated orphan drug in USA for the treatment of SSc (including the associated interstitial lung disease) in 2016, mesothelioma 2016, and for the treatment of patients with idiopathic pulmonary fibrosis in 2011.<sup>12</sup>

## PATIENT GROUP

### BACKGROUND

Systemic Sclerosis (SSc or Scleroderma) is an uncommon condition that results in hard, thickened areas of skin and sometimes problems with internal organs and blood vessels. SSc is caused by the immune system attacking the connective tissue under the skin and around internal organs and blood vessels. This causes scarring and thickening of the tissue in these areas. There are two main types of scleroderma, namely; localised scleroderma, which just affects the skin; and systemic sclerosis, which may affect blood circulation and internal organs as well as the skin.<sup>13</sup>

SSc can affect the joints, muscles, blood vessels and digestive system. It affects the lungs in about half the people with the condition.<sup>14</sup> It can also affect the kidneys and heart.<sup>14,15</sup> Systemic sclerosis develops because of changes that occur in the body's connective tissues. It leads to too much fibrous connective tissue, which is similar to scars that form after an injury. Scar tissue contains a protein called collagen. Having too much collagen can cause the body's tissues to stiffen and thicken. The exact reason of why this happens is not yet known. The immune system appears to be overactive and attacks healthy body tissues instead. This leads to cells in the connective tissue producing too much collagen, causing scarring and thickening (fibrosis) of the tissue. This is thought to be due to a mix of genetic and environmental factors. Having a close family member with the condition may increase the risk of developing the condition. However, systemic sclerosis isn't passed directly from one generation to another nor it is contagious.<sup>14</sup>

Symptoms of SSc include increased sensitivity to the cold, changes in the skin, pain or stiffness in the joints or muscles, and digestive problems. Inflammation and scarring of the lung tissue is called interstitial lung disease or ILD.<sup>13,14,16</sup> ILD is a common pulmonary manifestation among patients with SSc. The pathogenesis of SSc-ILD is not well understood. It is presumed to be related to abnormal interactions between endothelial cells, lymphocytes/monocytes and fibroblasts leading to an excess production of extracellular matrix by fibroblasts in the setting of tissue hypoxia and vascular hyper-reactivity.<sup>17</sup> In many, the ILD develops very early and very rapidly but once established can be very stable for years. In others, the ILD continues to damage the lung on an on-going basis. This situation is critically important to recognise since prevention of lung injury becomes the essential issue in treatment.<sup>16</sup> The most common presenting symptom of ILD is dyspnoea on exertion. Other indicators of ILD may include non-productive cough, fatigue and chest pain. The most common finding on physical examination is the presence of dry (velcro-like) crackles at the lung bases. However, some patients with SSc-ILD may not have any symptoms, and physical exam may be normal. Therefore, the clinician must remain ever vigilant, screening all patients initially and monitoring them frequently throughout the course of their disease. Changes in pulmonary function can occur before the onset of significant clinical symptoms. Therefore, it is important that all patients have screening pulmonary function tests (PFTs) at the time of presentation.<sup>18</sup>

Involvement of the lungs causes shortness of breath or fatigue during physical activity. Many patients with SSc become less physically active because of musculoskeletal complaints or the fatiguing nature of the illness. Lungs involvement in all its forms in patients with SSc has emerged to be the leading cause of death and disability.<sup>16</sup>

### CLINICAL NEED and BURDEN OF DISEASE

Because of the rarity and heterogeneous clinical presentation of SSc, reliable epidemiological studies on this condition have been particularly difficult to carry out.<sup>19</sup> The first epidemiological study of scleroderma in the UK, a population based study, was conducted in the West Midlands Region. This

study suggests prevalence rates of 13 and 48 per million in males and females respectively, with annual incidence rates of 1 and 6 per million.<sup>20</sup> The annual incidence rate of SSc in England was reported to be 3.7 per million in 1986. The worldwide prevalence of SSc is reported to vary from 3 - 24 per 100,000. The condition is more common in North America and Australia than in Europe. Women are affected more often than men, and those of African origin are also more affected. The peak age of onset is 40-50 years but it can affect any age group. It is rare in children.<sup>19, 21</sup> It is estimated that SSc-ILD affects up to 200,000 people in Europe, making it an orphan, or rare disease.<sup>1</sup>

