Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON

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Supplemental material

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A. Exclusion criteria for SENSCIS-ON

Patients who met any of the following criteria were not eligible:

1. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN)
2. Bilirubin >2 times the ULN
3. Creatinine clearance <30 mL/min calculated per Cockcroft-Gault formula
4. Clinically relevant anaemia
5. Bleeding risk, i.e. any of the following:
   a. Known genetic predisposition to bleeding
   b. Patients who required:
      i. Fibrinolysis, full-dose therapeutic anticoagulation
      ii. High-dose antiplatelet therapy
   c. Haemorrhagic central nervous system event after completion of the parent trial
   d. Any of the following after last treatment in the parent trial:
      i. Haemoptysis or haematuria
      ii. Active gastrointestinal bleeding or gastrointestinal ulcers
      iii. Gastric antral vale ectasia
      iv. Major injury or surgery
   e. Coagulation parameters: international normalised ratio >2, prolongation of prothrombin time and partial thromboplastin time by >1.5 time the ULN
6. New major thrombo-embolic events developed after completion of the parent trial:
   a. Stroke
   b. Deep vein thrombosis
   c. Pulmonary embolism
   d. Myocardial infarction
7. Major surgery (according to the investigator’s assessment) to be performed within the next 3 months

8. >12 weeks between last drug intake in SENSCIS, or >1 week between last nintedanib intake in the drug–drug interaction study, and initiation of nintedanib in SENSCIS-ON

9. Usage of any investigational drug after completion of the parent trial, or planned usage of an investigational drug during SENSCIS-ON

10. A disease or condition which in the opinion of the investigator may put the patient at risk or limit the patient’s ability to participate in this trial

11. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial patient or unlikely to complete the trial

12. Known hypersensitivity to nintedanib

13. Women who were pregnant, nursing, or who planned to become pregnant while in the trial

14. Previous enrolment in SENSCIS-ON
### B. Table S1. Baseline characteristics of patients in SENSCIS-ON in subgroups by mycophenolate use

|                        | Taking mycophenolate | Not taking mycophenolate |
|------------------------|----------------------|--------------------------|
|                        | Continued nintedanib | Initiated nintedanib     |
|                        | (n=105)              | (n=127)                  |
| Female, n (%)          | 74 (70.5)            | 94 (74.0)                |
| Age, years, mean (SD)  | 53.9 (10.8)          | 52.3 (11.9)              |
| Weight, kg, mean (SD)  | 72.5 (14.8)          | 72.2 (17.4)              |
| Body mass index, kg/m², mean (SD) | 26.7 (4.6) | 26.3 (5.5)                |
| Race, n (%)            |                      |                          |
| White                  | 87 (82.9)            | 99 (78.0)                |
| Asian                  | 7 (6.7)              | 17 (13.4)                |
| Black or African-American | 7 (6.7)        | 8 (6.3)                  |
| Other                  | 4 (3.8)              | 3 (2.4)                  |
| FVC, mL, mean (SD)     | 2379 (704)           | 2460 (863)               |
| FVC, % predicted, mean (SD) | 67.7 (16.8)   | 68.6 (18.7)              |
| mRSS, mean (SD)        | 9.6 (8.0)            | 8.9 (8.0)                |
| SGRQ total score, mean (SD) | 46.0 (21.0)   | 40.5 (22.4)              |
| UCLA SCTC GIT instrument total score, mean (SD) | 0.33 (0.33) | 0.38 (0.34)                |
C. Table S2. Bleeding and cardiovascular adverse events in SENSCIS and SENSCIS-ON

|                          | SENSCIS          | SENSCIS-ON       |
|--------------------------|------------------|------------------|
|                          | Nintedanib (n=288) | Placebo (n=288) | Continued nintedanib (n=197) | Initiated nintedanib (n=247) |
| Bleeding*                | 32 (11.1)        | 24 (8.3)        | 20 (10.2)          | 20 (8.1)          |
| Hypertension†            | 14 (4.9)         | 5 (1.7)         | 11 (5.6)          | 5 (2.0)          |
| Major adverse cardiovascular events‡ | 4 (1.4) | 5 (1.7) | 5 (2.5) | 5 (2.0) |
| Venous thromboembolism†  | 4 (1.4)          | 3 (1.0)         | 0                 | 1 (0.4)          |
| Haemorrhagic and ischaemic stroke† | 3 (1.0) | 1 (0.3) | 1 (0.5) | 1 (0.4) |
| Arterial thromboembolism† | 2 (0.7)         | 2 (0.7)         | 0                 | 1 (0.4)          |
| QT prolongation†         | 2 (0.7)          | 0               | 1 (0.5)          | 0                 |
| Myocardial infarction†   | 0               | 2 (0.7)         | 0                 | 1 (0.4)          |
| Cardiac failure†         | 1 (0.3)          | 1 (0.3)         | 4 (2.0)          | 2 (0.8)          |

