ILD highlights from the ATS 2017 congress
May 19 – May 24 / Washington, DC
Objectives and focus of this report

The preparation of the slide kit was sponsored by Boehringer Ingelheim International GmbH and contains personal opinions from leading ILD experts. ATS was neither author nor reviewer of the content. This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
Objectives and focus

ATS congress 2017
The American Thoracic Society (ATS) is one of the pioneer international organisations in the pulmonary field. The congress program 2017 included sessions highlighting the cutting-edge advancements in the field of interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF).

Objectives of this report
Provide current expert perspectives on the clinical importance of the data for healthcare professionals in research and daily practice.

Focus of this report
Up to date developments, main topics of discussion and highlights on idiopathic pulmonary fibrosis (IPF) and interstitial lung diseases (ILDs) presented in numerous sessions at the ATS 2017.

Please note that these slides report the data presented during the ATS 2017 in Washington D.C., USA.

Please check your local regulations and guidelines when prescribing treatment and managing patients with ILD.
Topic overview

► ILD clinical year in review
  • New insights in ILF and IPF

► Recent advances in ILD diagnosis
  • Early detection of pulmonary fibrosis
  • Multidisciplinary diagnosis (MDD)

► New insights into ILD management
  • Awareness and treatment compliance
  • Quality of life
  • Ambulant oxygen use

► Clinical trials in ILD
  • Immunosuppressants in ILD
  • Inhaled drug delivery in IPF
  • N-Acetylcysteine (NAC) in IPF
  • New therapeutic agents in development

► Registries in IPF
  • IPF-PRO registry
  • PROOF and Australian IPF registries

► New data on antifibrotic treatments
  • New data on nintedanib
  • New data on pirfenidone in IPF
  • Antifibrotic treatments – comparison
  • New molecules
  • Non-IPF fibrosis

► Predictors of disease progression, outcome and survival in ILD
  • Risk factors in IPF
  • FEV₁/FVC ratio and disease progression
  • New IPF staging
  • IPAF

► IPF pathobiology and potential biomarkers in ILD
  • Omics
  • Microbiome
  • Genetic markers
  • Autoantibodies
  • New insights on candidate biomarkers

► Appendix and acknowledgements
  • Abbreviations
  • Prescribing information
  • Acknowledgements
ILD clinical year in review
New insights in ILD and IPF

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New insights in ILD and IPF

**ILD diagnosis**
- Interstitial lung abnormalities (ILA) are considered a pre-stadium of ILD\(^1\),\(^2\)
- **Professional agreement in multidisciplinary discussion (MDD):** Good for IPF (weighted Kappa 0.71) and CTD-ILD (weighted Kappa 0.73), moderate for overall ILD (Kappa 0.50)\(^3\)
- Metalloproteinase 7 (MMP-7), surfactant protein D (SP-D) and osteopontin seem to be useful single- and multi-biomarkers to distinguish IPF from other ILDs\(^4\)

**ILD management**
- ATS/ERS 2015 guidelines give a weak recommendation in favor of antacid therapy in the IPF management, but this is associated with a significantly higher incidence of overall and pulmonary infections in patients with advanced IPF\(^5\)
- Both mycophenolate mofetil (MMF) and oral cyclophosphamide improve FVC % predicted in SSc-ILD (Systemic Sclerosis associated ILD) with no significant differences in efficacy between treatments. However, mycophenolate mofetil was associated with less toxicity\(^6\)

**IPF acute exacerbations**
- Definition of IPF acute exacerbations (AE) has been updated as follows:\(^7\)
  
  “An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality”
  
- New definition will include more cases so the frequency of AE-IPF may increase in the future

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Expert comments

Despite increasing awareness of MDD, biomarkers are still an unmet need and an emerging aspect in the differential diagnosis of ILDs.

Results from the Scleroderma Study II (MMF efficacy in SSc-ILD) prepare the way for further clinical trials in SSc or CTD-ILD with MMF as comparator.

Change in the definition of AE-IPF will probably lead to a revision of the epidemiological data and a different management approach.
Recent advances in ILD diagnosis

Early detection of pulmonary fibrosis | Multidisciplinary diagnosis

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Earlier detection of pulmonary fibrosis

Computed tomography (CT) of ILAs can indicate early pulmonary fibrosis

CT assessment of ILAs in patients (n=448) with surgical resections for pulmonary nodules were associated with

- Subpleural fibrosis
- Fibroblastic foci on histopathology

CT data from the COPDGene study (n=8345) showed that ILAs were associated with

- Lower lung function
- Decreased quality of life, and
- 63.1% higher mortality (n=6827)

Identification of genetic factors may improve accuracy of CT assessment

- More interstitial changes were associated with a genetic component, the MUC5B promoter polymorphism rs35705950, especially in non-Hispanic whites.
- Preclinical pulmonary fibrosis (PrePF) was shown to be common among relatives of patients with familial interstitial pneumonia (HRCT screening n=496)
- Combining clinical characteristics, MUC5B promoter genetic variant, and PBMC gene expression profiles was most reliable in predicting early pulmonary fibrosis

Visualization of ILAs on CT may help to identify pulmonary fibrosis early. Assessment of genetic variants and gene expression profiles could further improve diagnosis.

Accuracy of a multidisciplinary approach in ILD

**Expertise in ILD increases diagnostic accuracy**
- **ILD experts** diagnose IPF correctly more often than non-expert pulmonologists (93% vs 79%)\(^1\)
- **Interobserver** agreement on IPF diagnosis is greater between ILD experts (64%) than non-expert pulmonologists (54%)\(^2\)

**Addition of a rheumatologist to the MDT can increase diagnostic accuracy and reduce unnecessary invasive procedures**\(^3\)
- 21% (6 of 28) ILD patients diagnosed with IPF by a pulmonology MDT were found to have a CTD following rheumatological assessment\(^3\)
- Only 56% of CTD cases were identified by the MDT, causing 7 unnecessary bronchoscopies and 1 biopsy\(^3\)

**Multidisciplinary discussion (MDD) influences diagnosis and disease management**\(^4\)
- After ILD-MDT review of 90 suspected ILD cases, ILD diagnosis was revised in 53% of patients (increased diagnosis of hypersensitivity pneumonitis and CTD-ILD)
- Significantly increased use of pulmonary vasodilators, anti-fibrotic therapy, oxygen usage and entry to clinical trials

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**Expert comments**

ILAs are considered as precursors of pulmonary fibrosis and should be closely monitored. Evaluation through MDD could be helpful to identify early specific fibrosis patterns.

