Acute exacerbations in the INPULSIS® trials of nintedanib in idiopathic pulmonary fibrosis

Supplementary material

Acute Exacerbation Questionnaire for Completion By The Investigators

Boehringer Ingelheim	BIBF 1120 BIBF 1120 in IPF	Patient worksheet
BI Trial No. 1199.34		Patient No.

Acute Exacerbation Questionnaire

After completion, please fax the questionnaire to Michèle BRUN at +33 326 504 500

AE Number
(Please report the AE Number specified on the corresponding AE page of the eCRF)

For how many days has the patient suffered from worsening of dyspnoea? ____ days

Is cough present?

No ☐ Yes ☐

Increased frequency
No ☐ Yes ☐

Increased severity
No ☐ Yes ☐

Is sputum present?

No ☐ Yes ☐

Increased sputum production
No ☐ Yes ☐

Is the patient receiving oxygen?

No ☐ Yes ☐

Start of nasal oxygen
No ☐ Yes ☐

Increased use of nasal oxygen
No ☐ Yes ☐

Does the patient have other symptoms?

Fever
No ☐ Yes ☐

Night sweats
No ☐ Yes ☐

Chest pain
No ☐ Yes ☐

Note that all signs or symptoms should be documented on the adverse event page of the eCRF.

Provide all reports and documentation which you consider important for the evaluation of the potential acute exacerbation, for review by the adjudication committee – including but not limited to:

- Radiology report of HRCT/chest X-ray/other radiology study (**mandatory**)
- Summary on clinical course (e.g. discharge summary) (**mandatory**)
- Laboratory results which are not captured in the central laboratory
- Cytology (e.g. sputum, BAL)
- Echocardiogram

Provide here any **additional information** which you consider important for the adjudication committee's review:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Are the protocol criteria for acute exacerbation of IPF fulfilled?

No ☐ Yes ☐

Signature **Date**

Acute Exacerbation Worksheet for Completion by Adjudication Committee Members (Individually)

Boehringer Ingelheim

BIBF 1120

Effect BIBF 1120 on FVC (pivotal)

Site No. ____

BI Trial No. 1199.32

Patient No. ____

ACUTE EXACERBATION ADJUDICATION WORKSHEET **AE number** ____

Unexplained worsening or development of dyspnea within 30 days ..... 0☐ no 1☐ yes

Source document available: _____

New diffuse pulmonary infiltrates on chest X-ray since last visit ..... 0☐ no 1☐ yes

Source document available: _____

New HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit ..... 0☐ no 1☐ yes

Source document available: _____

Infection as per routine clinical practice with microbiological studies when available ..... 0☐ no 1☐ yes

Source document available: _____

Alternative causes as per routine clinical practice, including left heart failure, pulmonary embolism or identifiable cause of acute lung injury ..... 0☐ no 1☐ yes

Source document available: _____

Decision of the adjudication committee:

Confirmed acute IPF exacerbation ..... 1☐

Suspected acute IPF exacerbation ..... 2☐

NOT acute IPF exacerbation ..... 0☐

IAC Member Signature _____ Date ____ ____ ____

Appendix E3. Acute Exacerbation Adjudication Form for Completion by the Adjudication Committee (Based on Collective Medical Judgment)

Boehringer Ingelheim

BIBF 1120

Effect BIBF 1120 on FVC (pivotal)

Site No. |_|_|_|_|_|

BI Trial No. 1199.32

Patient No. |_|_|_|_|_|

ACUTE EXACERBATION ADJUDICATION FORM **AE number** |_|_|

Unexplained worsening or development of dyspnea within 30 days..... 0☐ no 1☐ yes

New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit..... 0☐ no 1☐ yes

Infection as per routine clinical practice with microbiological studies when available..... 0☐ no 1☐ yes

Alternative causes as per routine clinical practice, including left heart failure, pulmonary embolism or identifiable cause of acute lung injury..... 0☐ no 1☐ yes

Decision of the adjudication committee:

Confirmed acute IPF exacerbation ..... 1☐

Suspected acute IPF exacerbation..... 2☐

NOT acute IPF exacerbation ..... 0☐

Unanimous decision 1☐ yes 2☐ no

Chairman Signature _____ Date |_|_| |_|_|_| |_|_|

Supplementary table E1. Baseline Characteristics of Patients Who Had or Did Not Have ≥1 Investigator-Reported Acute Exacerbation by Treatment