Data are n (%) of patients with ≥1 such event reported over 52 weeks (or until 28 days after last drug intake if earlier in SENSCIS or until 7 days after last trial drug intake if earlier in SENSCIS-ON). *Based on pooled MedDRA terms. †Narrow standardised MedDRA query. ‡Based on fatal adverse events in the MedDRA system organ classes “cardiac disorders” and “vascular disorders”; any fatal and non-fatal events in the subordinate standardised MedDRA query “myocardial infarction” (broad); any fatal and non-fatal stroke events (based on selected MedDRA preferred terms); and the MedDRA preferred terms “sudden death”, “cardiac death” and “sudden cardiac death”.

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### D. Table S3. Serious adverse events (reported irrespective of causality) in SENSCIS and SENSCIS-ON

| Event                              | SENSCIS Nintedanib (n=288) | SENSCIS Placebo (n=288) | SENSCIS-ON Continued nintedanib (n=197) | SENSCIS-ON Initiated nintedanib (n=247) |
|------------------------------------|-----------------------------|--------------------------|----------------------------------------|----------------------------------------|
| Pneumonia                          | 8 (2.8)                     | 1 (0.3)                  | 8 (4.1)                                | 4 (1.6)                                |
| Dyspnoea                           | 3 (1.0)                     | 5 (1.7)                  | 2 (1.0)                                | 3 (1.2)                                |
| Pulmonary hypertension             | 4 (1.4)                     | 4 (1.4)                  | 4 (2.0)                                | 1 (0.4)                                |
| Liver injury                       | 0                           | 0                        | 0                                      | 4 (1.6)                                |
| Diarrhoea                          | 2 (0.7)                     | 2 (0.7)                  | 0                                      | 3 (1.2)                                |
| Skin ulcer                         | 1 (0.3)                     | 2 (0.7)                  | 3 (1.5)                                | 0                                      |
| Pulmonary arterial hypertension    | 3 (1.0)                     | 0                        | 1 (0.5)                                | 2 (0.8)                                |
| Drug-induced liver injury          | 1 (0.3)                     | 1 (0.3)                  | 0                                      | 3 (1.2)                                |
| Hepatic enzyme increased           | 0                           | 0                        | 0                                      | 3 (1.2)                                |
| Atrial fibrillation                | 1 (0.3)                     | 1 (0.3)                  | 1 (0.5)                                | 2 (0.8)                                |
| Pulmonary fibrosis                 | 3 (1.0)                     | 4 (1.4)                  | 0                                      | 2 (0.8)                                |
| Vomiting                           | 0                           | 2 (0.7)                  | 0                                      | 2 (0.8)                                |
| Pneumothorax                       | 1 (0.3)                     | 0                        | 0                                      | 2 (0.8)                                |
| Chest pain                         | 0                           | 0                        | 0                                      | 2 (0.8)                                |
| Cholelithiasis                     | 0                           | 0                        | 0                                      | 2 (0.8)                                |
| Basal cell carcinoma               | 1 (0.3)                     | 0                        | 0                                      | 2 (0.8)                                |
| Breast cancer                      | 0                           | 0                        | 2 (1.0)                                | 0                                      |
| Lung neoplasm malignant            | 0                           | 0                        | 2 (1.0)                                | 0                                      |

Serious adverse events were defined as adverse events that resulted in death, were life threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed to be serious for any other reason.

Serious adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events are shown based on single preferred terms. Data are n (%) of patients with ≥1 such event reported over 52 weeks (or until 28 days after last drug intake if earlier in SENSCIS or until 7 days after last trial drug intake if earlier in SENSCIS-ON). Events reported in ≥2 patients in either group in SENSCIS-ON are shown.
E. Table S4. Adverse events (reported irrespective of causality) in SENSCIS-ON by mycophenolate use at baseline

