

## **SUPPLEMENTARY MATERIAL**

### **Safety and tolerability of nintedanib in patients with fibrosing interstitial lung diseases: post-marketing data**

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**Table S1. Characteristics of cases of diarrhoea.**

|                                   | N (%) of cases |
|-----------------------------------|----------------|
| Sex                               |                |
| Male                              | 49,800 (57.5)  |
| Female                            | 34,295 (39.6)  |
| Unknown                           | 2499 (2.9)     |
| Age, years                        |                |
| ≤17                               | 31 (0.0)       |
| ≥18 to ≤64                        | 14,777 (17.1)  |
| ≥65 to ≤74                        | 28,568 (33.0)  |
| ≥75 to ≤84                        | 27,038 (31.2)  |
| ≥85                               | 4198 (4.8)     |
| Unknown                           | 11,982 (13.8)  |
| Medications*                      |                |
| Acetylsalicylic acid              | 4372 (5.0)     |
| Comorbidities†                    |                |
| Hypertension                      | 3556 (4.1)     |
| Gastro-oesophageal reflux disease | 2234 (2.6)     |
| Drug hypersensitivity             | 2155 (2.5)     |

A total of 86,594 cases (comprising 118,399 events) were reported; 3030 (2.6%) of the 118,399 events were reported as serious.

\*Medications reported in ≥5% of cases are shown. Data on medications were missing for 74.6% of cases.

†Comorbidities reported in ≥2% of cases are shown. Data on comorbidities were missing for 77.2% of cases.

**Table S2. Characteristics of cases of serious liver enzyme and bilirubin elevations (including drug-induced liver injury).**

|                                   | <b>N (%) of cases</b> |
|-----------------------------------|-----------------------|
| Sex                               |                       |
| Male                              | 858 (55.0)            |
| Female                            | 626 (40.1)            |
| Unknown                           | 77 (4.9)              |
| Age, years                        |                       |
| ≤17                               | 1 (0.1)               |
| ≥18 to ≤64                        | 261 (16.7)            |
| ≥65 to ≤74                        | 596 (38.2)            |
| ≥75 to ≤84                        | 453 (29.0)            |
| ≥85                               | 61 (3.9)              |
| Unknown                           | 189 (12.1)            |
| Medications*                      |                       |
| Acetylsalicylic acid              | 153 (9.8)             |
| Omeprazole                        | 82 (5.3)              |
| Comorbidities <sup>†</sup>        |                       |
| Hypertension                      | 209 (13.4)            |
| Gastro-oesophageal reflux disease | 91 (5.8)              |
| Diabetes mellitus                 | 82 (5.3)              |

A total of 1561 cases (comprising a total of 1776 events) were reported.

\*Medications used in ≥5% of cases are shown. Data on medications were unknown/missing for 54.1% of cases.

<sup>†</sup>Comorbidities reported in ≥5% of cases are shown. Data on comorbidities were unknown/missing for 56.2% of cases.

**Table S3. Most common bleeding events.**

|                    | <b>N (%)</b> |
|--------------------|--------------|
| Epistaxis          | 2769 (22.9)  |
| Contusion          | 1511 (12.5)  |
| Haematochezia      | 1480 (12.2)  |
| Haemorrhage        | 770 (6.4)    |
| Haemoptysis        | 715 (5.9)    |
| Rectal haemorrhage | 693 (5.7)    |

A total of 9313 cases (comprising 12,091 events) were reported. Bleeding events were coded based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA preferred terms reported in >5% of bleeding events are shown.

**Table S4. Characteristics of cases of myocardial infarction.**

|                         | <b>N (%) of cases</b> |
|-------------------------|-----------------------|
| Sex                     |                       |
| Male                    | 926 (71.8)            |
| Female                  | 326 (25.3)            |
| Unknown                 | 37 (2.9)              |
| Age, years              |                       |
| ≥18 to ≤64              | 162 (12.6)            |
| ≥65 to ≤74              | 433 (33.6)            |
| ≥75 to ≤84              | 446 (34.6)            |
| ≥85                     | 80 (6.2)              |
| Unknown                 | 168 (13.0)            |
| Comorbidities*          |                       |
| Hypertension            | 156 (12.1)            |
| Coronary artery disease | 102 (7.9)             |
| Diabetes mellitus       | 76 (5.9)              |

A total of 1289 cases (comprising 1390 events) were reported.

