National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness ***It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?***	British Lung Foundation	The British Lung Foundation supports the widening of access to nintedanib to PF-ILD patients. However, we would also like to see the review of this technology extended to include a review of its use for IPF patients also. Nintedanib was approved for IPF patients in January 2016. For many patients, these drugs can reduce the decline in their lung function. However, current NICE guidelines state that people are only eligible for them if they have a lung function between 50%-80%. Unfortunately, these limits mean that patients in the early stages of disease with lung function above 80% are not able to benefit from treatment. This is despite studies showing that patients with over 90% lung function receive the same benefit as patients with more impaired lung function. Currently, patients are put in the agonising position of having to wait until their disease gets worse, knowing that they have very limited life expectancy, before being prescribed these potentially life-extending drugs. Approximately 10,000 IPF Patients are in the early stages of the disease and do not currently have access to anti-fibrotic drugs.	The remit has been adjusted to exclude patients with idiopathic pulmonary fibrosis. Discussion at the scoping workshop indicated that because NICE technology appraisals guidance was already available on the use of nintedanib for treating idiopathic pulmonary fibrosis, patients with other types of progressive fibrosing-interstitial lung disease (PF-ILD) had the greatest clinical

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		The British Lung Foundation would like to see the thresholds for eligibility for nintedanib (as well as pirfenidone) reviewed so that any patient who would benefit from these drugs are able to receive them. Such a review and extension of eligibility would be a recognition of the progressive and terminal nature of IPF. Around 32,500 people in the UK live with IPF - it accounts for around 1 in 100 deaths a year in England. The average life expectancy in the UK following diagnosis is three to four years; a poorer prognosis than many cancers.	need at present. Also workshop attendees were not aware of any new clinical trial evidence on the use of either nintedanib or pirfenidone in idiopathic pulmonary fibrosis that would justify extending the remit of this appraisal to incorporate a rapid update of the existing guidance (both technology appraisals are due to be reviewed for update in 2021 according to current timelines).
	Association of Respiratory Nurse Specialists	Definitely appropriate. A trial of Nintedanib in patients with progressive fibrosing ILDs other than IPF (INBUILD) will report results in 2019. SENSCIS trial 2019 found the annual rate of decline in FVC was lower with Nintedanib in systemic sclerosis. As Nintedanib is already recommended for IPF by NICE then extending it to progressive fibrosing interstitial lung disease would be logical.	Comment noted. No action required.

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	British Thoracic Society (endorsed by Royal College of Physicians)	Yes appropriate as no evidence based therapies for progressive ILD and is an unmet need with significant impact on quality of life, morbidity and mortality	Comment noted. No action required.
	Boehringer Ingelheim Ltd.	Yes	Comment noted. No action required.
Wording ***Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.***	Association of Respiratory Nurse Specialists	Yes	Comment noted. No action required.
	Boehringer Ingelheim Ltd.	For clarification that the existing indication of IPF was excluded from the pivotal study (INBUILD) and is not expected to be in the marketing authorisation of PF-ILD, suggest the following wording: To appraise the clinical and cost effectiveness of nintedanib within its marketing authorisation for treating progressive fibrosing interstitial lung disease (PF-ILD), excluding idiopathic progressive fibrosis (IPF).	The remit has been adjusted to exclude patients with idiopathic pulmonary fibrosis.
Timing Issues ***What is the relative urgency of this proposed appraisal to the NHS?***	Association of Respiratory Nurse Specialists	As there is a prescient then this should be available as soon as possible	No action – the timing of a technology appraisal is aligned to information about the anticipated regulatory timeline with a view to providing guidance as soon as possible

