Official Title of Study:

A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of the Efficacy and the Safety and Tolerability of BMS-986278 in Participants with Pulmonary Fibrosis

NCT Number: NCT04308681

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Clinical Protocol IM027040

A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of the Efficacy and the Safety and Tolerability of BMS-986278 in Participants with Pulmonary Fibrosis

Short Title:

Phase 2 Study of the Efficacy and Safety of BMS-986278 in Pulmonary Fibrosis

Protocol Amendment 05

Incorporates Administrative Letter 05, 06, and 07

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DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Change
im027040-protamend05	22-Sep-2022	[redacted], Head of Clinical Development Immunology and Fibrosis	• Updated BMS Japan address. • Added clarifying sentence in Section 5.1 and 7.3.1 • Updated header and footnote c in Table 7. • Added clarifying text in Section 10.4.4.
im027040-admlet07	13-Jun-2022	[redacted] Clinical Scientist Team Lead BMS Immunology & Fibrosis Clinical Development	• Incorporated into im027040-protamend05.
im027040-admlet06	02-May-2022	[redacted] Clinical Scientist Team Lead BMS Immunology & Fibrosis Clinical Development	• Incorporated into im027040-protamend05.
im027040-admlet05	22-Feb-2022	[redacted] Clinical Scientist Team Lead BMS Immunology & Fibrosis Clinical Development	• Incorporated into im027040-protamend05.
im027040-admlet04-cn-specific	22-Dec-2021	[redacted] Medical Monitor	• Clarified 2 separate consistency errors in im027040-protamend01-cn (China-specific).
im027040-protamend04	21 Dec 2021	[redacted] Head of Immunology & Fibrosis Clinical Development Bristol-Myers Squibb	• Revised the PET tracer substudy to allow incorporation of participants with PF-ILD • Clarified phrasing in inclusion and exclusion criteria • Added 2 secondary endpoints evaluating the effect of BMS-986278 treatment
im027040-protamend01-cn China-specific	01 Nov 2021	[redacted] Head of Immunology & Fibrosis Clinical Development Bristol-Myers Squibb	• Removed biomarker assessments, Additional Research, and intensive PK substudy for all participants enrolled in mainland China. • Clarified objectives and endpoints for mainland China.
im027040-admlet03	13 Apr 2021	[redacted] Clinical Trial Physician	• Incorporated into im027040-protamend04

Document	Date of Issue	Approver(s)	Summary of Change
im027040-revprot03a-tw-specific	15 Mar 2021	[redacted] Clinical Program Lead - Fibrosis	• Removed eCOA measures from main study and optional treatment extension • Clarified language around dosing time and day collection prior to PK visits
im027040-admlet02	04 Mar 2021	[redacted] Clinical Trial Physician	• Incorporated into im027040-protamend04
im027040-revprot03	14 Jan 2021	[redacted] Clinical Program Lead - Fibrosis	• Updated sections throughout protocol to allow participants with PF-ILD to remain on stable background therapies. • Clarified restriction on concomitant use of anti-fibrotics during the main study. • Updated screening period from 28 to 42 days. • Updated several inclusion and exclusion criteria. • Added COVID-19-related risk assessment. • Added language for collecting AEs and SAEs related to COVID-19. • Added serum collections for possible assessments of SARS-CoV-2 serologic status and related exploratory objective and endpoint. • Added clinical laboratory sampling on Day 1 of the OTE. • Updated study treatment discontinuation criteria. • Added requirement to record date and time of last study treatment administration prior to PK study visits. • Modified language referring to number of participants enrolled per treatment arm in the PK substudy. • Revised language throughout protocol to provide sites more flexibility regarding order and timing of study procedures.

Document	Date of Issue	Approver(s)	Summary of Change
			• Clarified definitions for orthostatic hypotension and orthostatic tachycardia. • Clarified the Hepatitis B virus DNA serology testing. • Added AE intensity definitions. • Updated definitions for Full Analysis Set and Safety populations. • Clarified requirement for review of dosing diaries. • Added section for OTE rationale. • Revised language on nintedanib nonclinical toxicology. • Updated contact information for Clinical Trial Physician/Medical Monitor. • Added Clinical Scientist name and contact info to title page.
im027040-amend02-site-specific	22 Sep 2020	[redacted] Study Director	• Incorporated into im027040-revprot03
im027040-admlet01	17 Sep 2020	[redacted] Clinical Trial Physician	• Incorporated into im027040-revprot03
im027040-revprot02a-uk-specific	11 Sep 2020	[redacted] Clinical Program Lead - Fibrosis	• Incorporated into im027040-revprot03
im027040-revprot02	25 Jun 2020	[redacted] Clinical Program Lead - Fibrosis	• Changed Medical Monitor • Added an optional treatment extension for IPF and PF-ILD participants who complete the main study • Extended intensive PK substudy participation to the PF-ILD cohort

Document	Date of Issue	Approver(s)	Summary of Change
			and adjusted the number of participants to be included • Clarified the posttreatment HRCT requirement for the main study • Added spirometry measurements to Week 20 in the main study • Removed the FEF25-75 test from spirometry parameters • Added a sparse PK sample collection at the Week 4 visit in the main study • Modified the secondary and exploratory endpoints • Added a statistical analysis for the PF-ILD cohort once the cohort completes the main study • Incorporated changes requested by [redacted] Ethics Committee: o Added "end of study" definition o Excluded participants with total bilirubin greater than 1.5 x ULN and specified the range permitted for those with Gilbert's syndrome o Excluded participants with history of allergy to BMS-986278 or history of significant drug allergy o Clarified additional ECG assessments to be performed as clinically indicated o Added a caption title to create Table 10
im027040-amend01-site-specific	12 Mar 2020	[redacted] Clinical Development Team Lead - Fibrosis	Not applicable. PET-Tracer substudy will be conducted at selected US sites.
im027040-revprot01	24 Feb 2020	[redacted] Clinical Development Therapeutic Area Head, Fibrosis Bristol-Myers Squibb [redacted] Head of IMD Regulatory & Pharmaceutical Sciences Bristol-Myers Squibb	• Added Medical Monitor • Added eligibility check • Added pregnancy testing for women < 55 years of age [redacted] • Removed Study Acknowledgement/Disclosure page • Clarified drug dispensing frequency and treatment compliance check • Clarified when vital signs and orthostatic BP and HR will be measured