MDD has become a widely used tool that is considered essential for ILD differential diagnosis and treatment decisions or confirmation.

The involvement of a rheumatologist in the MDD can increase the diagnostic accuracy of the MDD, especially in IIPs with autoimmune features.

IIP = Idiopathic Interstitial Pneumonia, ILA = Interstitial Lung Abnormalities, ILD = Interstitial Lung Disease, MDD = Multidisciplinary Discussion
New insights into ILD management
Awareness and treatment compliance | Quality of life | Ambulant oxygen use

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## Awareness and treatment compliance in IPF

- Although IPF and NSCLC (non-small cell lung cancer) have similar survival outcomes, fewer IPF patients initiate and continue treatment\(^1\)
- Compliance to antifibrotic treatment is relatively low (60% commercially insured, ≤51% Medicare patients), indicating a high unmet need for management of side-effects\(^2\)

Better **awareness and education** of physicians and patients on the benefit of early antifibrotic treatment for IPF and importance of compliance may **improve outcomes**

### Patient ‘drop out’ at each stage of the journey

<table>
<thead>
<tr>
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<th>Symptoms/awareness</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Persistence</th>
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<tr>
<td><strong>IPF patient journey</strong></td>
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<tr>
<td>Total IPF patient drop out:</td>
<td>-135,200</td>
<td>-98,500</td>
<td>-47,600</td>
<td>-26,700</td>
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<tr>
<td>EU-5 (UK, France, Germany, Spain, and Italy)</td>
<td>27%</td>
<td>52%</td>
<td>44%</td>
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<td>US</td>
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<th>Symptoms/awareness</th>
<th>Diagnosis</th>
<th>Treatment</th>
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<tr>
<td><strong>NSCLC patient journey</strong></td>
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<tr>
<td>Total NSCLC patient drop out:</td>
<td>-953,700</td>
<td>-829,300</td>
<td>-623,400</td>
<td>-537,800</td>
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<tr>
<td>EU-5 (UK, France, Germany, Spain, and Italy)</td>
<td>13%</td>
<td>25%</td>
<td>14%</td>
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<td>US</td>
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\(1\) Denton J. et al. *AJRCCM*; 2017: A5436; 2\ Eldar-Lissai A. et al. *AJRCCM*; 2017: A5348
Quality of life (QoL) for patients with IPF

Cough in IPF and SSc-ILD

- Cough severity is related to dyspnea\(^1,2\) and pulmonary function\(^1\)
- Cough is significantly associated with poor quality of life\(^1\)
- Patients with IPF (n=77) have more frequent, more severe and more often productive cough than patients with SSc-ILD (n=67)\(^1\)

Trajectory of HRQoL\(^3\)

- Using data from the INSIGHTS-IPF registry (n=359), SGRQ significantly worsened during follow-up (+ 2.7 per year)

Impact of depression\(^4\)

- In 69 patients with mild-to-moderate IPF, 39% (n=27) had significant depressive symptoms (with no prior diagnosis of depression)
- Strong association was found between depressive symptoms and
  - Disease severity (GAP score, DL\(_{CO}\), 6MWD)
  - Symptom burden
  - HRQoL

\(\text{HRQoL} = \text{Health-Related Quality of Life, SSc-ILD = Systemic Sclerosis-associated ILD}\)


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**Cough severity and productiveness**

- **IPF: Productive/Non-productive**
- **SSc-ILD: Productive/Non-productive**

<table>
<thead>
<tr>
<th>Cough VAS Score</th>
<th>Patients in %</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>10</td>
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<td>20</td>
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<td>100</td>
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AmbOx – ambulatory oxygen in fibrotic lung disease\textsuperscript{1}

AmbOx: a multicenter, randomized, cross-over controlled (placebo air) trial assessed effect of ambulatory oxygen on quality of life in patients with fibrotic ILD over two weeks (n=74)

Ambulatory oxygen improved 6MWT performance and K-BILD scores for

- Health status (difference 3.7; 95% CI 1.8-5.7; p<0.0001)
- Breathlessness and activity (difference 8.7; 95% CI: 4.8-12.6; p<0.0001)
- Chest symptoms (difference 7.6; 95% CI: 1.9-13.2; p=0.009)

Ambulatory oxygen supply had no effect on psychological symptoms

The beneficial influence on symptoms and quality of life in patients with fibrotic ILD shows that ambulatory oxygen use should be considered in future ILD-specific guidelines.

\textsuperscript{1} Visca D. ATS 2017: Oral presentation B14
Expert comments

A multidisciplinary ILD team, involving respiratory physicians, other specialists, nurses and physiotherapists, can implement management strategies and increase patients’ quality of care and life.

Development of patient-centered outcome measures is crucial to improve understanding of patients’ unmet needs and monitor the efficacy of treatment decisions on QoL.