| Adverse event                  | Taking mycophenolate | Not taking mycophenolate |
|-------------------------------|----------------------|--------------------------|
|                               | Continued nintedanib | Initiated nintedanib     |
|                               | (n=105)              | (n=127)                  |
| Diarrhoea                     | 71 (67.6)            | 89 (70.1)                |
|                               | 63 (68.5)            | 81 (67.5)                |
| Nausea                        | 15 (14.3)            | 29 (22.8)                |
|                               | 17 (18.5)            | 31 (25.8)                |
| Vomiting                      | 11 (10.5)            | 30 (23.6)                |
|                               | 16 (17.4)            | 23 (19.2)                |
| Skin ulcer                    | 20 (19.0)            | 22 (17.3)                |
|                               | 16 (17.4)            | 21 (17.5)                |
| Nasopharyngitis               | 13 (12.4)            | 13 (10.2)                |
|                               | 15 (16.3)            | 20 (16.7)                |
| Upper respiratory tract infection | 18 (17.1)        | 16 (12.6)                |
|                               | 9 (9.8)              | 10 (8.3)                 |
| Cough                         | 16 (15.2)            | 15 (11.8)                |
|                               | 8 (8.7)              | 6 (5.0)                  |
| Weight decreased              | 8 (7.6)              | 16 (12.6)                |
|                               | 6 (6.5)              | 10 (8.3)                 |
| Abdominal pain                | 3 (2.9)              | 19 (15.0)                |
|                               | 3 (3.3)              | 14 (11.7)                |
| Liver test abnormalities      | 4 (3.8)              | 17 (13.4)                |
|                               | 18 (19.6)            | 31 (25.8)                |

Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events are shown based on single preferred terms except for "liver test abnormalities", which was based on the standardised MedDRA query "liver related investigations, signs and symptoms" (broad definition). Data are n (%) of patients with ≥1 such event reported over 52 weeks (or until 7 days after last trial drug intake if earlier). Events reported in >10% of patients in the continued nintedanib or initiated nintedanib groups in the overall population are shown.
F. Figure S1. Change from baseline in FVC (mL) over time in SENSCIS and SENSCIS-ON

| Week | Nintedanib in SENSCIS | Placebo in SENSCIS | Continued nintedanib in SENSCIS-ON | Initiated nintedanib in SENSCIS-ON |
|------|-----------------------|-------------------|------------------------------------|-----------------------------------|
| 0    | 0                     | 0                 | 0                                  | 0                                 |
| 2    | 0                     | 0                 | 0                                  | 0                                 |
| 4    | -20                   | -20               | -20                                | -20                               |
| 6    | -40                   | -40               | -40                                | -40                               |
| 8    | -60                   | -60               | -60                                | -60                               |
| 10   | -80                   | -80               | -80                                | -80                               |
| 12   | -100                  | -100              | -100                               | -100                              |
| 14   | -120                  | -120              | -120                               | -120                              |
| 16   | -140                  | -140              | -140                               | -140                              |
| 18   | -160                  | -160              | -160                               | -160                              |
| 20   | -180                  | -180              | -180                               | -180                              |
| 22   | -200                  | -200              | -200                               | -200                              |
| 24   | -220                  | -220              | -220                               | -220                              |
| 26   | -240                  | -240              | -240                               | -240                              |
| 28   | -260                  | -260              | -260                               | -260                              |
| 30   | -280                  | -280              | -280                               | -280                              |
| 32   | -300                  | -300              | -300                               | -300                              |
| 34   | -320                  | -320              | -320                               | -320                              |
| 36   | -340                  | -340              | -340                               | -340                              |
| 38   | -360                  | -360              | -360                               | -360                              |
| 40   | -380                  | -380              | -380                               | -380                              |
| 42   | -400                  | -400              | -400                               | -400                              |
| 44   | -420                  | -420              | -420                               | -420                              |
| 46   | -440                  | -440              | -440                               | -440                              |
| 48   | -460                  | -460              | -460                               | -460                              |
| 50   | -480                  | -480              | -480                               | -480                              |
| 52   | -500                  | -500              | -500                               | -500                              |

No. of patients
SENCSIS
Nintedanib 288 283 281 273 278 265 262 241
Placebo 288 283 281 280 283 280 268 257
SENCSIS-ON
Continued nintedanib 191 189 187 185 181 176
Initiated nintedanib 243 238 230 214 194 171

Patients who completed the SENCIS trial on treatment and attended a follow-up visit 28 days later were eligible to participate in SENCIS-ON. Baseline in SENCIS-ON was the last measurement on or before the date of first trial drug intake in SENCIS-ON.
G. Figure S2. Cumulative distribution of patients by change in FVC from baseline to week 52 of SENSCIS-ON

Absolute change from baseline in FVC % predicted at week 52
H. Figure S3. Change from baseline in FVC (mL) at week 52 in SENSCIS-ON by mycophenolate use at baseline

|                        | Taking mycophenolate | Not taking mycophenolate |
|------------------------|----------------------|--------------------------|
|                        | Continued nintedanib | Initiated nintedanib    |
|                        | n=94                 | n=93                     |
|                        | -47.3                | -22.1                    |
|                        |                      |                          |
|                        | Continued nintedanib | Initiated nintedanib    |
|                        | n=82                 | n=78                     |
|                        | -71.0                | -70.1                    |

Changes were based on data from patients with available data at baseline and at week 52.
I. Data availability

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (https://www.mystudywindow.com/msw/datasharing). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of informed consent.

Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing
J. SENSCIS-ON trial sites

Argentina: APRILLUS, Buenos Aires; CEMER-Centro Medico De Enfermedades Respiratorias, Buenos Aires; Hospital Militar Central Cirujano Mayor Dr. Cosme Argerich, Buenos Aires. Australia: St Vincent’s Hospital Melbourne, Fitzroy; Royal Adelaide Hospital, Adelaide; Liverpool Hospital, Liverpool; Royal Prince Alfred Hospital, Camperdown. Austria: Medical University of Innsbruck, Innsbruck. Belgium: UZ Leuven, Leuven; Centre Hospitalier Universitaire de Liège, Liège. Brazil: Edumed - Educacao e Saude SA, Curitiba. Canada: Hôpital du Sacré-Coeur, Quebec. Chile: Centro de Investigación del Maule, Talca; Hospital Clínico Regional de Concepción "Dr. Guillermo Grant Benavente", Concepción. China: Peking Union Medical College Hospital, Beijing; The First Hospital of China Medical University, Shenyang City; The First Hospital of Jilin University, Changchun City; West China Hospital, Chengdu City; Huashan Hospital, Fudan University, Shanghai; The First Affiliated Hospital of Anhui Medical University, Hefei City. Czech Republic: Institute of Rheumatology Prague, Prague. Denmark: Aarhus University Hospital, Aarhus; Odense University Hospital, Odense. Finland: HYKS, Keuhkosairauksien yksikkö, Helsinki; TYKS, Keuhkosairauksien klinikka, T-sairaala, Turku. France: CHU Rouen - Hôpital Charles Nicolle, Rouen; Hôpital Arnaud de Villeneuve, Montpellier; Hôpital Larrey, Toulouse; Hôpital Albert Calmette, Lille; Hôpital Hôtel-Dieu - CHU de Nantes, Nantes; CHRU LILLE - Hôpital Claude Huriez, Lille; Hôpital Pasteur, Nice; Hôpital Pontchaillou, Rennes; Hôpital Bichat, Paris; CHRU de Bretonneau, Tours; Groupement Hospitalier Est - Hôpital Louis Pradel, Bron; Hôpital Cochin, Paris; Hôpital Avicenne, Bobigny. Germany: Universitätsklinikum Schleswig-Holstein Campus Kiel, Kiel; Universitätsklinikum Münster, Münster; Universitätsklinikum Carl Gustav Carus der Technischen Universität Dresden, Dresden; Klinik Donaustauf, Donaustauf; Universitätsmedizin Greifswald, Greifswald; Universitätsklinikum Erlangen, Erlangen; Asklepios Kliniken Hamburg GmbH, Hamburg; Medizinische Hochschule Hannover, Hannover; Universitätsklinikum Tübingen, Tübingen; Thoraxklinik-Heidelberg GmbH am Universitätsklinikum, Heidelberg. Greece: General Hospital of Athens "Laiko", Athens. India: Getwell Hospital & Research Institute, Nagpur; Care Hospital, Banjara Hills, Hyderabad; Postgraduate Institute of Medical Education and Research, Chandigarh; SIR Gangaram Hospital, New Delhi; All India Institute of Medical Science, New Delhi; B.J. Medical College and Saseen General Hospital, Pune; Asthma Bhawan, Jaipur; Ramaiah Medical College and Hospitals, Bangalore; Nizam's Institute of Medical Sciences, Hyderabad. Israel: Sourasky Tel Aviv Medical Center Rheumatology Department, Tel Aviv; Rabin Medical Center Beilinson, Petah Tiqwa; Bnai Zion Medical Center, Haifa; Rambam Medical Center Rheumatology Department, Haifa. Italy: A.O. San Gerardo di Monza, Monza; Azienda Universitaria-Università La Sapienza, Roma; Università degli Studi di Padova, Padova; Università degli Studi di Genova, Genova; A.O Università – Università degli Studi della Campania Luigi Vanvitelli, Campania. Japan: Sapporo Medical University Hospital, Hokkaido; Toho University Omori Medical Centre, Tokyo; Nippon Medical School Hospital, Tokyo; St. Marianna University School of Medicine Hospital, Kanagawa; Kitasato University Hospital, Kanagawa; Kanagawa Cardiovascular and Respiratory Center, Kanagawa; Hamamatsu University Hospital, Shizuoka; Tosei General Hospital, Aichi; Osaka Medical College Hospital, Osaka; National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka; Kindai University Hospital, Osaka; National Hospital Organization Himeji Medical Center, Hyogo; Tokushima University Hospital, Tokushima; Kurume University Hospital, Fukuoka; Nagasaki University Hospital, Nagasaki; Saitama Medical University Hospital, Saitama; Institute of Rheumatology Tokyo Women's