Document	Date of Issue	Approver(s)	Summary of Change
			• Removed approximate blood volumes to be collected throughout the study • Clarified when to withhold study treatment • Clarified "progression" definition for PF-ILD inclusion criteria • Lowered age limit for PF-ILD cohort • Broadened language about excluding significant lung disease from both cohorts • Permitted stable DMARD use for PF-ILD participants • Added HBcAb and pregnancy test, and removed cannabinoids from Laboratory Assessments
Original Protocol	07 Jan 2020	[redacted] Clinical Development Therapeutic Area Head, Fibrosis Bristol-Myers Squibb [redacted] Head of IMD Regulatory & Pharmaceutical Sciences Bristol-Myers Squibb	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 05

The primary purpose of this protocol amendment is to implement the following changes:

- Add clarification that the optional treatment extension (OTE) for the IPF and PF-ILD cohorts will be unblinded after the respective database locks occur at the end of Week 26 of the main study for each cohort.
- Clarify that select efficacy (eg, FVC) and safety data from the OTE portion of the IPF cohort will also be reviewed by the sponsor at the time of the IPF cohort main study database lock.
- Implement protocol changes from administrative letters 5, 6, and 7.
- Edits made to ensure clarity and alignment between sections and with previous protocol versions.

All changes applied to the body were applied to the synopsis, as necessary, although not all synopsis changes are included in the table below.

Generally, only major additions and deletions are provided in this summary of changes, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes are not included.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Cover Page	Updated BMS Study Director as described in im027040-admlet07 and updated BMS Japan address	To update the Study Director following a change in personnel and to change BMS address in Japan
2 Schedule of Activities, Table 2	Updated footnote c as described in im027040-admlet06	To rectify an inconsistency in the previous protocol version
5.1 Overall Design	Added clarifying sentence	To clarify that the OTE phase for IPF and PF-ILD cohorts will be unblinded after database lock at Week 26

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.3.1 Maintaining the Blind	Added clarifying sentence	Add clarification that the optional treatment extension (OTE) components of the study for the IPF and PF-ILD cohorts will be unblinded after the respective database locks occur at the end of Week 26 of the main study for each cohort. As such, when the IPF OTE becomes unblinded upon DBL for the IPF main study, the PF-ILD cohort will remain blinded until database lock at Week 26 for PF-ILD main study.
9.5 Pharmacokinetics	Corrected inconsistency between the previous protocol version and the participant's document as described in im027040-admlet05	To clarify that participants in the main study should also record date and time of morning and evening doses on the day prior to Week 12 study visit in addition to those of Weeks 4 and 26
9.5.2 Intensive PK Substudy, Table 7	Updated header and footnote c	To rectify an inconsistency in the previous protocol version
10.4.4 Other Analyses	Added clarifying text	Add clarification that the optional treatment extension (OTE) components of the study for the IPF and PF-ILD cohorts will be unblinded after the respective database locks occur at the end of Week 26 of the main study for each cohort.
APPENDIX 8: Site-specific Protocol for Qualified PET-tracer Sites in US Section 1.3, Table 1 Section 4.1, Figure 1	Updated screening period	To change screening period of the PET-tracer substudy

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of the Efficacy and the Safety and Tolerability of BMS-986278 in Participants with Pulmonary Fibrosis

Short Title:

Phase 2 Study of the Efficacy and Safety of BMS-986278 in Pulmonary Fibrosis

Study Phase:

Phase 2

Rationale:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease that is characterized by worsening dyspnea, cough, and progressive loss of lung function due to scar formation in the lung. The diagnosis of IPF is based on integration of clinical, radiologic, and when available, pathologic data to exclude known causes of usual interstitial pneumonia (UIP) (eg connective tissue disease or environmental exposure). BMS-986278, a lysophosphatidic acid receptor 1 (LPA_1) antagonist, is being developed for the treatment of patients with IPF. Lysophosphatidic acid (LPA) is a bioactive lysophospholipid that regulates numerous aspects of cellular function and has been recognized as a mediator of wound healing and tissue fibrosis. LPA signals through a family of G protein-coupled receptors designated LPA_{1-6}. LPA_1 antagonism inhibits the production of profibrotic matrix proteins, such as collagen.

Beyond IPF, some patients with other forms of chronic fibrotic interstitial lung disease (ILD) develop a progressive phenotype characterized by worsening respiratory symptoms, lung function, progressive fibrosis on imaging and early mortality. There is a high unmet need for effective and tolerable treatments for patients with non-IPF, fibrotic ILD that exhibit disease progression. Because of the clinical and pathophysiological similarities among these diseases, it has been suggested that such disorders have a common pathobiologic mechanism regardless of the cause – with resultant progressive lung fibrosis – and thus could have a response to similar treatment as IPF. Indeed, in the recently published INBUILD trial, patients with non-IPF, progressive fibrotic ILD (PF-ILD) with diverse etiologies were treated with nintedanib or placebo. Those treated with nintedanib had slower progression of lung fibrosis than those who received placebo, as demonstrated by a lower annual rate of decline in forced vital capacity (FVC) over the 52-week study period. The absolute treatment effects in the PF-ILD cohort were similar in magnitude to those observed in the pivotal INPULSIS trials that led to approval of nintedanib for treatment of IPF and based on data from the INBUILD trial, a number of health authorities have also approved nintedanib for patients with PF-ILD.