New data on ambulatory oxygen for patients with fibrotic ILD demonstrates beneficial influence on symptoms and QoL. This is the beginning of a new era of trials in supportive care in ILD.
Clinical trials in ILD

Immunosuppressants in ILD | Inhaled drug delivery in IPF | NAC in IPF | New therapeutic agents

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Immunosuppressants in ILD treatment

Intravenous cyclophosphamide\(^1\)
- 307 ILD patients were treated with cyclophosphamide (CYC) for 6-12 months
- Patients with idiopathic myositis had the best response to therapy
  - No deaths on treatment, only ~4.8% of patients with a decline in FVC>10% during treatment
- Treatment response in cHP (chronic hypersensitivity pneumonitis) and unclassifiable ILD groups was less convincing
  - 50% of patients experienced disease progression or death on treatment

Use of CYC in stabilizing lung function in a range of ILDs is confirmed with the most benefit seen in idiopathic myositis

Mycophenolate mofetil (MMF) in SSc-ILD & cHP
- Treatment with MMF improved FVC% predicted and DL\(_{\text{CO}}\)% predicted compared to placebo over 12 months in patients with SSc-ILD\(^2\)

Retrospective review of chronic hypersensitivity pneumonitis (cHP) patients treated with MMF:\(^3\)

Pulmonary function in cHP

- MMF has potential as a steroid-sparing agent and may help to stabilize pulmonary function in HP patients\(^3\)

Inhaled drug delivery in IPF

Pharmacokinetics of aerosolized interferon-γ¹

- 10 TB and 24 IPF patients were treated with aerosolized IFN-γ
- Within 1 h of IFN-γ dose, BAL fluid showed a significant increase in IFN-γ levels in both groups
- The level of IFN-γ was inversely proportional to time of BAL since last dose
- Aerosol IFN-γ was well tolerated
- Pharmacokinetics of aerosol IFN-γ support an increased lung deposition level in TB and IPF patients

TOPICAL study: comparing devices for inhaled salbutamol delivery²

- Spinning disk aerosol generator showed
  - Highest % total deposition of radiolabelled salbutamol in the lungs vs volumatic spacer (pMDI) or nebuliser
  - Higher dose-normalised plasma salbutamol levels vs pMDI use (lower plasma levels were observed following nebulisation)
- Inhaled delivery of salbutamol is feasible in IPF patients: this data could also optimize inhaled drug delivery of novel therapies in patients with IPF

¹ D’Annunzio S. et al. AJRCCM; 2017: A5405; ² Maher T.M. et al. AJRCCM; 2017: A5382

pMDI = pressurized Metered Dose Inhaler
N-Acetylcysteine in polymorphism subtypes of IPF

• Although NAC received a weak recommendation against its use in IPF patients\(^1,2\) it might be useful in a subset of patients with TOLLIP polymorphism\(^3\)
  
• Findings from the COMET study (n=59) show that DL\(_{CO}\) genes, that are normally down-regulated in IPF patients, are not down-regulated in patients receiving NAC\(^1,3\)
  
  • NAC use up-regulates immune pathway genes
  
  • This effect was shown for DL\(_{CO}\) gene score (GS)-signatures, not single genes

New therapeutic agents in development

**Recombinant human thrombomodulin (rhTM) in IIP**
- Safety and efficacy of thrombomodulin rhTM (n=39, 380 U/kg/day) in addition to conventional treatment for AE-IIP was evaluated in a non-randomized, open-label trial.
- Survival was significantly better after rhTM treatment in comparison to conventional therapy alone (p=0.04).
- Frequency of adverse events was similar in both groups.

**O mipalisib (GSK2126458)**
- A randomized, placebo-controlled, double-blind, repeat dose escalation (phase 1b) study showed that omipalisib is reasonably well-tolerated in IPF patients.
- Target engagement has been demonstrated for omipalisib doses to which patients were exposed during this study.

**CC-90001**
- CC-90001 is a JNK1-biased inhibitor that has been tested in phase 1a and 1b trials.
- Shows a favorable safety profile and dose-dependent inhibition of UV-B induced phospho-c-Jun.
- JNK1-biased inhibitor should be further evaluated as a new therapeutic agent for IPF.

Expert comments

The approval of two antifibrotic drugs for IPF has triggered the development of new compounds in IPF.

N-acetylcysteine (NAC) is not completely ruled out as a treatment for IPF, as new results from the PANTHER trial show that subsets of IPF patients with specific gene polymorphisms may benefit from NAC monotherapy.

Several drugs for aerosolized administration are under investigation in phase I and phase II clinical trials.

Several studies confirmed the efficacy of immunosuppressants in the treatment of CTD-ILD, HP and LAM, in terms of stabilization of lung function decline.

HP = Hypersensitivity Pneumonitis, LAM = lymphangioleiomyomatosis
Registries in IPF
IPF-PRO registry | PROOF and Australian IPF registries

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### Current IPF-PRO registry outcomes

| Pulmonary hypertension (PH) in newly diagnosed patients with IPF<sup>1</sup> | • PH at baseline ~10% in the IPF Prospective Outcomes (IPF-PRO) registry  
• Associated with increased age (72 vs 70 years, p=0.021), lower DL<sub>CO</sub> (9.7 vs 12.5 mL/min/mmHg, p=0.041), supplemental oxygen use, and reduced HRQoL  
• Implications for screening and treatment if PH is found to be a distinct clinical phenotype |
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<td>Staging and patient-reported outcomes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• Differentiation of HRQoL, as defined by SGRQ or CASA-Q cough symptom score, was more precise with CPI than with the GAP staging system</td>
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| Characteristics of patients receiving anti-fibrotic therapy<sup>3</sup> | • In a US study, 232/419 patients were treated with nintedanib or pirfenidone; 187 untreated  
• Demographics of patient groups were similar at baseline, but anti-fibrotic treated patients tended to have worse DLco, symptoms, physical function and HRQoL than untreated patients at baseline |
| Frequency of diagnostic testing<sup>4</sup> | • In clinical practice, multidisciplinary diagnosis takes place only in a minority of cases  
• Repeat HRCTs are performed frequently and increase radiation exposure and costs |

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Further updated registry findings