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			following regulatory approval. However, there was a delay due to COVID-19 and then the company requested a delay to the starting of the appraisal.
	British Thoracic Society (endorsed by Royal College of Physicians)	Urgent unmet need in this patient group as no evidence based therapies at present and any therapy used is off licence	No action – the timing of a technology appraisal is aligned to information about the anticipated regulatory timeline with a view to providing guidance as soon as possible following regulatory approval. However, there was a delay due to COVID-19 and then the company requested a delay to the starting of the appraisal.
	Boehringer Ingelheim Ltd.	Currently there are no licensed therapies for the treatment of PF-ILD, with its attendant humanistic and economic burden. The upcoming indication of nintedanib in PF-ILD patients is expect to address this unmet need. Therefore, BI will work with NICE so that patients and clinicians in the NHS to be able to access nintedanib in PF-ILD indication as close to marketing authorisation as possible.	No action – the timing of a technology appraisal is aligned to information about the anticipated regulatory timeline with a view to

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			providing guidance as soon as possible following regulatory approval. However, there was a delay due to COVID-19 and then the company requested a delay to the starting of the appraisal.
Additional comments on the draft remit	Boehringer Ingelheim Ltd.	Any additional comments on the draft remit The updated remit PF-ILD (excluding IPF), needs to be reflected in the rest of the draft scope – especially in the background.	The remit has been adjusted to exclude patients with idiopathic pulmonary fibrosis. The background section has been edited in line with comments received at the scoping workshop.

Comment 2: the draft scope

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Background information ***Consider the accuracy and***	Association of Respiratory Nurse Specialists	Good	The background section has been edited in line with comments received at the scoping workshop.

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completeness of this information.	British Thoracic Society (endorsed by Royal College of Physicians)	Estimates of new cases seem low when the BLF report suggests IPF new cases to be above 5000 per year so new cases must be more than 2-4000 per year. Need to use current available studies on prevalence/incidence to help guide this Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris Boris Duchemann1,2, Isabella Annesi-Maesano3, Camille Jacobe de Naurois4, Shreosi Sanyal3, Pierre-Yves Brillet2,5, Michel Brauner5, Marianne Kambouchner6, Sophie Huynh7, Jean Marc Naccache8, Raphael Borie9, Jacques Piquet10, Arsène Mekinian11, Jerôme Virally7, Yurdagul Uzunhan1,2, Jacques Cadranel8, Bruno Crestani9, Olivier Fain11, Francois Lhote12, Robin Dhote13, Nathalie Saidenberg-Kermanac'h14, Paul-André Rosental15, Dominique Valeyre1,2 and Hilario Nunes1,2 The term EAA is confusing – please use up to date classification of Hypersensitivity pneumonitis	The background section has been edited to reflect the prevalence data reported by the British Lung Foundation. Hypersensitivity pneumonitis now replaces the term extrinsic allergic alveolitis (EAA). Anxiety and depression have been added to the list of commonly reported symptoms.

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		Anxiety and depression is also a common symptom and should be mention Reference: Garibaldi et al Respirology 2016 And Voice of the patient FDA	
	Boehringer Ingelheim Ltd.	• Please update general wording here to reflect the expected license and remit - PF-ILD (excluding IPF) • PF-ILD is not a “subtype” of ILDs. It is a “phenotype” – or behaviour/ manifestation of this disease. For clarity, “Patients with ILD can develop a progressive phenotype that causes pulmonary fibrosis, leading to lung function decline, deterioration in quality of life and early mortality similar to IPF, the most frequent form of idiopathic interstitial pneumonias. On the basis of the clinical and pathophysiological similarities among these diseases, it has been postulated that such disorders with a progressive phenotype have a common pathobiologic mechanism regardless of the cause and thus could all have a response to similar treatment.” (https://www.nejm.org/doi/full/10.1056/NEJMoa1908681) • Please replace “extrinsic allergic alveolitis (EAA)” (older terminology) with “hypersensitivity pneumonitis (HP)”. • Please delete this statement “Some people with ILD may have no symptoms.” – while this is true for all ILDs – by definition of PF-ILD, patients with PF-ILD are symptomatic	The background section has been edited in line with the comment where relevant. Specifically: • the description of the PF-ILD as a phenotype has been expanded • the term ‘extrinsic allergic alveolitis (EAA)’ has been removed • the statement ‘Some people with ILD may have no symptoms’ has been retained because it is clear that this applies to ILD not PF-ILD • prevalence has been updated