This study is the first evaluation of BMS-986278 in participants with pulmonary fibrosis. This study is designed to provide an initial evaluation of the efficacy of BMS-986278 in participants with IPF, further demonstrate the safety of BMS-986278, and provide information on

pharmacokinetics (PK) of BMS-986278 in participants with IPF. In addition, a secondary cohort consisting of PF-ILD participants will be enrolled, with the same schedule of activities and endpoints, in order to assess safety, tolerability, and efficacy of BMS-986278 in PF-ILD. The 2 cohorts (and subsets within the cohorts) will be analyzed separately.

Study Populations:

Eligible participants will be males and females 40 years of age and older with a diagnosis of IPF (primary cohort) or males and females 21 years of age and older with a diagnosis of PF-ILD (secondary cohort). Females must not be of childbearing potential, defined as being postmenopausal or surgically sterilized.

The primary cohort includes participants with IPF. Background standard of care (SOC) with either pirfenidone or nintedanib therapy is allowed. Randomization will be stratified by country (non-Japan versus Japan), and by concomitant use of approved IPF therapy (pirfenidone versus nintedanib versus none).

A separate population of participants with PF-ILD, will be enrolled in a secondary cohort. Although there is no global standard of care (SOC) for PF-ILD, participants in the PF-ILD cohort will be allowed to remain on stable background therapies commonly used as part of their usual care, including nintedanib, pirfenidone, and/or select immunosuppressive medications. Randomization within the PF-ILD cohort will be stratified by UIP pattern of lung injury (present versus absent) and by category of background therapy (ILD-targeted immunosuppression [ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus] alone versus anti-fibrotics [nintedanib, pirfenidone] with or without ILD-targeted immunosuppression versus no ILD-targeted immunosuppression or anti-fibrotics).

In order to augment knowledge about safety, tolerability, and efficacy of BMS-986278 in lung fibrosis patients, an optional treatment extension (OTE) will be offered to those participants that complete the 26-week main study.

Objectives and Endpoints:

Objective	Endpoint(s)
Primary	
• To evaluate the rate of change in percent predicted forced vital capacity (ppFVC) from baseline to Week 26 in IPF participants randomized to receive BMS-986278 at 30 mg or 60 mg twice daily (BID) compared to those randomized to receive placebo.	• Rate of change in ppFVC (%) from baseline to Week 26 in IPF participants
Secondary	
• To evaluate the safety and tolerability of BMS-986278 through 26 weeks of treatment by comparing results observed in participants with IPF and PF-ILD randomized to receive BMS-986278 at 30 mg or 60 mg BID with those	• Adverse events (AEs) • Serious AEs (SAEs) • AEs leading to early discontinuation of study treatment • Treatment-emergent deaths

Objective	Endpoint(s)
who receive placebo. The IPF and PF-ILD cohorts will be analyzed separately.	• Clinical laboratory findings • Electrocardiograms (ECGs) • Vital signs • Physical exam findings
• To evaluate the rate of change in ppFVC from baseline to Week 26 in PF-ILD participants randomized to receive BMS-986278 at 30 mg or 60 mg twice daily (BID) compared to those randomized to receive placebo.	• Rate of change in ppFVC (%) from baseline to Week 26 in PF-ILD participants
• To evaluate the effect of treatment with BMS-986278 on clinical assessments of lung fibrosis in IPF and PF-ILD participants randomized to receive BMS-986278 at 30 mg or 60 mg BID compared with participants randomized to receive placebo through Week 26. The IPF and PF-ILD cohorts will be analyzed separately.	• Proportion of participants with ≥ 10% absolute decline in ppFVC (%) at Weeks 4, 8, 12, 16, 20, and 26 • Proportion of participants with > 0% change in ppFVC at Weeks 4, 8, 12, 16, 20, and 26 • Time to first acute exacerbation • Time to first ≥ 10% absolute decline in ppFVC (%) • Absolute change in FVC (mL) from baseline to Week 26 • Absolute change in ppFVC (%) from baseline to Week 26 • Absolute change in single-breath diffusing capacity of carbon monoxide (DLCO SB) (mL/min/mmHg) (corrected for hemoglobin) from baseline to Week 26 • Absolute change in percent predicted single-breath diffusing capacity of carbon monoxide (ppDLCO SB) (%) (corrected for hemoglobin) from baseline to Week 26 • Change in walking endurance/distance from baseline at Week 26 as measured using the 6-minute walk test (6MWT) • Proportion of participants with acute exacerbations of lung fibrosis defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality, as follows: 1. Acute worsening or development of dyspnea (< 1 month duration) 2. Imaging with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern of lung fibrosis 3. Respiratory deterioration not fully explained by cardiac failure or fluid overload
• To characterize the pharmacokinetics (PK) of BMS-986278 in IPF participants.	• Cmax, Tmax, and AUC(0-8) on Day 1 and Week 4 and Ctrough on Week 4 and Week 12 of intensive PK substudy

Overall Design:

This is a Phase 2 randomized, double-blind, placebo-controlled clinical study investigating the efficacy and the safety and tolerability of BMS-986278 in participants with pulmonary fibrosis. In the primary cohort, a total of approximately 240 participants with IPF will be randomized to receive 30 mg or 60 mg BMS-986278 twice daily (BID) or placebo BID at a ratio of 1:1:1 for 26 weeks in the main study. Stable SOC background therapy for IPF with either nintedanib or pirfenidone will be allowed.