**PROOF registry**

**Demographics and healthcare utilization**
- 93.4% of patients had definite IPF
- Most common symptoms were breathlessness, Velcro® crackles and cough
- Most frequently used medications at baseline were antifibrotics, anticoagulants, antithrombotics, statins, and antihypertensives
- 67.9% of hospitalizations were for respiratory reasons: median (range) duration of hospitalization was 5 (1-30) days

**Australian IPF registry**

**Patient reported outcome measures (PROMs) from 522 patients**
- Weak correlation between FVC% and SGRQ, USOB and depression, but no significant correlation with anxiety
- Milder disease correlated with better PROM scores
- Higher SGRQ (HR: 1.02 95% CI 1.01-1.03; p=0.002), USOB (HR: 1.16, 95% CI 1.07-1.25; p<0.001) and depression (HR: 1.16, 95% CI 1.01-1.12, p=0.019) were associated with increased mortality

1 Wuyts W.A. et al. AJRCCM; 2017: A1127; 2 Jo H.E. et al. AJRCCM; 2017: A1542, P895

USOB = UCSD Shortness Of Breath Questionnaire
Expert comments

Patient data collected by registries can be used to build predictive multivariate models for disease progression and outcome can be built based on this data.

Subgroup analyses give insights on factors that influence the likelihood of treatment initiation and treatment choice.

Data collected on hospitalizations, comorbidities, complications and quality of care, can help shape decision making in healthcare and change the approach to ILD treatment.
New data on antifibrotic treatments

New data on nintedanib | New data on pirfenidone in IPF | Antifibrotic treatments — comparison | New molecules | Non-IPF fibrosis
New data on nintedanib

New analyses  |  Long-term & real-world  |  Possible treatment in other ILDs
New analyses on nintedanib

**Hepatic safety**

- Patients with hepatic impairment have a higher systemic exposure to nintedanib as compared to healthy subjects
- A single dose of nintedanib 100 mg had an acceptable safety and tolerability profile in subjects with hepatic impairment
- Patients with low BSA (=BMI) have increased hepatotoxicity at a dose of 150 mg twice daily (Japanese study)

**Cardiovascular safety**

- Patients were excluded from the TOMORROW and INPULSIS trials if they had: myocardial infarction in the previous 6 months, unstable angina in the previous month, or stroke in the previous year
- Pooled analysis from these trials showed that incidence of major adverse cardiovascular (CV) events was similar in patients with higher CV risk and in patients with lower CV risk (at baseline) between the nintedanib and placebo groups

**Efficacy**

- The effect of nintedanib on FVC decline is similar with and without dose reductions or treatment interruptions
- Pooled INPULSIS data show that a higher proportion of patients treated with nintedanib than placebo had no decline or an improvement in FVC over 52 weeks

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Long-term and real-world data on nintedanib in IPF

Long-term data from INPULSIS-ON

- Analysis of INPULSIS-ON showed consistent treatment effect (FVC decline) of nintedanib over 2 years across various demographic and characteristic subgroups.\(^1\)
- Long-term efficacy was maintained in patients who required dose adjustment.\(^2\)

Real-world safety

- Retrospective analysis of data from 3 tertiary ILD centers in the UK (n=187) showed an acceptable safety profile of nintedanib in a real-world setting.\(^3\)

![Annual rate of FVC decline](image)

1 Kreuter M. et al. AJRCCM; 2017: A5397; 2 Crestani B. et al. AJRCCM; 2017: A5408; 3 Toellner H. et al. AJRCCM; 2027: A5384
Nintedanib in CTD-ILDs\(^1\)

- Nintedanib was found to inhibit immune-stimulating and pro-fibrotic mediators with relevance to connective tissue disease-associated interstitial lung disease (CTD-ILD) other than IPF in human blood peripheral blood mononuclear cells (PBMC).
- Clinical trials to further investigate the efficacy of nintedanib in CTD-ILDs such as SSc-ILD and RA-ILD (rheumatoid arthritis ILD) are currently ongoing:
  - **SENSCIS** trial: nintedanib in SSc-ILD (NCT02597933)
  - **PF-ILD** trial: nintedanib in non-IPF progressing fibrosis (NCT02999178)

1 Wollin L. et al. *AJRCCM*; 2017: A2450
New data on pirfenidone in IPF

Efficacy  |  Safety
Pirfenidone efficacy

New pooled analyses from ASCEND and CAPACITY

- Pirfenidone has clinically meaningful benefits for all-cause mortality (ACM) and FVC decline in patients with impaired lung function compared to placebo
  - Baseline %FVC <50% and/or
  - Baseline %DLCO <35%
- Analysis on quartile FVC changes at 3, 6, 9, and 12 months showed a consistent effect of pirfenidone versus placebo in reducing the decline in FVC in both patients in upper and lower quartile FVC decline at 12 months

1 Nathan S.D. et al. AJRCCM; 2017: A5390; 2 Bonella F. et al. AJRCCM; 2017: A5395
Safety data on pirfenidone

Real-world safety

- Pooled data from EAP (Expanded Access Program) and PASSPORT found that the long-term safety of pirfenidone in the overall population is consistent with the known safety profile\(^1\)
- A study\(^2\) (n=1009) found that **factors associated with pirfenidone discontinuation** are:
  - Female gender
  - Older age
  - COPD
  - Steroid use prior to study entry
- More **intense care monitoring and adverse-event management** for those subsets of patients may be appropriate to enable them to continue treatment\(^2\)

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**Observed ADR* rates (%)**

- Photosensitivity, 4.1
- Anorexia, 4.4
- Dyspnea, 6
- Dizziness, 6.2
- Decreased weight, 7.9
- Rash, 9.8
- Decreased appetite, 9.7
- GERD, 4.2
- Nausea, 21.7
- Fatigue, 18.9
- Diarrhea, 10.7

*ADR = Adverse Drug Reactions
GERD = GastroEsophageal Reflux Disease
Anti-fibrotic treatments — comparison
Real-world comparison of nintedanib and pirfenidone | Combined pirfenidone and nintedanib safety in IPF

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Comparing real-world data on antifibrotic treatments

- Nintedanib and pirfenidone are prescribed with nearly equal frequency and physicians’ selection was mainly based on side effect profile\(^3\). A study of 75 well-informed patients in the USA, however, revealed a 91% preference for nintedanib to pirfenidone as the initial agent.\(^5\)

- Compliance to antifibrotic treatments (nintedanib, pirfenidone) was found to be only 50-60%, indicating a high unmet need for better side effect management\(^1,4\).