	Patients who had ≥1 investigator-reported acute exacerbation		Patients who did not have an investigator-reported acute exacerbation	
	Nintedanib (n=34)	Placebo (n=35)	Nintedanib (n=604)	Placebo (n=388)
Age, years, mean (SD)	70·0 (7·7)	68·3 (6·9)	66·4 (8·1)	66·9 (8.0)
Male	29 (85·3%)	29 (82·9%)	478 (79·1%)	305 (78·6%)
Race				
Asian	10 (29·4%)	10 (28·6%)	184 (30·5%)	118 (30·4%)
Other (White/Black/missing*)	24 (70·6%)	25 (71·4%)	420 (69·5%)	270 (69·6%)
Weight, kg, mean (SD)	76·8 (18·1)	76·6 (17·7)	79·4 (16·5)	78·8 (16·4)
Ex or current smoker	26 (76·5%)	27 (77·1%)	438 (72·5%)	274 (70·6%)
Concomitant medications				
Corticosteroids	6 (17·6%)	11 (31·4%)	130 (21·5%)	78 (20·1%)
Bronchodilators	4 (11·8%)	7 (20·0%)	125 (20·7%)	65 (16·8%)

Proton pump inhibitor or histamine receptor-2 blocker	14 (41·2%)	19 (54·3%)	230 (38·1%)	143 (36·9%)
Supplemental oxygen	10 (29·4%)	6 (17·1%)	47 (7·8%)	29 (7·5%)
Emphysema†	9 (26·5%)	13 (37·1%)	245 (40·6%)	153 (39·4%)
Honeycombing on HRCT	20 (58·8%)	19 (54·3%)	306 (50·7%)	222 (57·2%)
FVC, mL, mean (SD)	2342 (640)	2265 (600)	2734 (758)	2770 (814)
FVC, % predicted, mean (SD)	70·2 (15·0)	67·4 (14·4)	80·3 (17·6)	80·3 (18·2)
FEV_1/FVC ratio, %, mean (SD)	83·7 (5·7)	84·3 (5·6)	81·5 (5·8)	81·4 (6·0)
DL_{CO}, % predicted, mean (SD)	43·6 (16·6)	42·8 (18·1)	47·6 (13·3)	47·3 (12·9)
SGRQ total score, mean (SD)	46·7 (18·0)	51·4 (17·9)	39·1 (19·2)	38·5 (18·3)

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; SGRQ: St George's Respiratory Questionnaire.
Patients were categorised into subgroups depending on whether, between randomisation and the end of the post-treatment follow-up period, they experienced or did not experience an investigator-reported acute exacerbation. Values are n (%) unless otherwise stated.
*In France, regulation did not permit the collection of data on race. †Based on qualitative assessment of HRCT scans.

Supplementary table E2. Baseline Characteristics of Patients with ≥1 Adjudicated Confirmed or Suspected Acute Exacerbation or For Whom All Events Were Adjudicated as Not Acute Exacerbations

	Patients who had ≥1 event that was adjudicated as a confirmed or suspected acute exacerbation (n=39)	**Patients who had ≥1 event that was adjudicated and all events were adjudicated as not an acute exacerbation (n=36)**
Age, years, mean (SD)	69·3 (8·2)	68·0 (7·0)
Male	34 (87·2%)	28 (77·8%)
Race		
Asian	11 (28·2%)	12 (33·3%)
Other (White/Black/missing*)	28 (71·8%)	24 (66·7%)
Weight, kg, mean (SD)	75·7 (15·6)	76·3 (19·4)
Ex or current smoker	33 (84·6%)	23 (63·9%)
Concomitant medications		