In the secondary cohort, a population of participants with PF-ILD, will be randomized and analyzed separately from the IPF cohort. In the PF-ILD cohort, a total of approximately 120 participants with PF-ILD will be randomized to receive 30 mg or 60 mg BMS-986278 BID or placebo BID at a ratio of 1:1:1 for 26 weeks. Participants with PF-ILD will be allowed to remain on stable background therapies commonly used as part of their usual care, including nintedanib, pirfenidone, and/or select immunosuppressive medications.

IPF and PF-ILD participants receiving 30 mg or 60 mg (or placebo) BMS-986278 BID in the main study who meet low blood pressure (BP) criteria may be dose reduced to 10 mg BMS-986278 BID (or placebo for 10 mg BID) (refer to Section 5.1.2.1).

A study schematic is provided in Section 2, and in Figure 1 for the IPF cohort and Figure 2 for the PF-ILD cohort. Following a screening period of up to 42 days, eligible participants with IPF or PF-ILD will be randomized to receive 1 of 2 dose levels of BMS-986278 (30 mg or 60 mg BID) or placebo for 26 weeks. In the IPF cohort, randomization will be stratified by country (non-Japan versus Japan) and according to concomitant use of approved IPF therapy (pirfenidone versus nintedanib versus none). In the PF-ILD cohort, randomization will be stratified by UIP lung injury pattern (present versus absent) and by category of background therapy (ILD-targeted immunosuppression [ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus] alone versus anti-fibrotics [nintedanib, pirfenidone] with or without ILD-targeted immunosuppression versus no ILD-targeted immunosuppression or anti-fibrotics).

All participants randomized in the main study will undergo safety, functional, quality-of-life, laboratory, PK, and biomarker assessments according to the Schedule of Activities (Table 1).

A 26-week OTE will be offered to IPF and PF-ILD participants that complete the 26-week main study. All participants will receive active treatment in the OTE. Participants who received 30 mg placebo tablets in the main study will be randomized to receive 30 mg or 60 mg BMS-986278 BID, and participants who received 30 mg or 60 mg BMS-986278 BID in the main study will continue with the assigned doses. Participants receiving 30 mg or 60 mg BMS-986278 BID in the OTE will remain blinded to study treatment until the database lock for analyses of the 26-week main study in IPF and PF-ILD cohorts, respectively. At the time of main study database lock in each cohort, the OTE will be unblinded for that cohort. Participants who dose reduced and received 10 mg BMS-986278 BID or placebo for 10 mg BMS-986278 BID in the main study will receive 10 mg BMS-986278 BID unblinded in the OTE. Participants receiving 30 mg or 60 mg BMS-986278 BID in the OTE who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID (refer to Section 5.1.2.1). See study schematic in Section 2 and in Figure 3.

All participants in the OTE will undergo safety, functional, quality-of-life, laboratory, PK, and biomarker assessments according to the Schedule of Activities (Table 2).

Blood Pressure Monitoring:

At all study visits, including the screening visit, participants will be carefully monitored for symptoms associated with low BP, assessed for orthostatic intolerance, orthostatic hypotension, orthostatic tachycardia, and asymptomatic parameters of low BP. Vital signs (including orthostatic assessments) will be performed as listed in the Schedule of Activities (Section 2). Refer to Section 5.1.2.1 for details on BP monitoring.

PK Assessments:

Participants will have PK samples collected as shown in Table 6. In addition, an intensive PK substudy will be conducted in approximately 10 participants per treatment arm in both the IPF and PF-ILD cohorts, for which additional PK samples will be collected and additional electrocardiogram (ECG), BP, and heart rate assessments will be performed, as shown in Table 7.

Positron Emission Tomography (PET) Tracer Substudy:

Participants in either cohort at selected sites will participate in a PET-Tracer substudy to evaluate the distribution of a radiolabeled analog of BMS-986278, [^{18}F]BMS-986327 in each dose group. The substudy is described in APPENDIX 8.

Clinical Outcome Assessments (COAs):

Patient experience data will be collected using the following COA measures in the main study:

- Living with Pulmonary Fibrosis Questionnaire (L-PF)
- St. George's Respiratory Questionnaire (SGRQ)
- University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ)
- Cough severity visual analog scale (VAS)
- Patient global impression of lung fibrosis symptom severity (PGI-S) and patient global impression of lung fibrosis symptom severity change (PGI-C)
- 6-minute walk test (6MWT)

In the OTE, patient experience data will continue to be collected with the L-PF, PGI-S, PGI-C, and 6MWT.

Posttreatment Follow-up:

At the end of treatment in the 26-week main study, participants that do not continue in the OTE will undergo a posttreatment follow-up visit which should occur 28 days (± 7 days) after the Week 26 visit.

At the end of treatment in the main study, participants that elect to continue in the OTE will receive active treatment within 1 to 15 days from the Week 26 visit. Study visits and procedures

during the OTE are described in the study design schematic (Figure 3) and the Schedule of Activities (Table 2).

Participants in the OTE that discontinue study treatment with BMS-986278 before Week 26 will complete the remaining study visits according to the Schedule of Activities (Table 2), including the post OTE treatment follow-up visit.

Number of Participants:

In the primary study population, a total of approximately 240 IPF participants will be randomized to receive 30 mg or 60 mg BMS-986278 BID or placebo BID at a ratio of 1:1:1.

In the secondary cohort, a total of approximately 120 PF-ILD participants will be randomized to receive 30 mg or 60 mg BMS-986278 BID or placebo BID at a ratio of 1:1:1.