- Treatment with nintedanib or pirfenidone was not associated with increased cardiac, bleeding or airways complications in patients who subsequently underwent lung transplantation\(^2\)

**Combined pirfenidone and nintedanib safety in IPF**¹

**Design**
- Phase IV single-arm, open-label study of pirfenidone and nintedanib co-administration (n=41)

**Safety profile**
- 85.4% (35 patients) completed 12 weeks of treatment
- 78.2% (32 patients) experienced treatment-related treatment-emergent adverse events (TEAEs; figure)

<table>
<thead>
<tr>
<th>Patients with at least one TEAE, n (%)</th>
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<tbody>
<tr>
<td><strong>All TEAE</strong></td>
</tr>
<tr>
<td>1 TEAE</td>
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<tr>
<td>1 serious TEAE</td>
</tr>
<tr>
<td><strong>Treatment related TEAEs</strong></td>
</tr>
<tr>
<td>1 TEAE</td>
</tr>
<tr>
<td>1 serious TEAE</td>
</tr>
<tr>
<td>Gastrointestinal TEAE</td>
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<tr>
<td>Hepatic TEAE</td>
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<tr>
<td>Photo sensitivity or rash</td>
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Combined use of pirfenidone and nintedanib in IPF did not suggest a different AE profile to that expected for either treatment alone.
New molecules
PBI-4050 + nintedanib and PBI-4425 | TD139
PBI-4050 and PBI-4425

PBI-4050 + nintedanib in IPF\(^1\)

- PBI-4050 (800 mg daily oral treatment) demonstrated a strong safety profile, either alone or in combination with nintedanib or pirfenidone in a phase 2a trial (figure)
- PBI-4050 alone and in combination with nintedanib demonstrated promising efficacy, in contrast to PBI-4050 + pirfenidone
- Further investigation of PBI-4050 alone and in combination with nintedanib is ongoing

PBI-4425\(^2,3\)

- Demonstrated direct inhibitory effect on human fibroblasts via collagen I and CTGF mRNA expression\(^2\)
- Showed potential as a novel treatment for emphysema and scleroderma in a mouse model\(^3\)

<table>
<thead>
<tr>
<th></th>
<th>Safe</th>
<th>Effective*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBI-4050</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PBI-4050 + nintedanib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PBI-4050 + pirfenidone</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>

12 week study

*Mean change in FVC from baseline

CTGF = Connective Tissue Growth Factor

1 Parker J. et al., AJRCCM; 2017: A7606; 2 Leduc M. et al., AJRCCM; 2017: A6360; 3 Gagnon L. et al., AJRCCM; 2017: A6454
TD139 in IPF

- TD139, an inhibitor of galectin-3, affecting TGF-β mediated signaling, was well tolerated and safe in patients with IPF (n=24, dosing: 0.3 mg, 3 mg, and 10 mg once daily for 14 days)
- Efficacy could be measured in terms of suppressed Gal-3 expression on bronchoalveolar lavage (BAL) macrophages
- A phase IIb study is planned in patients with IPF to further investigate the effects of TD139

1 Hirani N. et al., AJRCCM; 2017: A7560
Non-IPF fibrosis
Management of non-IPF fibrosis
## Management of non-IPF fibrosis

<table>
<thead>
<tr>
<th></th>
<th><strong>CYC</strong></th>
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<tbody>
<tr>
<td></td>
<td>• The utility of cyclophosphamide (CYC) in stabilizing lung function across a range of severe, <strong>progressive ILDs</strong> was confirmed in a retrospective analysis from the UK (n=307). Further studies such as RECITAL (NCT01862926) are needed to assess cyclophosphamide efficacy in ILDs.</td>
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<tr>
<th></th>
<th><strong>MMF</strong></th>
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<tbody>
<tr>
<td></td>
<td>• Mycophenolate (MMF) is associated with an improved course of FVC and DL(_{CO}) over 12 months in patients with <strong>SSc-ILD</strong> (n=148). This effect appeared more robust than that reported of cyclophosphamide (CYC) compared to placebo (SLS I). MMF is also well tolerated in <strong>chronic hypersensitivity pneumonitis</strong> (cHP) with a potential to stabilize lung function (n=38).</td>
</tr>
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<thead>
<tr>
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<th><strong>Sirolimus</strong></th>
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<tbody>
<tr>
<td></td>
<td>• Low dose sirolimus could stabilize lung function decline in patients with <strong>lymphangioleiomyomatosis</strong> (LAM) similar to the conventional dose, with a similar safety profile.</td>
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<th></th>
<th><strong>PPI</strong></th>
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<tbody>
<tr>
<td></td>
<td>• The MESA study found that proton pump inhibitor (PPI) use was associated with reduced percentage of <strong>high attenuation areas</strong> (HAA) in subclinical ILD, while histamine 2-receptor blockers (H2B) were not.</td>
</tr>
</tbody>
</table>

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Expert comments

Combined treatment with pirfenidone and nintedanib, which should be administered exclusively in a clinical trial setting, did not show a different AE profile in comparison to each treatment alone.