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		• Paragraph #3 under background, on prevalence – needs to be updated to reflect that the remit here does not include IPF. In addition, closer estimates to the indication would be "Progressive fibrosing ILD is rare, with prevalence estimates of 0.22 to 2.00 per 10,000 in Europe" • Please update this "Treatment for PF-ILD may depend on the underlying cause, where known." With "Treatment for ILDs may depend on the underlying cause, where known. IPF currently has two licensed therapies, including nintedanib. Patients with PF-ILD (excluding IPF) do not currently have any disease modifying therapy options for their PF-ILD" • Please update last sentence to include "methotrexate" in that list and delete "…or rituximab. NICE has produced an evidence summary on infliximab for sarcoidosis and rituximab for scleroderma (NICE evidence summary 2 and 7)" – as rituximab and infliximab, while not indicated in any ILDs, are also not expected to be used for PF-ILD.	• the first sentence about treatment has been amended so it only refers to ILD, not PF-ILD. • the current wording of the scope makes it clear that there are NICE recommended licensed therapies for idiopathic pulmonary fibrosis. As nintedanib has now received a marketing authorisation for PF-ILD the statement about there being no licensed therapy for other PF-ILDs has been removed. • the reference to evidence summary 7 has been removed because it does not include any discussion of the evidence for rituximab for treating lung involvement in systemic sclerosis. However, rituximab is retained in the penultimate sentence as comments from other stakeholders have indicated that it is a relevant comparator.

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			• NICE evidence summary 2 relates to the use of infliximab so methotrexate has not been added to the sentence. • Methotrexate has been removed as comments from stakeholders (including those who attended the scoping workshop) did not indicate that methotrexate was an important treatment in NHS practice. Also the current wording of the scope is broad enough that it can be considered, therefore it was not deemed necessary to add it.
The technology/ intervention ***Is the description of the technology or technologies accurate?***	Association of Respiratory Nurse Specialists	yes	Comment noted. No action required.
	British Thoracic Society (endorsed by Royal College of Physicians)	Yes	Comment noted. No action required.

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	Boehringer Ingelheim Ltd.	• Please update “brand name unknown” with “OFEV” • Please update “” with “Fibrosing ILDs with a progressive phenotype show commonalities in clinical behaviour and in the pathogenic mechanisms that drive disease worsening. Nintedanib is an intracellular inhibitor of tyrosine kinases that has been approved for treatment of IPF and has recently been shown to reduce the rate of lung function decline in patients with ILD associated with systemic sclerosis (SSc-ILD). In vitro data demonstrate that nintedanib inhibits several steps in the initiation and progression of lung fibrosis, including the release of pro-inflammatory and pro-fibrotic mediators, migration and differentiation of fibrocytes and fibroblasts, and deposition of extracellular matrix. Nintedanib also inhibits the proliferation of vascular cells. Studies in animal models with features of fibrosing ILDs such as IPF, SSc-ILD, rheumatoid arthritis-ILD, hypersensitivity pneumonitis and silicosis demonstrate that nintedanib has anti-fibrotic activity irrespective of the trigger for the lung pathology. This suggests that nintedanib inhibits fundamental processes in the pathogenesis of fibrosis.” (https://erj.ersjournals.com/content/early/2019/06/26/13993003.00161-2019)	The brand name of the technology has been updated in line with the comment. The scope already includes a brief description of the possible mechanism of action of nintedanib; more detail is not normally provided here.
Population ***Is the population defined appropriately? Are there groups within this population that should be***	Association of Respiratory Nurse Specialists	Already separate standards for IPF	No action – patients with idiopathic pulmonary fibrosis remain excluded from the population.
	British Thoracic Society	Need to also consider IPF patients above 80% who decline	No action – patients with idiopathic pulmonary fibrosis