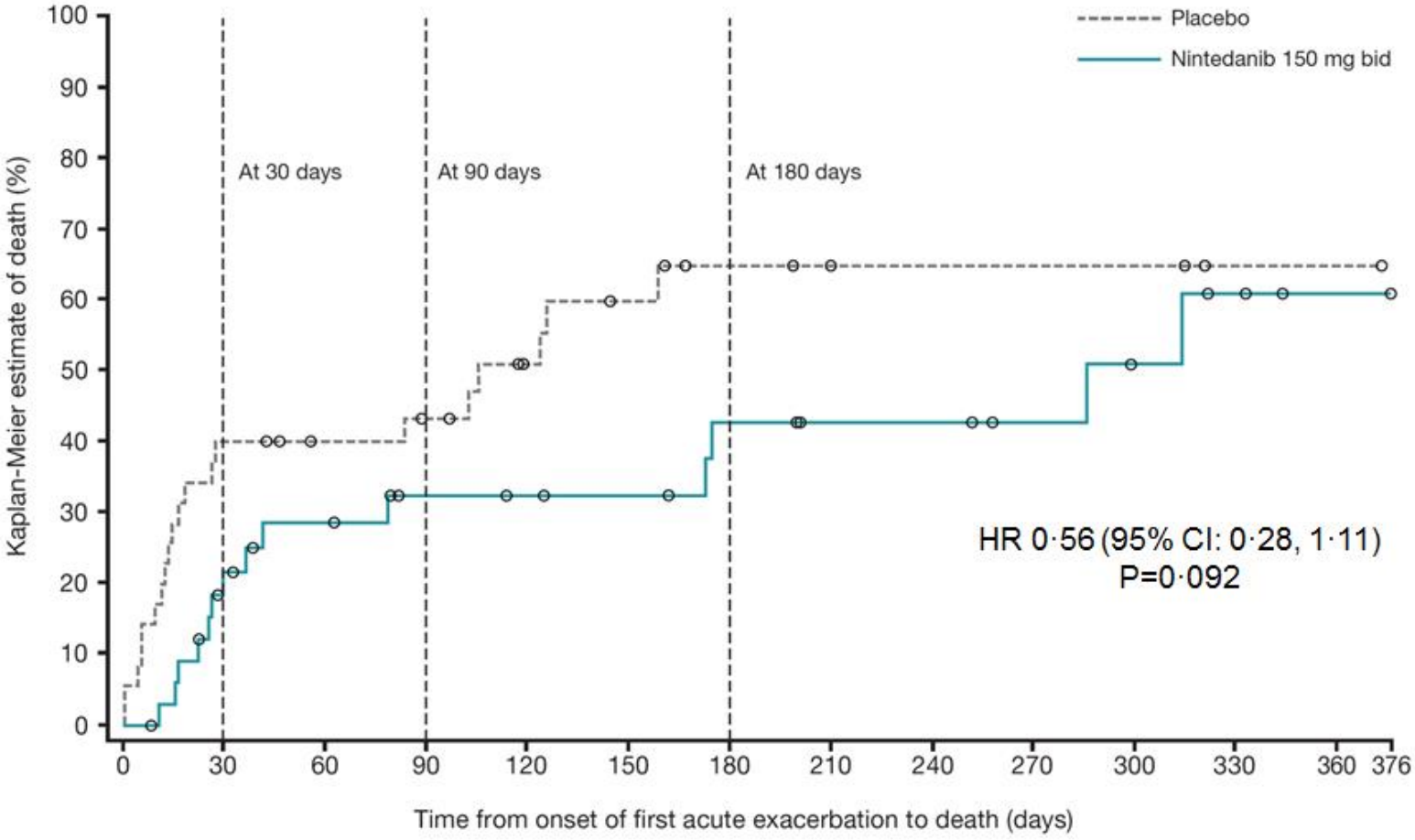
Corticosteroids	9 (23·1%)	12 (33·3%)
Bronchodilators	7 (17·9%)	9 (25·0%)
Proton pump inhibitor or histamine receptor-2 blocker	21 (53·8%)	15 (41·7%)
Supplemental oxygen	8 (20·5%)	9 (25·0%)
Emphysema[†]	14 (35·9%)	11 (30·6%)
Honeycombing on HRCT	23 (59·0%)	21 (58·3%)
FVC, mL, mean (SD)	2343 (580)	2266 (626)
FVC, % predicted, mean (SD)	69·5 (13·6)	68·6 (15·4)
FEV_1/FVC ratio, %, mean (SD)	83·5 (6·0)	84·2 (5·0)
DL_{CO}, % predicted, mean (SD)	44·3 (16·5)	41·8 (17·3)
SGRQ total score, mean (SD)	50·2 (16·6)	48·9 (19·8)

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; SGRQ: St George's Respiratory Questionnaire.
Patients were categorised into subgroups depending on whether, between randomisation and the end of the post-treatment follow-up period, they experienced at least one adjudicated confirmed or suspected acute exacerbation, or at least one event that was adjudicated with all events adjudicated as not an acute exacerbation.
Values are n (%) unless otherwise stated.
*In France, regulation did not permit the collection of data on race. [†]Based on qualitative assessment of HRCT scans.