For non-IPF fibrosis there is an increasing number of observational studies and trials to assess the efficacy of immunosuppressants in SSc-ILD and hypersensitivity pneumonitis.
Predictors of disease progression, outcome and survival in ILD

Risk factors in IPF | FEV₁/FVC ratio and disease progression | New IPF staging | IPAF
Risk factors in IPF

Air pollution
- Increased exposure to ambient air pollution (NO₂, O₃, PM₂.₅ and PM₁₀) assessed by home monitoring (n=25) was shown to be associated with reduced FVC, worse dyspnea, and faster disease progression (figure)¹
- Exposure to dust contributes to the etiology of IPF (meta analysis of 14 case control studies, n=1949). Prevention by reducing workplace exposure could potentially attenuate up to 13% of IPF disease burden.²

Helicobacter pylori
- Helicobacter pylori serum antibody (≥2.3 U/ml) was identified as a risk factor for acute exacerbations in IPF (prospective study, n=142).³

FEV₁/FVC ratio and disease progression in IPF

• In a retrospective, post-hoc analysis of the RAINIER trial control arm (n=248) a prodromal decline in FVC% predicted over 14 weeks was identified as a risk factor for disease progression in IPF¹

• Patients who showed a 10% decline in FVC during the course of the PANTHER trial were selected (n=85). Time to 10% change in baseline FVC was compared to time to 10% change in baseline FEV₁/δFVC ratio (figure)²

A 10% decline in FEV₁/ δFVC ratio may be an earlier marker of disease progression in IPF than FVC alone.


δFVC = change in FVC
A new staging system for IPF patients

A new staging system for prediction of mortality in IPF was designed based on data from 65 patients in a retrospective analysis (2008-2015)\(^1\)

Predictors of mortality were:

- 1-year BMI (p=0.021)
- 1-year %FVC (p=0.005)
- respiratory hospitalization within one year of diagnosis (p<0.001)

The presence of autoantibodies is not correlated with survival in IPF patients\(^2\)

In the new staging system, patients are divided into 3 stages based on changes in BMI and %FVC (baseline value minus 1-year value) and respiratory hospitalization within 1-year\(^1\)

The new BFR* staging system showed a clear survival difference between stages in the analyzed cohort of IPF patients

* BFR: Body mass index forced vital capacity, and respiratory hospitalization

1 Kishaba T. ATS 2017: Oral presentation C14; 2 Goobie et al, AJRCCM ; 2017: A5443
Interstitial pneumonia with autoimmune features (IPAF)

Patients with IIP and undifferentiated CTD-ILD were assessed for IPAF criteria to characterize features and domains, comparing survival to other ILD cohorts

- 144/422 patients met with ERS/ATS proposed IPAF criteria (clinical, serological, and morphological aspects)
- IPAF was associated with a worse survival than CTD-ILD (p<0.001), but mildly improved compared to IPF
- IPAF with non-usual interstitial pneumonia (non-UIP) pattern was associated with improved survival compared to IPAF with UIP

% IPAF patients positive for each domain

- **Clinical IPAF domain (47-62.5%)**
  - Inflammatory arthritis
  - Reynaud's phenomena
  - Mechanic's hands

- **Serological IPAF domain (91.1-93.0%)**
  - Anti-tRNA-synthetase
  - Antinuclear antibody ≥1:320
  - Anti-Ro Anti (SSA)
  - Rheumatoid factor

- **Morphological IPAF domain (79.0-98.2%)**
  - Non-specific interstitial pneumonia pattern
  - Vasculopathy
  - Airways disease
  - Pleural disease

There is a need to better differentiate between IPAF and CTD-ILD patients using a more precise assessment of clinical, serological and morphological features

Expert comments

‘Influencers’ of disease progression in ILD have become an actively researched topic.

Autoantibodies appear to be common in IPF but were not correlated with survival or disease progression.

Interstitial pneumonia with autoimmune features (IPAF) is a new ‘research term’ identifying patients with initial diagnosis of idiopathic interstitial pneumonia (IIP) but positive autoimmune serology. Only a proportion of these IPAF patients develop a connective tissue disease (CTD) later on. Comparison of characteristics of IIP, IPAF and CTD-ILD patients will help to define the clinical meaning of IPAF.
IPF pathobiology and potential biomarkers in ILD

Omics | Microbiome | Genetic markers | Autoantibodies | New insights on candidate biomarkers

The preparation of the slide kit was sponsored by Boehringer Ingelheim International GmbH and contains personal opinions from leading ILD experts. ATS was neither author nor reviewer of the content. This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
# Omics in pulmonary fibrosis

While the ‘omics’ influence the pathogenesis of IPF, changes in a single omic can be a predictor for the disease

<table>
<thead>
<tr>
<th>Omic</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Genome</td>
<td>The genome is a driver of pulmonary fibrosis. Genes involved in epithelial integrity, such as desmoplakin (DSP) and DPP9, are associated with fibrosis due to deterioration of cell-cell adhesion which predisposes to injury in response to stimuli.¹</td>
</tr>
<tr>
<td>Transcriptome</td>
<td>A great therapeutic potential was identified for the microRNA, miR-29, in preclinical investigations. Intravenous delivery of a mir-29 mimic effectively attenuated late bleomycin-induced and adenoviral TGF-β1-mediated pulmonary fibrosis.²</td>
</tr>
<tr>
<td>Proteome</td>
<td>MZB1 was identified as a marker for fibrosis and correlates with deterioration in lung function.³</td>
</tr>
<tr>
<td>Metabolome</td>
<td>Increased activity of the glycolytic metabolism in the lung correlates with severity and mortality in idiopathic pulmonary fibrosis. Glycolytic enzymes are potential targets for future treatment.⁴</td>
</tr>
<tr>
<td>Mechanome</td>
<td>Alterations in the mechanical properties of tissues occur early in injury, therefore the mechanome is a driver for injury towards fibrosis. Promising candidates that might be involved in this process and need further investigation are integrins, FAK, Rho/ROCK, YAP/TAZ, MKL/MRTF, TRPV4.⁵</td>
</tr>
</tbody>
</table>