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considered separately?	(endorsed by Royal College of Physicians)		remain excluded from the population. Discussion at the scoping workshop indicated that because NICE technology appraisals guidance was already available on the use of nintedanib for treating idiopathic pulmonary fibrosis, patients with other types of PF-ILD had the greatest clinical need at present. Also workshop attendees were not aware of any new clinical trial evidence on the use of either nintedanib or pirfenidone in idiopathic pulmonary fibrosis that would justify extending the remit of this appraisal to incorporate a rapid update of the existing guidance (both technology appraisals are due to be reviewed for update in 2021 according to current timelines).
	Boehringer Ingelheim Ltd.	• Yes (as also noted in the remit – in line with expected Marketing Authorisation). • The two primary populations for analysis were the overall population and patients with a UIP-like fibrotic pattern.	No action – patients with idiopathic pulmonary fibrosis remain excluded from the population. Discussion at the scoping workshop indicated

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		• PF-ILDs (ILDs with PF phenotype) were postulated to have a common pathobiologic mechanism regardless of the cause and thus could all have a response to similar treatment. Results of the INBUILD trial show that data support the hypothesis that progressive fibrosing interstitial lung diseases, regardless of clinical diagnosis, have a similar pathobiologic mechanism. (https://www.nejm.org/doi/full/10.1056/NEJMoa1908681)	that consideration of patients with a UIP-like fibrotic pattern as a separate group was not a priority.
Comparators ***Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?***	Association of Respiratory Nurse Specialists	Yes-limited licenced treatment although used currently	Comment noted. No action required.
	British Thoracic Society (endorsed by Royal College of Physicians)	No established evidence based practise – all treatments are not licenced. Must compare to best supportive care. Need to also compare to the cost of lung transplantation as this is where a proportion of patients are heading, BSC should include GP visits , hospitalisation, use of health care and social services, lung transplant, oxygen services, pulmonary rehab	No action – discussion at the scoping workshop indicated that nintedanib would not be considered an alternative to lung transplant. Clinical experts suggested that it was more likely that nintedanib would be used to try to slow disease progression in patients who may ultimately receive a transplant. For this reason it was not included as a comparator in the scope but has been included as an outcome.

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	Boehringer Ingelheim Ltd.	• Please add – methotrexate • Please delete – rituximab and infliximab (as requested above) • Of note, is that there are no other licensed therapies for this indication • Best supportive care includes various components to it (like, pulmonary rehabilitation, oxygen therapy, community nursing support, etc.)	No action. Overall comments from stakeholders (including those who attended the scoping workshop) did not indicate that methotrexate was an important treatment in NHS practice. Also, the current wording of the scope is broad enough that it can be considered, therefore it was not deemed necessary to add it. Comments from other stakeholders have indicated that rituximab and infliximab are relevant comparators.
Outcomes ***Will these outcome measures capture the most important health related benefits (and harms) of the technology?***	Association of Respiratory Nurse Specialists	Yes	Comment noted. No action required.
	British Thoracic Society (endorsed by Royal College of Physicians)	All reasonable; lung function is listed but to ensure this includes gas transfer as well as usual FVC and FEV1 etc	No action. Outcomes listed in the scope are those that are considered important to NICE's decision-making (i.e. those important to patients or carers), which are not necessarily the outcomes

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			measured in the relevant clinical studies. Also, outcomes listed are not meant to be exhaustive.
	Boehringer Ingelheim Ltd.	• Please delete “physical function” and “progression-free survival”. • For clarity, lung function is captured as “annual rate of decline in the FVC, as assessed over a 52-week period”, and is the primary outcome of the pivotal clinical trial INBUILD	Outcomes listed in the scope are those that are considered important to NICE’s decision-making (i.e. those important to patients or carers), which are not necessarily the outcomes measured in the relevant clinical studies. Also, outcomes listed are not meant to be exhaustive. The outcome ‘progression-free survival’ has been removed – it is acknowledged that this is not relevant given that the population of interest has progressive disease. The remaining outcomes in the list have been re-organised to indicate which are considered measures of disease progression. It is recognised that physical function can impact health-related quality of life but it is also considered to be a potentially useful measure