Supplementary Figure E1. Time to Death Following Respiratory Events

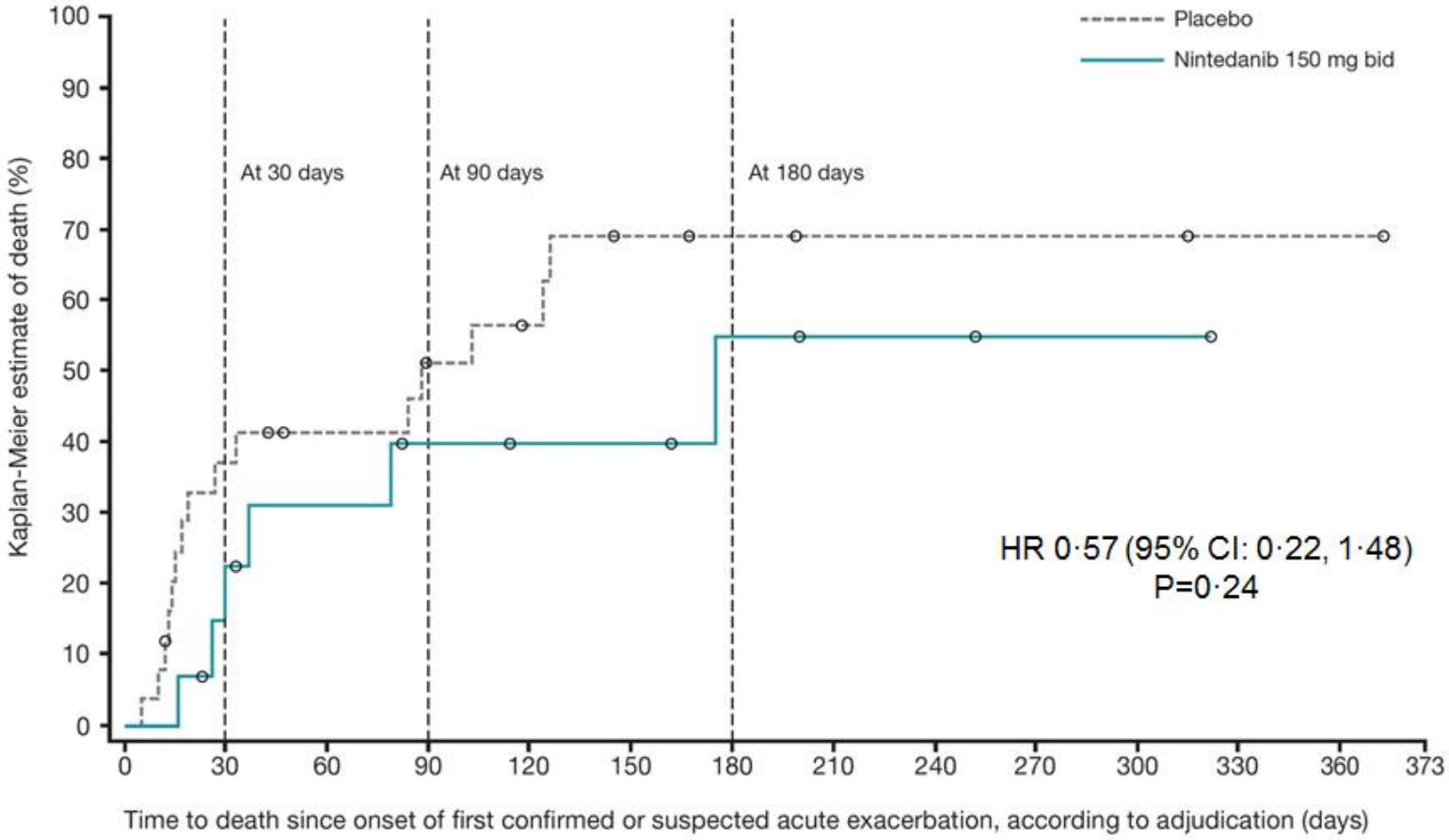
Figure legend: A) Investigator-Reported Acute Exacerbations, B) Adjudicated Confirmed/Suspected Acute Exacerbations, and C) Events Adjudicated as Not Acute Exacerbations. Analyses were conducted by treatment arm (nintedanib vs placebo).