The microbiome in IPF

- The bacterial composition in IPF patients affects the host’s
  - transcriptome (changes in the expression of NLRC4, PGLYRP1, MMP9, DEFA4 and the antimicrobial peptides SLPI and CAMP)\(^1\)
  - immune response (down-regulation of NOD-, TOLL- and RIG1-like receptor immune response pathways)
  - progression-free survival\(^2\)
- Changes in the bacterial load are associated with acute exacerbations\(^3\)

In patients with IPF (n=60), compared to healthy controls (n=40), no significant difference in the community structure of the lower airways mycobiome could be determined\(^1\)

*Pneumocystis jirovecii* was identified in stable IPF (~4.7%, n=42) and AE-IPF (~33.3%, n=18) samples (>50% total reads), but not in control subjects and therefore requires further investigation\(^1\)

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Genetic markers in pulmonary fibrosis

Telomere length is not ruled out as a biomarker in pulmonary fibrosis

- IPF is a late-onset manifestation of telomere length and telomerase gene mutations\(^1\)
- Townsley et al. (2016) showed that androgens induce telomere elongation in patients with disorders involving very short telomeres\(^2\)
- This effect could not be confirmed via the gold standard method (flowFISH) of telomere length measurement\(^1,2\)

Although the efficacy of androgens could not be explained by their effect on telomere length, usage of telomere length as a biomarker in pulmonary fibrosis for precision medicine remains promising

MUC5B polymorphism: predictor of possible or definite UIP pattern in subpopulations\(^3\)

- Data from the AGES-Reykjavik (n=5,308) and COPDGene (n=9,292) cohort studies showed ILAs were associated with MUC5B polymorphism in subpopulations

### Presence of ILA

<table>
<thead>
<tr>
<th>Presence of ILA [%]</th>
<th>AGES-Reykjavik</th>
<th>COPDGene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>NHW</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>AA</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

NHW = Non-Hispanic Whites, AA = African-Americans, Association with MUC5B promoter polymorphism

Auto-antibodies as biomarkers in ILD

**MDA5-antibody**
- ILD patients with classic dermatomyositis (DM), clinically amyopathic DM (CADM) or features of the antisynthetase syndrome and pneumomediastinum should be tested for MDA5 antibody
- If test is positive prompt and aggressive immunosuppressive therapy is advised

**Serum KL-6**
- High serum KL-6 levels at baseline are associated with more severe lung function impairment in IPF and CTD-ILD
- Serum KL-6 level correlates with extensive disease on HRCT scan and may be a useful biomarker for predicting disease progression in SSc-ILD
- S100A12, a new IPF biomarker candidate, was more associated with prognostic variable than serum KL-6 or SP-D in IPF patients

1 Borker P. et al., AJRCCM 2017; A1579, 2 Morer L. et al., AJRCCM 2017; A5422, 3 Watanabe S. et al., AJRCCM 2017; A5424, 4 Yamamoto Y. et al., AJRCCM 2017; A5437
New insights on candidate biomarkers in IPF

### S100A12

- A calcium-binding protein secreted by neutrophils and related to production of pro-inflammatory cytokines
- Significantly elevated in IPF patients
- Positively correlates with GAP index, FVC, DL\textsubscript{CO} and mortality risk

### Adipokines

- Concentrations of serum \textit{adiponectin} and \textit{leptin} at AE-IPF (10.2 μg/mL, \textit{p}=0.007) were significantly higher than those in stable IPF (10.6 ng/mL, \textit{p}=0.027)
- Adipokines may be associated with poor prognosis in IPF patients with acute exacerbations

### CYFRA-21-1

- Baseline levels of CYFRA-21-1, a tumor tissue antigen, were prognostic and associated with mortality (\textit{p}<0.01; \textit{n}=180) in IPF

### BAL cytokines

- Stable and progressive IPF patients have different bronchoalveolar lavage fluid (BALF) profiles
- BAFF/IL-4R ratio higher in stable IPF
- VEGF-A/IL-8 ratio higher in progressive IPF

### Profibrotic cytokines

- Elevated plasma TGF-β1 levels predict both FVC and DL\textsubscript{CO} declines in IPF patients
- Elevated plasma CCL-18 levels predict decline in DL\textsubscript{CO}

### miRNA

- \textit{Mir-29b} levels are decreased in serum and lung of IPF patients in comparison to controls
- Lower Mir-29b levels are associated with decreased survival

---

Expert comments

To unravel the pathobiology of IPF, new aspects are being investigated within the ‘omics’ field: genome, transcriptome, metabolome, microbiome, exposome and mechanome.

Circulating and genetic biomarkers are considered the bridge to precision medicine and targeted treatment in ILD.

New findings that fungi (e.g. Pneumocistis jirovecii) could be involved in worsening of IPF, need further investigation.

Telomere length and telomerase activity have not been ruled out as genetic biomarkers, though their association to treatment response is controversial.

Autoantibody-positive serology in patients with idiopathic interstitial pneumonia represents a diagnostic dilemma, as they only give meaningful feedback in subsets of ILD patients.

Extracellular matrix stress results in profibrotic transcriptome changes and lung function impairment. Mechanical stress as measured with sophisticated tools and could act as an early biomarker of lung fibrosis.
Appendix and acknowledgments

Abbreviations | Summary of product characteristics | Acknowledgements

The preparation of the slide kit was sponsored by Boehringer Ingelheim International GmbH and contains personal opinions from leading ILD experts. ATS was neither author nor reviewer of the content. This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
**Abbreviations**