NHS Digital, Hospital Episode Statistics for England 2016-17 shows that there were 3,654 hospital admissions for SSc (ICD 10 code: M34), 3,842 Finished Consultant Episodes (FCE), and 3,849 FCE bed days. Regarding other interstitial lung diseases with fibrosis (ICD 10 code: J84.1), there were 7,526 hospital admissions, 12,846 FCE, and 46,339 FCE bed days.<sup>22</sup>

A retrospective study in the UK assessed the mortality rate and predictors of mortality in a cohort of 204 patients with SSc who enrolled onto the Royal National Hospital for Rheumatic Diseases Connective Tissue Disease database between 1999 and 2010. The overall Standardised Mortality Rate (SMR) was 1.34 (95% confidence interval 1.00–1.75). The SMR was higher in males. The most common cause of SSc-related mortality was pulmonary complications. ILD was among the factors that were found to adversely affect survival.<sup>23</sup>

## **PATIENT PATHWAY**

## **RELEVANT GUIDANCE**

### **NICE GUIDANCE**

- NICE technology appraisal in development. Idiopathic pulmonary fibrosis - pirfenidone (review TA282) (ID837). Expected date of issue to be confirmed.
- NICE technology appraisal. Nintedanib for treating idiopathic pulmonary fibrosis (TA379). January 2016
- NICE technology appraisal. Pirfenidone for treating idiopathic pulmonary fibrosis (TA282). April 2013
- NICE clinical guideline. Idiopathic pulmonary fibrosis in adults: diagnosis and management (CG163). June 2013 (updated: May 2017).
- NICE quality standard. Idiopathic pulmonary fibrosis in adults (QS79). January 2015.

### **NHS ENGLAND and POLICY GUIDANCE**

- NHS England. Clinical Commissioning Policy: Rituximab for connective tissue disease associated with interstitial lung disease. 170015/P. June 2017

### **OTHER GUIDANCE**

- The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Interstitial lung disease guideline. 2008.<sup>24</sup>

## **CURRENT TREATMENT OPTIONS**

Patients with advanced SSc-ILD need to be treated, and patients with earlier disease should also have therapeutic intervention, especially when there is a high risk of disease progression.<sup>25</sup> There is currently no licensed therapy for SSc-ILD and few drugs have been assessed in clinical trials for this disease.<sup>1</sup> Treatment approaches of SSc-ILD include:

- Immunosuppression: this involves cyclophosphamide, glucocorticoids, mycophenolate mofetil, pirfenidone, intravenous immunoglobulin, and hematopoietic stem cell transplantation.<sup>18,25</sup>
- Anti-fibrotic therapy: two new drugs – perfinidone and nintedanib – have been approved by the FDA for the treatment of patients with IPF.<sup>18</sup>
- Supportive care measures, including:<sup>18</sup>
  - Supplemental oxygen if indicated
  - Vaccinations against Influenza and Streptococcus pneumonia
  - Prophylaxis against *Pneumocystis jirovecii* if indicated
  - Pulmonary rehabilitation
  - Treatment of Gastroesophageal reflux disease (GERD)
  - Medications (PPI, H2-antagonists)
  - Reflux precautions
- Intravenous immunoglobulin therapy, which may be a useful adjunctive measure when conventional treatment proves inadequate.<sup>18,25</sup>
- Lung transplantation: this should be considered for patients who progress to end-stage lung disease despite medical treatment, however, transplant centres have been reluctant to consider SSc-ILD patients given the high prevalence of gastroesophageal reflux and its attendant risks for aspiration, bronchiolitis obliterans and allograft rejection.<sup>18,25</sup>