Randomization and Duration:

In the primary cohort, eligible participants with IPF will be randomized to receive 1 of 2 dose levels of BMS-986278 (30 mg or 60 mg BID) or placebo at a ratio of 1:1:1 for 26 weeks in the main study. Randomization will be stratified by country (non-Japan versus Japan) and according to concomitant use of approved IPF therapy (pirfenidone vs nintedanib vs none).

In the PF-ILD cohort, eligible participants will be randomized to receive 1 of 2 dose levels of BMS-986278 (30 mg or 60 mg BID) or placebo at a ratio of 1:1:1 for 26 weeks in the main study. Randomization will be stratified by UIP lung injury pattern (present versus absent) and by category of background therapy (ILD-targeted immunosuppression [ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus] alone versus anti-fibrotics [nintedanib, pirfenidone] with or without ILD-targeted immunosuppression versus no ILD-targeted immunosuppression or anti-fibrotics).

For those participants that do not elect to continue in the OTE, the clinical study will last approximately 36 weeks including a 6-week screening period and a 4-week follow-up period.

For those participants that elect to continue in the OTE, the clinical study will last up to approximately 64 weeks (including the main study and the OTE). The main study will last up to approximately 32 weeks (including the 6-week screening period and a 26-week treatment period), and the OTE will last up to approximately 32 weeks (including a 1- to 15-day off-treatment period, a 26-week treatment period, and a 4-week post OTE treatment follow-up period).

Study Treatment for the Main Study:

Study Treatment for Study IM027040		
Study Treatment	**Potency**	**IP/Non-IP**
BMS-986278 oral tablet	10 mg	IP
BMS-986278 oral tablet	30 mg	IP
Placebo to match 10 mg oral tablets	NA	IP
Placebo to match 30 mg oral tablets	NA	IP

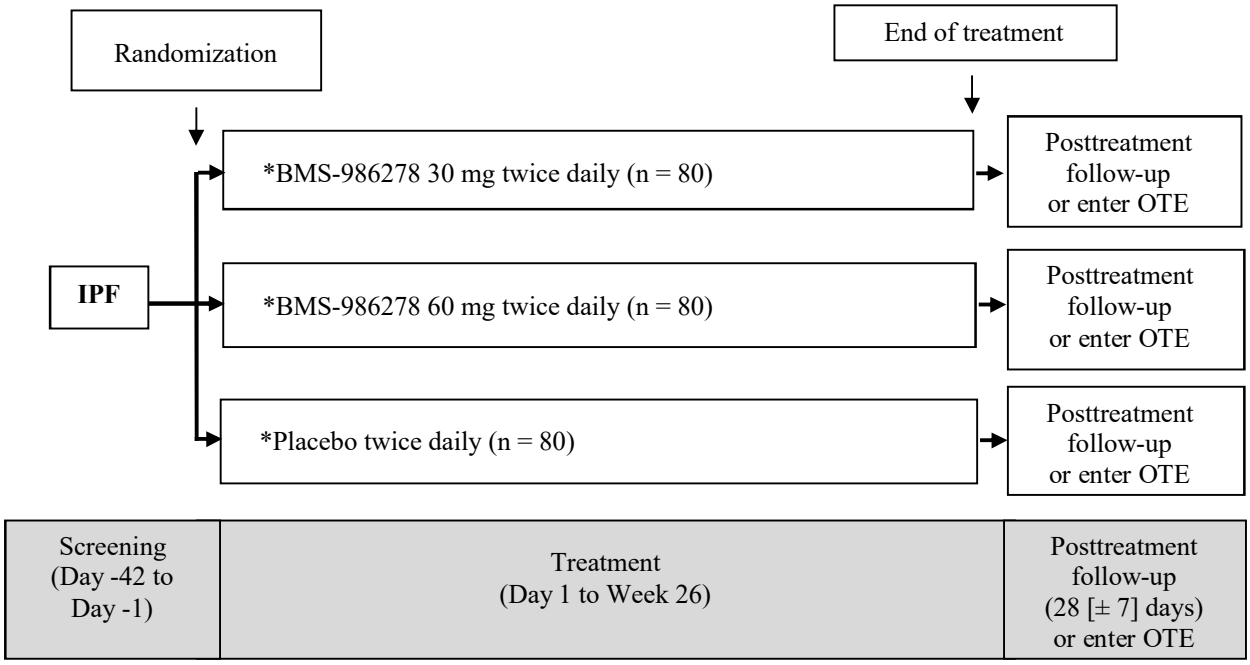
IP = investigational product; NA = not applicable; non-IP = noninvestigational product

In the OTE, participants will receive one of 3 active doses of BMS-986278 oral tablets: 30 mg BID, 60 mg BID, or 10 mg BID.