- 6MWD: 6-Minute Walk Distance
- 6MWT: 6-Minute Walk Test
- ACM: All-Cause Mortality
- ADR: Adverse Drug Reaction
- AE: Acute Exacerbation
- ANA: Anti-Nuclear Antibodies
- ATS: American Thoracic Society
- BAL: BronchoAlveolar Lavage
- BALF: BronchoAlveolar Lavage Fluid
- BMI: Body Mass Index
- BSA: Body Surface Area
- CAD: Coronary Artery Disease
- CADM: Clinically Amyopathic Dermatomyositis
- CASA-Q: Cough And Sputum Assessment Questionnaire
- cHP: Chronic Hypersensitivity Pneumonitis
- CPI: Composite Physiology Index
- CTD: Connective Tissue Disease
- CTGF: Connective Tissue Growth Factor
- CYC: Cyclophosphamide
- D1–CO: Diffusion capacity for Carbon monoxide
- DM: Dermatomyositis
- DSP: Desmoplastic
- DPP9: Dipeptidyl Peptidase 9
- EAP: Expanded Access Program
- EU: European Union
- ENA: Extractable Nuclear Antigens
- FEV₁: Forced Expiratory Volume in 1 second
- FVC: Forced Vital Capacity
- GAP: Gender, Age, and Physiology index
- GER: GastroEsophageal Reflux
- GERD: GastroEsophageal Reflux Disease
- HAD: Hospital and Anxiety Score
- HR: Hazard Ratio
- HRCT: High Resolution Computed Tomography
- HRQoL: Health-Related Quality of Life
- IIP: Idiopathic Interstitial Pneumonia
- ILD: Interstitial Lung Disease
- IPAF: Interstitial Pneumonia with Autoimmune Features
- IPF: Idiopathic Pulmonary Fibrosis
- K-BILD: King's Brief Interstitial Lung Disease Questionnaire
- KL: Krebs von den Lungen
- LAM: Lymphangioleiomyomatosis
- MDD: MultiDisciplinary Discussion
- MDI: Multidisciplinary Team
- MMF: Mycophenolate MoFetil
- MMP: Matrix MetalloProteinase
- MUC: MUCin
- NAC: N-Acetylcysteine
- NSCLC: Non Small Cell Lung Cancer
- PBMC: Peripheral Blood Mononuclear Cell
- PF: Pulmonary Fibrosis
- PH: Pulmonary Hypertension
- PM².₅: Particulate Matter (2.5 µm)
- pMDI: Pressurized Metered Dose Inhaler
- PRO: Patient-Reported Outcome
- QoL: Quality of Life
- SGRQ: St George’s Respiratory Questionnaire
- SNP: Single Nucleotide Polymorphism
- SP: Surfactant Protein
- Sc: Systemic Sclerosis
- TEAE: Treatment-Emergent Adverse Event
- TERT: Telomerase Reverse Transcriptase
- TGF: Transforming Growth Factor
- TOLLIP: TOLL-Interacting Protein
- UK: United Kingdom
- USOB: UCSD Shortness Of Breath Questionnaire
- VAS: Visual Analog Scale

- This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
Abbreviated summary of product characteristics

Ofev® 100 mg/150 mg soft capsules, for oral use. **Active substance:** Nintedanib. **Qualitative and quantitative composition:** One capsule contains 100 mg/150 mg nintedanib (as esilate). Excipient(s) with known effect: Each capsule contains 1.2 mg of soya lecithin./Each capsule contains 1.8 mg of soya lecithin. List of excipients: Capsule content: Triglycerides, medium-chain; hard fat; lecithin (soya) (E322). Capsule shell: Gelatin, glycerol (85%), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172). Printing ink: Shellac glaze, iron oxide black (E172), propylene glycol (E1520). **Indication:** Ofev® is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF). **Contraindications:** Hypersensitivity to nintedanib, peanut or soya, or to any of the excipients listed above.

**Pregnancy and breast feeding:** As nintedanib may cause foetal harm also in humans, it must not be used during pregnancy. There is no information on the excretion of nintedanib and its metabolites in human milk. Pre-clinical studies showed that small amounts of nintedanib and its metabolites (≤0.5% of the administered dose) were secreted into milk of lactating rats. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Ofev®.

**Effects on ability to drive and use machines:** Ofev® has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines during treatment with Ofev®.

**Adverse reactions:** Very common: Diarrhoea, nausea, abdominal pain, hepatic enzyme increased. Common: Weight decreased, decreased appetite, bleeding, vomiting, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, gamma-glutamyltransferase (GGT) increased. Uncommon: Thrombocytopenia, hypertension, pancreatitis, hyperbilirubinaemia, blood alkaline phosphatase (ALKP) increased. Not known (cannot be estimated from the available data): Drug-induced liver injury. Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, **ATC code:** L01XE31. **Mechanism of action:** Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. Nintedanib binds competitively and blocks the intracellular signalling.

**Warnings and precautions:** See SmPC. **Posology:** The recommended dose of nintedanib is 150 mg twice daily administered approximately 12 hours apart. The 100-mg twice-daily dose is only recommended to be used in patients who do not tolerate the 150-mg twice-daily dose. **Special populations:** Elderly patients: Patients ≥75 years may be more likely to require dose reduction to manage adverse effects. Renal impairment: The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min creatinine clearance). Hepatic impairment: Exposure increased in patients with hepatic impairment (Child Pugh A and Child Pugh B). In patients with mild hepatic impairment (Child Pugh A), the recommended dose of Ofev® is 100 mg twice daily approximately 12 hours apart. In patients with mild hepatic impairment (Child Pugh A), treatment interruption or discontinuation for management of adverse reactions should be considered. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Ofev® is not recommended. Paediatric population: The safety and efficacy of Ofev® in children aged 0-18 years have not been established. No data are available.

**Medicinal product subject to restricted medical prescription.** State of information: 2017-01-09. Further Information: See SmPC. **Distributed by:** Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany.

The state of the information is dated with the EU Commission Decision = 09 Jan 2017.
Acknowledgments

Boehringer Ingelheim would like to extend a special thank you to our ILD expert, Dr. Francesco Bonella, for the preparation of this report and his excellent guidance prior to and during the ATS 2017 in Washington, D.C.

We are also grateful to the many ILD experts who have given us kind permission to use content from presentation slides and posters displayed at the ATS 2017.

Boehringer Ingelheim GmbH – Corporate TA Respiratory

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infill healthcare communication GmbH, Germany

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