A)



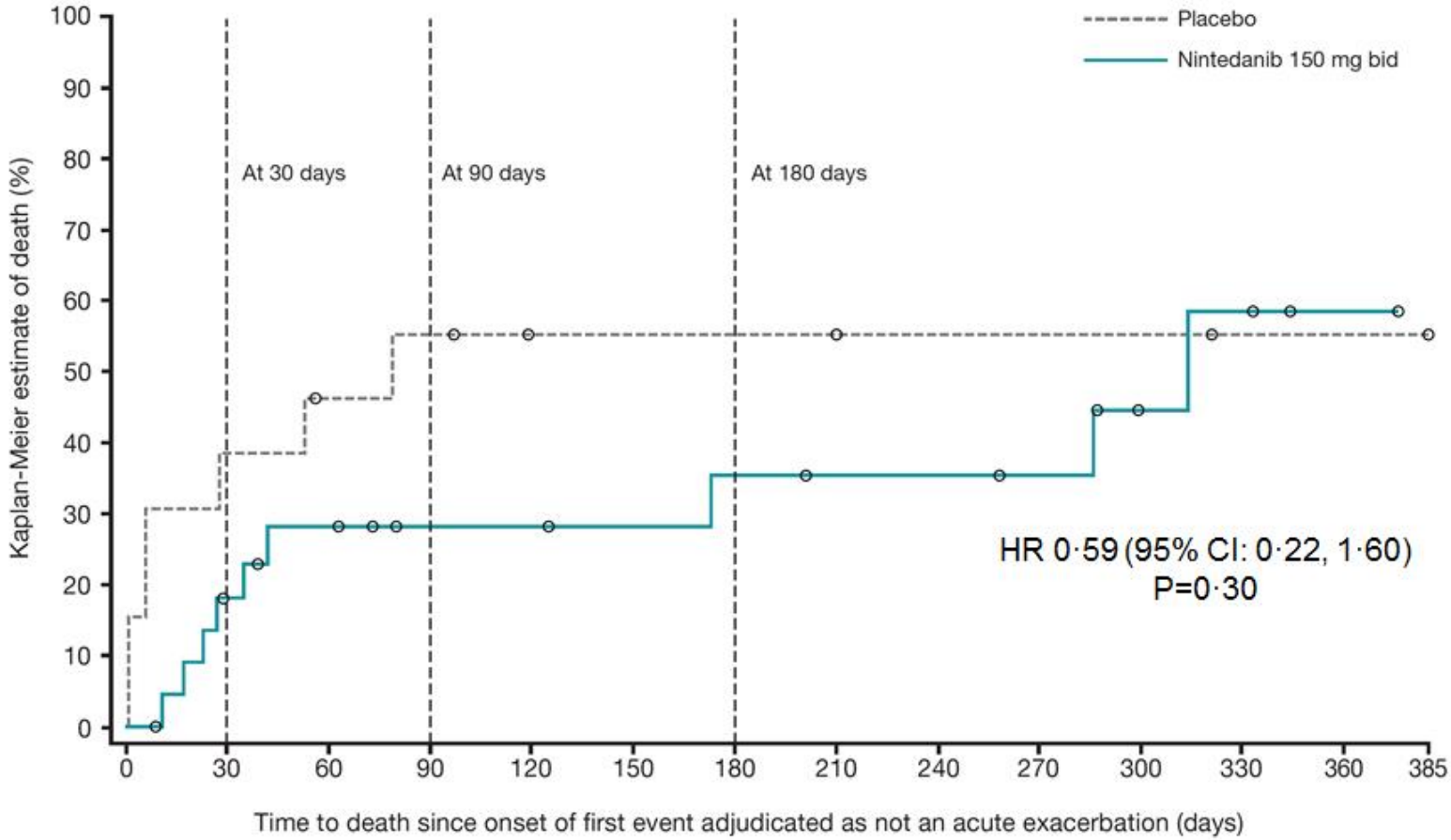
Number at risk													
Placebo	35	21	18	16	11	8	5	4	3	3	3	1	1
Nintedanib 150 mg bid	34	25	20	16	15	14	11	9	9	7	5	3	1	1

B)



Number at risk														
Placebo	25	15	12	9	7	4	3	2	2	2	2	1	1	1
Nintedanib 150 mg bid	14	11	8	6	5	5	3	2	2	1	1			

C)



Number at risk														
Placebo	13	8	6	5	3	3	3	3	2	2	2	1	1	1
Nintedanib 150 mg bid	23	17	14	11	11	10	9	8	8	7	4	3	1	