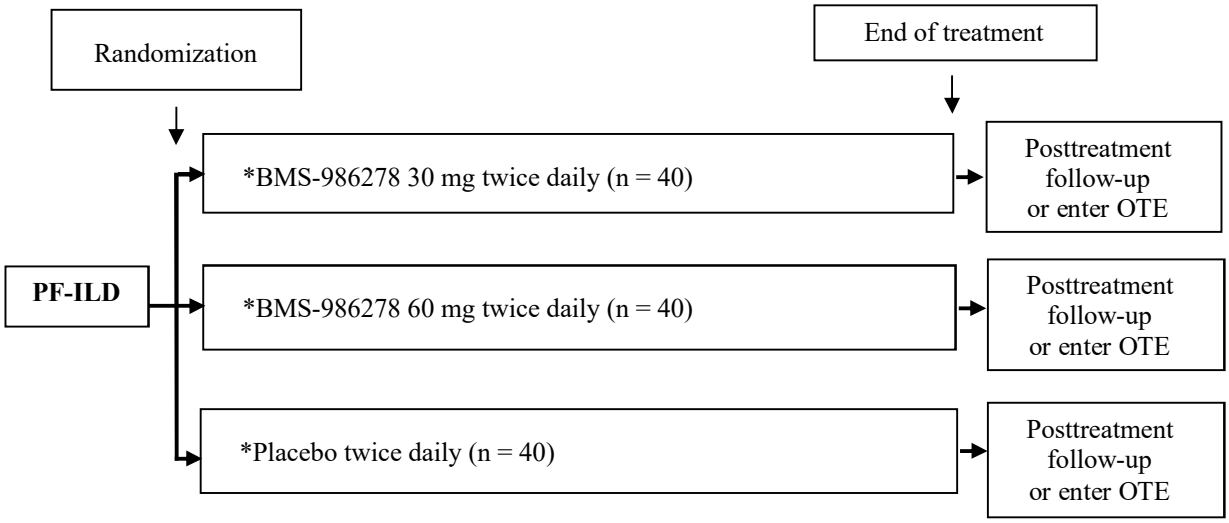
1.2 Schema

Following a screening period of up to 42 days, eligible participants with IPF or PF-ILD will be randomized in a 1:1:1 ratio to receive 1 of 2 dose levels of BMS-986278 (30 mg or 60 mg BID) or placebo for 26 weeks. Participants will then have the option to either end study treatment or continue in the OTE. Participants that opt to end study treatment will undergo a 4-week posttreatment follow-up. See page below for IPF and PF-ILD cohort study designs.

Study Design of IPF Cohort (Main Study):



Study Design of PF-ILD Cohort (Main Study):

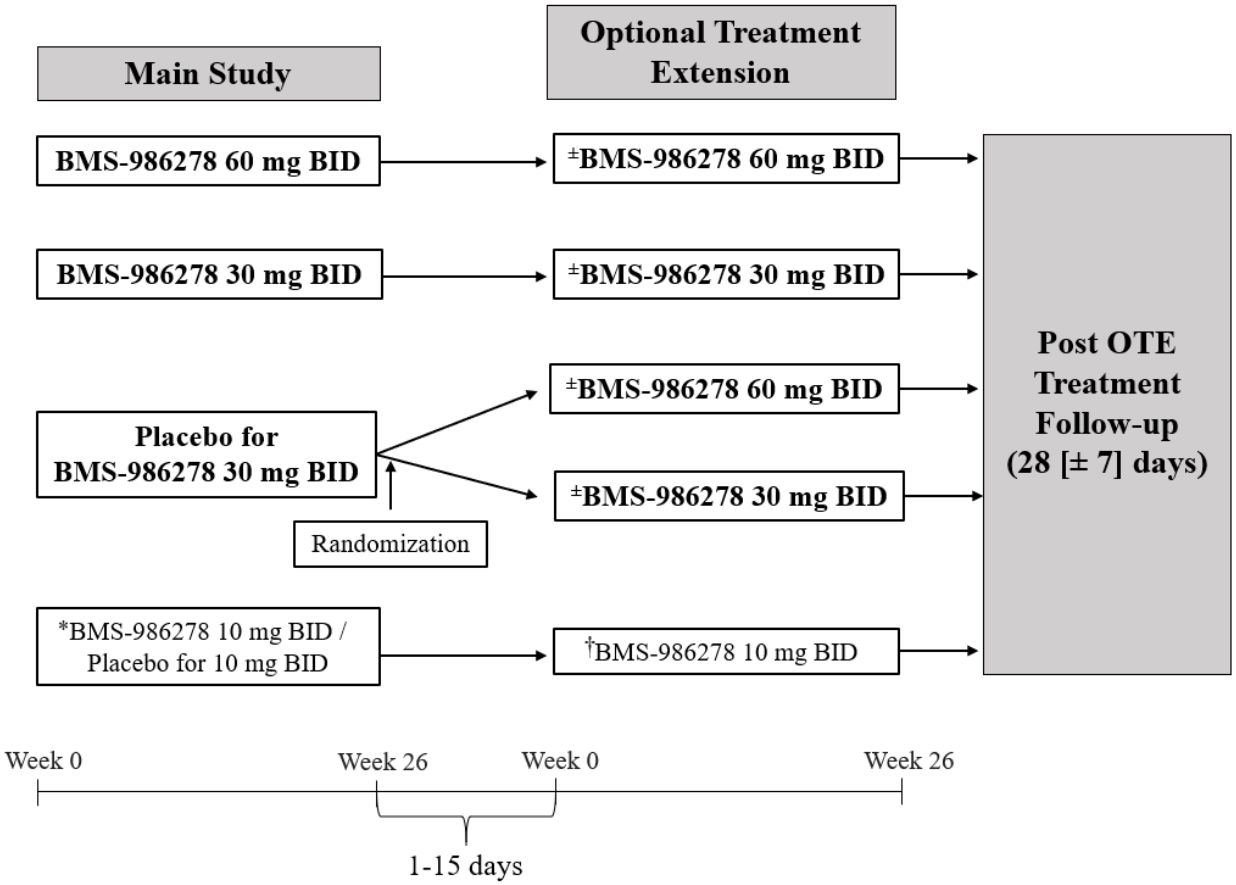


BID = twice daily; BP = blood pressure; IPF = idiopathic pulmonary fibrosis; OTE = optional treatment extension; PF-ILD = non-IPF, progressive fibrotic interstitial lung disease

* Participants receiving 30 mg or 60 mg (or placebo) BMS-986278 BID in the main study who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID (or placebo for 10 mg BID)

At the end of treatment in the 26-week main study, participants in the IPF and PF-ILD cohorts will have the opportunity to participate in the OTE. See below for the OTE study design.