## EFFICACY and SAFETY

<b>Trial</b>	<b>SENSCIS™ ; NCT02597933; 1199.214; nintedanib vs placebo; phase III</b>	<b>NCT03313180; nintedanib; phase III extension.</b>
<b>Sponsor</b>	Boehringer Ingelheim	Boehringer Ingelheim
<b>Status</b>	Ongoing, not recruiting.	Ongoing, not recruiting.
<b>Source of Information</b>	Trial registry, <sup>5</sup> manufacturer. <sup>4</sup>	Trial registry <sup>26</sup>
<b>Location</b>	EU (incl UK), USA, Canada and other countries	Netherlands
<b>Design</b>	Randomised, placebo-controlled, double blind.	Single group assignment, open-label, extension trial.
<b>Participants</b>	n= 535, aged 18 years and older, males and females; fulfilled the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc; SSc disease onset (defined by first non-Raynaud symptom) within 7 years; SSc related Interstitial Lung Disease confirmed by high-resolution computed tomography (HRCT), extent of fibrotic disease in the lung $\geq$ 10%; Forced Vital Capacity (FVC) $\geq$ 40% of predicted normal; diffusing capacity of the lung for carbon monoxide (DLCO) 30% to 89% of predicted normal	n= 400 (planned) , aged 18 years and older, males and females; completed the parent trial 1199.214 per protocol and did not permanently discontinue blinded treatment; Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly as well as one barrier method for 28 days prior to nintedanib treatment initiation, during the trial and for 3 months after last intake of nintedanib.
<b>Schedule</b>	Randomised to nintedanib 150 mg twice daily over 52 weeks up to a maximum of 100 weeks; or placebo capsules identical to those containing active drug.	Participants received nintedanib twice daily (no further information reported about treatment regimen)
<b>Follow-up</b>	Active treatment for 52 weeks up to a maximum of 100 weeks; follow-up for 52 weeks.	Active treatment period: not reported. Follow up: 34 months
<b>Primary Outcomes</b>	Annual rate of decline in FVC in millilitres [ Time Frame: 52 weeks ]	Incidence of overall adverse events over the course of this extension trial [ Time Frame: Up to 34 months ]
<b>Secondary Outcomes</b>	Time frame: 52 weeks: <ul style="list-style-type: none"> <li>• Time to all-cause mortality</li> <li>• Absolute change from baseline in functional assessment of chronic</li> </ul>	Not reported

	illness therapy (FACIT) dyspnoea score <ul style="list-style-type: none"> <li>• Absolute change from baseline in the modified Rodnan Skin Score (mRSS)</li> <li>• Absolute change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score</li> <li>• Annual rate of decline in FVC in percent predicted</li> <li>• Absolute change from baseline in FVC in millilitres</li> <li>• Relative change from baseline (%) of mRSS</li> <li>• Absolute change from baseline in DLCO in per cent predicted</li> <li>• Absolute change from baseline in digital ulcer net burden (defined as the number of new digital ulcers (DUs) plus the number of DUs that have been verified at any earlier assessment during the trial)</li> <li>• Absolute change from baseline in the Scleroderma Health Assessment Questionnaire (SHAQ) total score</li> </ul>	
<b>Key Results</b>	-	-
<b>Adverse effects (AEs)</b>	-	-
<b>Expected reporting date</b>	Study completion date reported as November 2018.	Study completion date reported as July 2021.

## ESTIMATED COST and IMPACT

### COST

Nintedanib (Ofev®) is already marketed in the UK for the treatment of IPF.<sup>27</sup> The company has agreed a patient access scheme with the Department of Health.<sup>28</sup>

The NHS indicative price for nintedanib (Ofev) capsules (Boehringer Ingelheim Ltd) is as follows:<sup>27</sup>

A pack of 60 x 100mg capsules costs £ 2,151.10 (hospital only)

A pack of 60 x 150mg capsules costs £ 2,151.10 (hospital only).

## IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

### IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *reduced use of secondary care/specialist services*

☐ Other

☐ None identified

### OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified



## REFERENCES

- <sup>1</sup> Boehringer Ingelheim GmbH. *New Phase III study of nintedanib in people with systemic sclerosis and lung fibrosis*. 8 December 2015. Available from: <https://www.boehringer-ingelheim.com/press-release/new-phase-iii-study-nintedanib-people-systemic-sclerosis-and-lung-fibrosis> [Accessed 6 December 2017].
- <sup>2</sup> Suliman S, Al Harash A, Roberts WN, Perez RL, Roman J. Scleroderma-related interstitial lung disease. *Respir Med Case Rep*. 2017 Jul 15; 22: 109-112. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5524221/pdf/main.pdf> [Accessed 14 December 2017].
- <sup>3</sup> Boehringer Ingelheim GmbH. *Boehringer Ingelheim's OFEV™ (nintedanib\*) approved by the FDA for the treatment of idiopathic pulmonary fibrosis*. Available from: <https://www.boehringer-ingelheim.com/press-release/boehringer-ingelheim-s-ofev-nintedanib-approved-fda-treatment-idiopathic-pulmonary> [Accessed 27<sup>th</sup> November 2017].
- <sup>4</sup> Boehringer Ingelheim GmbH. *Orphan Drug Designation Granted to Nintedanib for Treatment of Systemic Sclerosis, including Associated Interstitial Lung Disease*. Available from: <https://www.boehringer-ingelheim.com/press-release/orphan-drug-designation-granted-nintedanib-treatment-systemic-sclerosis> [Accessed 27<sup>th</sup> November 2017].
- <sup>5</sup> ClinicalTrials.gov. *A Trial to compare nintedanib with placebo for patients with scleroderma related lung fibrosis: NCT02597933*. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT02597933?view=record> [Accessed 27<sup>th</sup> November 2017].
- <sup>6</sup> Boehringer Ingelheim GmbH. *Clinically meaningful data for oral nintedanib in mesothelioma presented at World Conference on Lung Cancer*. 7<sup>th</sup> December 2016. Available from: <https://www.boehringer-ingelheim.com/press-release/positive-data-nintedanib-mesothelioma-world-conference-lung-cancer> [Accessed 15 January 2018].
- <sup>7</sup> ClinicalTrials.gov. *Nintedanib (BIBF 1120) in Mesothelioma*. Available from: <https://clinicaltrials.gov/ct2/show/NCT01907100> [Accessed 15 January 2018].
- <sup>8</sup> Boehringer Ingelheim GmbH. *Boehringer Ingelheim Phase III study now enrolling patients with progressive fibrosing lung diseases*. 20<sup>th</sup> March 2017. Available from: <https://www.boehringer-ingelheim.com/press-release/boehringer-ingelheim-study-enrolling-in-progressive-fibrosing-lung-diseases> [Accessed 15 January 2018].
- <sup>9</sup> ClinicalTrials.gov. *Efficacy and safety of nintedanib in patients with progressive fibrosing interstitial lung disease (PF-ILD) (PF-ILD)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT02999178> [Accessed 15 January 2018].
- <sup>10</sup> European Medicines Agency. *Ofev: nintedanib*. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003821/human\\_med\\_001834.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003821/human_med_001834.jsp&mid=WC0b01ac058001d124) [Accessed 27<sup>th</sup> November 2017].
- <sup>11</sup> European Medicines Agency: Committee for Orphan Medicinal Products (COMP). *Public summary of opinion on orphan designation: Nintedanib for the treatment of systemic sclerosis* 22 September 2016. . Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Orphan\\_designation/2016/10/WC500213513.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2016/10/WC500213513.pdf) [Accessed 14 December 2017].
- <sup>12</sup> U.S. Food and Drug Administration. *Search orphan drug designations and approvals: nintedanib*. Available from: <https://www.accessdata.fda.gov/scripts/opdlisting/ood/listResult.cfm> [Accessed 15<sup>th</sup> January 2018].
- <sup>13</sup> NHS choices. *Scleroderma*. Available from: <https://www.nhs.uk/conditions/scleroderma/#causes-of-scleroderma> [Accessed 6 December 2017].
- <sup>14</sup> Arthritis Research UK. *Systemic sclerosis (scleroderma)*. Available from: <https://www.arthritisresearchuk.org/arthritis-information/conditions/systemic-sclerosis.aspx> [Accessed 6 December 2017].
- <sup>15</sup> Meune C, Vignaux O, Kahan A, Allanore Y. Heart involvement in systemic sclerosis: evolving concept and diagnostic methodologies. *Arch Cardiovasc Dis*. 2010 Jan; 103(1): 46-52. Available from: [https://ac.els-cdn.com/S187521360900240X/1-s2.0-S187521360900240X-main.pdf?\\_tid=333875d6-f9e2-11e7-b80d-00000aacb361&acdnat=1516013746\\_8f702907bbf3aca4c31e13d2a4194aa5](https://ac.els-cdn.com/S187521360900240X/1-s2.0-S187521360900240X-main.pdf?_tid=333875d6-f9e2-11e7-b80d-00000aacb361&acdnat=1516013746_8f702907bbf3aca4c31e13d2a4194aa5) [Accessed 15 January 2018].
- <sup>16</sup> University of Michigan: the Department of Internal Medicine. *Scleroderma Program: Division of Rheumatology: Lung Involvement*. Available from: <https://www.med.umich.edu/scleroderma/patients/lung.htm> [Accessed 6 December 2017].
- <sup>17</sup> Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. *Eur Respir Rev*. 2013 Mar 1; 22(127):6-19. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103193/pdf/nihms-493268.pdf> [Accessed 6 December 2017].