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			of mortality risk. For this reason, it has been retained as a potential measure of disease progression
Economic analysis ***Comments on aspects such as the appropriate time horizon.***	Boehringer Ingelheim Ltd.	No changes proposed	Comment noted. No action required.
Equality and Diversity ***NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet***	Association of Respiratory Nurse Specialists	No-it would mean equality with IPF patients	Comment noted. No action required.
	British Thoracic Society (endorsed by Royal College of Physicians)	Assessing non-IPF patients only – disadvantages IPF patients who are declining and gave an FVC above 80%	This issue does not relate to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please see previous responses regarding the decision to exclude patient with idiopathic pulmonary fibrosis

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these aims. In particular, please tell us if the proposed remit and scope: • ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*** • ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*** • ***could have any adverse impact on people with a particular***	Boehringer Ingelheim Ltd.	Not identified for PF-ILD – these (e.g. gender preponderance) could be aetiology-specific, but are likely balanced out in overall PF-ILD.	Comment noted. No action required.

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disability or disabilities. • ***Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.***			
Other considerations ***Suggestions for additional issues to be covered by the proposed appraisal are welcome.***	Association of Respiratory Nurse Specialists	This will only be initiated by specialists	No action – it was recognised by attendees at the scoping workshop that treatment would be initiated by a specialist, but this was not deemed to have any impact on the wording of the scope.
	British Thoracic Society (endorsed by Royal College of Physicians)	If positive appraisal what about IPF above 80% who are declining?	No action – patients with idiopathic pulmonary fibrosis remain excluded from the population. Discussion at the scoping workshop indicated that because NICE technology appraisals guidance was already available on the use of nintedanib for treating idiopathic pulmonary fibrosis, patients with other types of PF-ILD had the greatest clinical need at present. Also

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			workshop attendees were not aware of any new clinical trial evidence on the use of either nintedanib or pirfenidone in idiopathic pulmonary fibrosis that would justify extending the remit of this appraisal to incorporate a rapid update of the existing guidance (both technology appraisals are due to be reviewed for update in 2021 according to current timelines).
	Boehringer Ingelheim Ltd.	As biologics are not indicated for PF-ILDs (see points on rituximab and infliximab above), the statement “The availability and cost of biosimilar products should be taken into account” may not apply. Reference to infliximab and rituximab in the “Related NICE recommendations and NICE Pathways”	No action - infliximab and rituximab have been retained as comparators for the reasons stated in the response above. The following wording is standard text and has been retained in the scope ‘The availability and cost of biosimilar products should be taken into account’.
Innovation ***Do you consider the technology to be innovative in its potential to make a***	Association of Respiratory Nurse Specialists	Nintedanib has been shown to slow progression of the fibrosis, giving patients a better quality of life and extending the life expectancy.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal

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significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.			committee when formulating its recommendation.
	Boehringer Ingelheim Ltd.	There are currently no licensed medicines for the treatment of PF-ILD, and the treatments currently used off-label cannot alter the course of the disease. Nintedanib is expected to be the first approved drug for PF-ILD, and is expected to reduce disease progression by slowing the decline of lung function, as demonstrated in the published results of the pivotal INBUILD study (https://www.nejm.org/doi/full/10.1056/NEJMoa1908681). Nintedanib (OFEV) will therefore be a step-change in the management of PF-ILD.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendation.
Questions for consultation ***Please answer any of the questions for consultation if not***	Association of Respiratory Nurse Specialists	On the draft-to be discussed at the September meeting	The scoping workshop was delayed. An attendee from the Association of Respiratory Nurse Specialists provided comments on the scope at re-