Study Design of OTE (for each of the separate IPF and PF-ILD Cohorts):



BID = twice daily; IPF = idiopathic pulmonary fibrosis; OTE = optional treatment extension; PF-ILD = non-IPF, progressive fibrotic interstitial lung disease

* Participants that were dose-reduced in the main study

† Participants on 10 mg BMS-986278 BID are unblinded in the OTE

± Participants receiving 30 mg or 60 mg BMS-986278 BID in the OTE who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID

Data Monitoring Committee:

Study results will be monitored by an Independent Data Monitoring Committee (DMC); the scope of responsibility of the DMC will be outlined in the DMC Charter. Safety results will be reviewed by the DMC after approximately 30 randomized participants with either IPF or PF-ILD have completed at least 4 weeks after the first dose and at subsequent points outlined in the DMC Charter. Based on their reviews, the DMC will make recommendations to the sponsor on whether the study should be allowed to continue or be modified or terminated. Additional DMC meetings may also be scheduled to review the study data during the treatment period, as described in the DMC Charter.

Based on their overall benefit/risk evaluation, the DMC recommendations may include proceeding with the study without modification, proceeding with the study with modification, or study suspension. The scope, conduct, membership, processes, and accountabilities of the DMC are specified in the DMC Charter.

2 SCHEDULE OF ACTIVITIES (SOA)

All schedules of activities will be the same for the primary study cohort of IPF participants and for those in the PF-ILD secondary cohort.

Refer to Table 1 for the main study SOA and Table 2 for the OTE SOA.

In the event assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK and biomarker blood sampling will be done after the ECG and vital signs recordings have been conducted, with PK and biomarker blood sampling being performed as close to the planned time as possible. Clinical laboratory blood samples may be taken thereafter.

Table 1: Schedule of Activities for Study IM027040 (Main Study)

	Screening (Day -42 to Day -1)	Treatment (Day 1 to Week 26)[a]									Post-treatment follow-up[c] (28 ± 7 days after Week 26)	Notes
		Day 1	Day 2[b]	Day 8	Day 29	Day 57	Day 85	Day 113	Day 141	Day 183		
				Week 1 (± 3 days)	Week 4 (± 3 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 26 (+ 5 days)		
Informed consent	X											
Eligibility check	X	X										Predose on Day 1.
Medical and medication history	X											Including but not limited to oxygen use, hospitalizations, smoking history.
Demographics	X											
Hepatitis and HIV screening	X											See Section 9.4.4 and Table 5 for further details.
Test for drugs of abuse	X											See Section 9.4.4 and Table 5 for further details.
Pregnancy test		X										Urine pregnancy test prior to Day 1 dosing in women < 55 years of age. Pregnancy testing to be performed any time pregnancy is suspected during the study.
Blood sample for FSH	X											Postmenopausal women (< 55 years of age only) to confirm menopausal state (see APPENDIX 4).
Randomization		X										Randomization within 3 days prior to Day 1 is permitted.
Update medical and medication history		X										

Table 1: Schedule of Activities for Study IM027040 (Main Study)

	Screening (Day -42 to Day -1)	Treatment (Day 1 to Week 26)[a]									Post-treatment follow-up[c] (28 ± 7 days after Week 26)	Notes
		Day 1	Day 2[b]	Day 8 Week 1 (± 3 days)	Day 29 Week 4 (± 3 days)	Day 57 Week 8 (± 5 days)	Day 85 Week 12 (± 5 days)	Day 113 Week 16 (± 5 days)	Day 141 Week 20 (± 5 days)	Day 183 Week 26 (+ 5 days)		
Height and weight measurement	X	X					X			X		Height measured at screening only.
Laboratory/Safety Assessments												
12-lead ECG	X	X			X		X			X		All ECGs must be performed prior to bronchodilator administration OR at least 20 hours after bronchodilator administration. ECG on Day 1, Weeks 4 and 12 to be collected before morning dosing. See Section 9.4.3 for further details.
Serial ECG for participants enrolled in intensive PK substudy		See notes.										Intensive PK substudy only. According to schedule in Table 7.
Clinical laboratory samples	X	X		X	X	X	X	X	X	X	X	Hematology, chemistry, and urinalysis.
Physical examination	X	X			X		X			X	X	
Vital signs for all participants	X	X[d]	X	X	X	X	X	X	X	X	X	Predose vital signs include body temperature, respiration rate, and orthostatic BP and HR. Refer to Section 9.4.2 for further details on vital signs.

Table 1: Schedule of Activities for Study IM027040 (Main Study)

	Screening (Day -42 to Day -1)	Treatment (Day 1 to Week 26)[a]									Post-treatment follow-up[c] (28 ± 7 days after Week 26)	Notes
		Day 1	Day 2[b]	Day 8 Week 1 (± 3 days)	Day 29 Week 4 (± 3 days)	Day 57 Week 8 (± 5 days)	Day 85 Week 12 (± 5 days)	Day 113 Week 16 (± 5 days)	Day 141 Week 20 (± 5 days)	Day 183 Week 26 (+ 5 days)		
												During post-Day 1 visits, additional BP monitoring is required (similar to Day 2 visit) if either *asymptomatic* or *symptomatic* low BP criteria are met, as specified in Section 5.1.2.1.
Orthostatic evaluations	See notes.											At every visit, including screening, symptoms that could indicate the presence of orthostatic intolerance, orthostatic hypotension, and orthostatic tachycardia will be gathered. Refer to section 9.4.2 and section 5.1.2.1 further details on orthostatic evaluations.
Serial BP and HR for participants enrolled in intensive PK substudy		See notes.										Intensive PK substudy only. According to schedule in Table 7.
Pharmacokinetic and Biomarker Assessments												
Blood samples for sparse PK profiling		See notes.										According to schedule in Table 6.
Blood samples for intensive PK profiling		See notes.										Intensive PK substudy only. According to schedule in Table 7.