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- <sup>18</sup> Silver KC, Silver RM. Management of Systemic-Sclerosis-Associated Interstitial Lung Disease. *Rheum Dis Clin North Am*. 2015 Aug; 41(3):439-57. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4515778/pdf/nihms684300.pdf> [Accessed 6 December 2017].
- <sup>19</sup> Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. *Autoimmun Rev*. 2010 Mar; 9(5): A311-8. Available from: [https://ac.els-cdn.com/S1568997209001815/1-s2.0-S1568997209001815-main.pdf?\\_tid=4c4d0986-e0cb-11e7-81fd-00000aacb362&acdnat=1513255122\\_4c2b7d723170face70fcd6941bf1e2b](https://ac.els-cdn.com/S1568997209001815/1-s2.0-S1568997209001815-main.pdf?_tid=4c4d0986-e0cb-11e7-81fd-00000aacb362&acdnat=1513255122_4c2b7d723170face70fcd6941bf1e2b) [Accessed 14 December 2017].
- <sup>20</sup> Silman A, Jannini S, Symmons D, Bacon P. An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol*. 1988 Aug; 27(4):286-90. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/?term=An+epidemiological+study+of+scleroderma+in+the+West+Midlands> [Accessed 14 December 2017].
- <sup>21</sup> Harding M. *Systemic sclerosis: scleroderma*. Patient Platform Limited. 10 Nov 2016. Available from: <https://patient.info/doctor/systemic-sclerosis-scleroderma#nav-1> [Accessed 6 December 2017].
- <sup>22</sup> NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17*. Available from: <http://digital.nhs.uk/catalogue/PUB22378> [Accessed 23<sup>rd</sup> October 2017].
- <sup>23</sup> Strickland G, Pauling J, Cavill C, Shaddick G, McHugh N. Mortality in systemic sclerosis-a single centre study from the UK. *Clin Rheumatol*. 2013 Oct; 32(10):1533-9. Available from: <https://link.springer.com/article/10.1007/s10067-013-2289-0?no-access=true> [Accessed 6 December 2017].
- <sup>24</sup> Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax*. 2008 Sep; 63 Suppl 5:v1-58. Available from: [http://thorax.bmj.com/content/thoraxjnl/63/Suppl\\_5/v1.full.pdf](http://thorax.bmj.com/content/thoraxjnl/63/Suppl_5/v1.full.pdf) [Accessed 6 December 2017].
- <sup>25</sup> Yasuoka H. Recent Treatments of Interstitial Lung Disease with Systemic Sclerosis. *Clin Med Insights Circ Respir Pulm Med*. 2016 Jan 19; 9(Suppl 1): 97-110. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4720185/pdf/ccrpm-suppl.1-2015-097.pdf> [Accessed 6 December 2017].
- <sup>26</sup> ClinicalTrials.gov. *A Trial to Evaluate the Safety of Long Term Treatment With Nintedanib in Patients With Scleroderma Related Lung Fibrosis: NCT03313180*. Available from: [https://clinicaltrials.gov/ct2/show/NCT03313180?sfpd\\_d=14](https://clinicaltrials.gov/ct2/show/NCT03313180?sfpd_d=14) [Accessed 14 December 2017].
- <sup>27</sup> National Institute for Health and Care Excellence. *BNF: nintedanib*. Available from: <https://bnf.nice.org.uk/drug/nintedanib.html> [Accessed 6 December 2017].
- <sup>28</sup> NHS Northern, Eastern and Western Devon Clinical Commissioning Group. *Risk Sharing Schemes (RSS) and Patient Access Schemes (PAS)*. May 2016 Available from: <https://www.newdevonccg.nhs.uk/file/?rid=110696&download=true> [Accessed 25<sup>th</sup> Jan 2018].