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covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines).			scheduled meeting in November 2019 which have been taken into account.
	British Thoracic Society (endorsed by Royal College of Physicians)	**Questions for consultation** **At what point in the treatment pathway will nintedanib be used in people with PF-ILD? Will it be considered for all people with PF-ILD or only some (i.e. those with clinically significant disease)?** Should use the trial criteria which were any two of: 1. FVC >10% 2. Any Worsening symptoms and FVC 5-10% decline 3. FVC decline 5-10% and Any Progression on HRCT 4. ANYWorsening of symptoms and ANY progression on HRCT **What is the estimated prevalence of people with PF-ILD? What proportion of people with IPF and SSc-ILD will have PF-ILD?** Uncertain about the accurate figure is for this. Anything from 20-30%. **Have all relevant comparators for nintedanib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for PF-ILD? Does the choice of treatment differ depending on the underlying cause of PF-ILD? If so, how does this differ for each underlying condition?**	Discussion at the scoping workshop indicated that: • the population of the INBUILD trial are the population of interest for the appraisal. Only patients whose lung function and respiratory symptoms or chest imaging have worsened despite treatment were included in INBUILD. On this basis it was determined that nintedanib would only be used in patients who had received prior treatment for ILD • all patients with idiopathic pulmonary fibrosis have progressive disease, the proportion of patients with other ILDs who have progressive-fibrosing disease is unknown. The scope has been edited to reflect data published by Olson 2018

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		No established evidence based practise – all treatments are not lisenced. Must compare to best supportive care. Need to also compare to the cost of lung transplantation as this is where a proportion of patients are heading, BSC should include GP visits , hospitalisation use of health care and social services. **Are infliximab and rituximab used in the NHS to treat PF-ILD?** • Infliximab/Rituximab are costly treatments, occasionally used for such patients but this requires a hospital day case admission at minimum. Currently there is no funding to support patients who require these treatments, meaning treatment needs to be considered on a 'case by case' basis and individual funding requests need to be completed via NHSE each time. Many PF-ILD patients are currently referred through to rheumatology so such treatments can be provided without the requirement for IFR requests. • Mycophenolate and other immunosuppressants have many side effects and potential drug interactions. Costs of monitoring and managing side effects should be considered. • Similarly, corticosteroids have many systemic side effects and can cause cascade prescribing to manage sequalae. • Infective exacerbations induced by immunosuppressants will usually warrant health resource utilisation. • PF-ILD is a sub-type of ILD which appears to have some auto-immune involvement. It has no clear treatment, hence, there is an unmet treatment need. Immunosuppressants and mabs are	which suggests that up to 20% of patients with sarcoidosis develop fibrotic disease • infliximab and rituximab should been retained as comparators because they are in use in clinical practice • lung transplant is not a relevant comparator but may be a relevant clinical endpoint • the exclusion of patients with idiopathic pulmonary fibrosis from the scope is not an equalities issue because it does not relate to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please see previous responses regarding the decision to exclude patient with idiopathic pulmonary fibrosis.

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		reasonable comparator treatments and have been used to treat this with varying results. The use of Nintedanib in such patients would offer alternative, less toxic therapy to potentially slow disease progression and potentially improve mortality. **How should best supportive care be defined?** Supportive care inclusing oxygen therapy, pulmonary rehab referral to palliative service; social impact with increased use of services, hospitalisations, health care resource, lung transplant. **Are the outcomes listed appropriate? Are there any other outcomes that should be included?** Yes FVC decline, hospitalisation, Qof L. Mortality difficult to assess in clinical trials with small numbers. **Are there any other subgroups of people in whom nintedanib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Are there any specific comparators used in any specific subgroups?** **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:**	Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee. Where relevant and appropriate, benefits not captured by QALY may be considered by the committee.

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		• **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which nintedanib will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** It would be discriminatory if this is a positive appraisal but progressive IPF is excluded ie those above 80%. Need a more accurate estimation of prevalence using literature and local databases Cost of best supportive care **Do you consider nintedanib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes will improve survival in this group of patients where there is no or very limited evidence based therapy.	