\* Comorbidities reported in ≥5% of cases are shown. Data on comorbidities were missing for 62.1% of cases.

**Table S5. Characteristics of cases of ischaemic stroke.**

|                      | N (%) of cases |
|----------------------|----------------|
| Sex                  |                |
| Male                 | 802 (62.4)     |
| Female               | 448 (34.9)     |
| Unknown              | 35 (2.7)       |
| Age, years           |                |
| ≥18 to ≤64           | 111 (8.6)      |
| ≥65 to ≤74           | 354 (27.5)     |
| ≥75 to ≤84           | 541 (42.1)     |
| ≥85                  | 116 (9.0)      |
| Unknown              | 163 (12.7)     |
| Medications*         |                |
| Acetylsalicylic acid | 139 (10.8)     |
| Omeprazole           | 72 (5.6)       |
| Comorbidities†       |                |
| Hypertension         | 157 (12.2)     |

A total of 1285 cases (comprising 1448 events) were reported.

\*Medications used in ≥5% of cases are shown. Data on medications were missing for 63.8% of cases.

†Comorbidities reported in ≥5% of cases are shown. Data on comorbidities were missing for 64.4% of cases.

**Table S6. Characteristics of cases of venous thromboembolism.**

|                                   | N (%) of cases |
|-----------------------------------|----------------|
| Sex                               |                |
| Male                              | 508 (65.0)     |
| Female                            | 246 (31.5)     |
| Unknown                           | 27 (3.5)       |
| Age, years                        |                |
| ≥18 to ≤64                        | 116 (14.9)     |
| ≥65 to ≤74                        | 267 (34.2)     |
| ≥75 to ≤84                        | 250 (32.0)     |
| ≥85                               | 38 (4.9)       |
| Unknown                           | 110 (14.1)     |
| Medications*                      |                |
| Prednisolone                      | 62 (7.9)       |
| Acetylsalicylic acid              | 56 (7.2)       |
| Apixaban                          | 45 (5.8)       |
| Comorbidities†                    |                |
| Hypertension                      | 95 (12.2)      |
| Gastro-oesophageal reflux disease | 46 (5.9)       |

A total of 781 cases (comprising 866 events) were reported.

\*Medications used in ≥5% of cases are shown. Data on medications were missing for 58.4% of cases.

†Comorbidities reported in ≥5% of cases are shown. Data on comorbidities were missing for 60.1% of cases.

**Table S7. Most common gastrointestinal perforation events.**

|                              | <b>N (%)</b> |
|------------------------------|--------------|
| Intestinal perforation       | 77 (19.5)    |
| Gastric perforation          | 44 (11.1)    |
| Large intestine perforation  | 39 (9.9)     |
| Gastrointestinal perforation | 37 (9.4)     |
| Appendicitis perforated      | 33 (8.4)     |
| Anal fistula                 | 16 (4.1)     |
| Diverticular perforation     | 15 (3.8)     |
| Peritonitis                  | 14 (3.5)     |

A total of 356 cases (comprising 395 events) were reported. Gastrointestinal perforation events were coded based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA).

MedDRA preferred terms reported in  $\geq 3.5\%$  of gastrointestinal perforation events are shown.

**Table S8. Characteristics of cases of gastrointestinal perforation.**

|                                   | N (%) of cases |
|-----------------------------------|----------------|
| Sex                               |                |
| Male                              | 229 (64.3)     |
| Female                            | 112 (31.5)     |
| Unknown                           | 15 (4.2)       |
| Age, years                        |                |
| ≥18 to ≤64                        | 50 (14.0)      |
| ≥65 to ≤74                        | 114 (32.0)     |
| ≥75 to ≤84                        | 119 (33.4)     |
| ≥85                               | 15 (4.2)       |
| Unknown                           | 58 (16.3)      |
| Medications*                      |                |
| Acetylsalicylic acid              | 28 (7.9)       |
| Prednisone                        | 21 (5.9)       |
| Comorbidities†                    |                |
| Hypertension                      | 37 (10.4)      |
| Gastro-oesophageal reflux disease | 18 (5.1)       |

A total of 356 cases (comprising 395 events) were reported.

\*Medications used in ≥5% of cases are shown. Data on medications were missing for 60.7% of cases.

†Comorbidities reported in ≥5% of cases are shown. Data on comorbidities were missing for 59.3% of cases.