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		Do you consider that the use of nintedanib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? QALYs would be a reasonable measure of cost effectiveness and presumably ICERs will be calculated too. Patient reported measures (such as for breathlessness, noting SGRQ is mainly applied in COPD). Health resource utilisation such as GP visits/ ED presentations are useful to include in cost effectiveness. Surrogate markers like use of oxygen may be useful as if patients are maintained at a better lung function they will not need to progress to oxygen. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).**	

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	Boehringer Ingelheim Ltd.	**At what point in the treatment pathway will nintedanib be used in people with PF-ILD?** • INBUILD trial inclusion criteria help define which patients nintedanib has been clinically tested on for PF-ILD (https://www.nejm.org/doi/full/10.1056/NEJMoa1908681): ○ The patients were required to meet at least one of the following criteria for progression of interstitial lung disease within the 24 months before screening, despite standard treatment with an agent other than nintedanib or pirfenidone: a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, or worsening of respiratory symptoms and an increased extent of fibrosis. At the time of enrollment, patients were required to have an FVC of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin) of 30 to less than 80% of the predicted value. ○ Patients who were treated with azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids (at a dose of more than 20 mg per day for glucocorticoids) were excluded. At the discretion of the investigator, initiation of these medications was allowed after 6 months of trial treatment in patients with clinically significant deterioration of interstitial lung disease or connective tissue disease.	Discussion at the scoping workshop indicated that: • the population of the INBUILD trial are the population of interest for the appraisal. Only patients whose lung function and respiratory symptoms or chest imaging have worsened despite treatment were included in INBUILD. On this basis it was determined that nintedanib would only be used in patients who had received prior treatment for ILD • all patients with idiopathic pulmonary fibrosis have progressive disease, the proportion of patients with other ILDs who have progressive-fibrosing disease is unknown. The scope has been edited to reflect data published by Olson 2018 which suggests that up to 20% of patients with sarcoidosis

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		• In addition, with antifibrotic treatment like nintedanib (OFEV) for IPF possible only after MDT diagnosis of patients' IPF in ILD clinics at selected tertiary centres in the NHS, there is already a consistent, well established patient pathway in the UK for patients with PF-ILD **Will it be considered for all people with PF-ILD or only some (i.e. those with clinically significant disease)?** • PF-ILD is a phenotype – see comment #2 under 'background information' as well as the definition of 'progression' under the trail inclusion criteria in this section above. To meet the definition of PF-ILD, patients need to already have clinically significant dissease. See also the points above the point that PF-ILDs, regardless of aetiology, behave similarly pathophysiologically and in therapeutic response to nintedanib **What is the estimated prevalence of people with PF-ILD? What proportion of people with IPF and SSc-ILD will have PF-ILD?** • Progressive fibrosing ILD is rare, with prevalence estimates of 0.22 to 2.00 per 10,000 in Europe • Remit and indication under consideration include non-IPF PF-ILD. The incidence of PF SSc-ILD is currently unknown **Comparator considerations** • See response to item above	• consideration of patients with a UIP-like fibrotic pattern as a separate group was not a priority.

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		Outcome considerations • See response to item above **Are there any other subgroups of people in whom nintedanib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Are there any specific comparators used in any specific subgroups?** • See response to 'population' item above • The two primary populations for analysis were the overall population and patients with a UIP-like fibrotic pattern. • PF-ILDs (ILDs with PF phenotype) were postulated to have a common pathobiologic mechanism regardless of the cause and thus could all have a response to similar treatment. Results of the INBUILD trial show that data support the hypothesis that progressive fibrosing interstitial lung diseases, regardless of clinical diagnosis, have a similar pathobiologic mechanism. (https://www.nejm.org/doi/full/10.1056/NEJMoa1908681) **Equality considerations** • See response to item above **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** • With antifibrotic treatments like nintedanib (OFEV) for IPF possible only after MDT diagnosis of patients' IPF in ILD clinics at selected tertiary centres in the NHS, there is already a	

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		consistent, well established patient pathway in the UK for patients with PF-ILD **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).** • Agree	
Additional comments on the draft scope	British Thoracic Society (endorsed by Royal College of Physicians)	The INBUILD paper of Nintedanib in progressive fibrosis has been published and the key results from the paper should be noted. Specifically the magnitude of therapeutic benefit when compared to placebo and the fact that this treatment is effective in both UIP and non-UIP progressive fibrosis – so all comers with progressive ILD.	The committee will consider the evidence to support the use of nintedanib for PF-ILD throughout the course of the appraisal.
	Boehringer Ingelheim Ltd.	No further comments	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None