Table 1: Schedule of Activities for Study IM027040 (Main Study)

	Screening (Day -42 to Day -1)	Treatment (Day 1 to Week 26)[a]									Post-treatment follow-up[c] (28 ± 7 days after Week 26)	Notes
		Day 1	Day 2[b]	Day 8 Week 1 (± 3 days)	Day 29 Week 4 (± 3 days)	Day 57 Week 8 (± 5 days)	Day 85 Week 12 (± 5 days)	Day 113 Week 16 (± 5 days)	Day 141 Week 20 (± 5 days)	Day 183 Week 26 (+ 5 days)		
Blood samples for biomarkers		See notes.										See Section 9.6 and Table 9 for further details.
Efficacy-related Assessments												
HRCT	X									X		Screening HRCT must be read by central reader before randomization. See Section 9.1.3 and Section 6.4.1 for further details.
Spirometry[e]	X	X			X	X	X	X	X	X		See Section 9.1.1 for further details.
DLCO SB	X	X					X			X		See Section 9.1.2 for further details.
Clinical Outcome Assessments (COAs)												
L-PF		X					X			X		If possible, eCOAs should be administered using the electronic device prior to other study related procedures (except for the Day 1 visit where COAs should be administered after vital signs and ECG).
SGRQ		X					X			X		
UCSD SOBQ		X					X			X		
Cough VAS		X					X			X		
PGI-S		X					X			X		
PGI-C							X			X		
6MWT		X					X			X		If possible, to be administered after eCOAs. Separate instructions on the 6MWT will be provided. See Section 9.1.4.6 for further details.

Table 1: Schedule of Activities for Study IM027040 (Main Study)

	Screening (Day -42 to Day -1)	Treatment (Day 1 to Week 26)[a]									Post-treatment follow-up[c] (28 ± 7 days after Week 26)	Notes
		Day 1	Day 2[b]	Day 8 Week 1 (± 3 days)	Day 29 Week 4 (± 3 days)	Day 57 Week 8 (± 5 days)	Day 85 Week 12 (± 5 days)	Day 113 Week 16 (± 5 days)	Day 141 Week 20 (± 5 days)	Day 183 Week 26 (+ 5 days)		
O2 Titration Test	X											An oxygen titration test is required for all participants at screening.
Study Treatment/Concomitant Medication												
Dispense study treatment		Participants will receive study treatment twice daily for a total of 26 weeks (from Day 1 to Day 182 of Week 25). At every study visit, morning administration of study treatment will occur at the clinical research site. Fed/fasted status and time of meal (if fed) at every visit must be recorded on the case report form. A sufficient study treatment supply will be dispensed to each participant at every scheduled study visit, except for the Day 8 visit. New study treatment supplies will be provided to those participants whose dose is reduced (see Section 7).										Any leftover study treatment should be returned to the site for the drug accountability. Treatment compliance should be performed at each study visit between Day 29 (Week 4) and Week 26. Treatment compliance will also be performed at the time of dose reduction or dose discontinuation (if applicable).
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	Collected throughout the study.
Adverse Events												
Adverse events		See notes.										Collected from first dose and throughout the study.
Serious adverse events	See notes.											Serious adverse events to be recorded starting from the time of informed consent until 30 days from last visit.

6MWT = 6-Minute Walk Test; BP = blood pressure; DLCO SB = single-breath diffusing capacity of carbon monoxide; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; HRCT = high-resolution computed tomography; L-PF = Living with Pulmonary Fibrosis Questionnaire; O2 = oxygen; OTE = optional treatment extension; PGI-C = patient global impression of lung fibrosis symptom severity change; PGI-S =

patient global impression of lung fibrosis symptom severity; SGRQ = St. George's Respiratory Questionnaire; UCSD SOBQ = University of California San Diego Shortness of Breath Questionnaire; VAS = visual analog scale

[a] Visit windows may be extended to accommodate participants' schedules on a case-by-case after consultation with the Medical Monitor.

[b] Participants will only attend the Day 2 visit if required due to defined low BP criteria being met on Day 1. If dose reduction is decided on or after the Day 8 visit, the participant is required to follow the Day 2 BP monitoring instructions at the site (see Section 5.1.2.1).

[c] Only participants that choose not to enter the OTE will attend the posttreatment follow-up visit in the main study.

[d] In addition to the predose measurements, orthostatic BP and HR will be performed at 1.5, 2, and 4 hours post dose on Day 1 for all participants. Refer to BP monitoring in Section 5.1.2.1.

[e] Measurements must be performed more than 6 hours after administration of short-acting β-agonists or anticholinergics, at least 12 hours after administration of a long-acting bronchodilator, and at least 24 hours after administration of longer-acting agents.

Table 2: Schedule of Activities for Study IM027040 (Optional Treatment Extension)

	Treatment (Day 1 to Week 26)[a]						Post OTE treatment follow-up (28 ± 7 days after OTE Week 26)	Notes
	OTE Day 1	OTE Day 2[b]	OTE Day 8 / Week 1 (± 3 days)	OTE Day 29 / Week 4 (± 3 days)	OTE Day 113 / Week 16 (± 5 days)	OTE Day 183 / Week 26 (+ 5 days)		
Informed consent	X							Informed consent for the OTE can be obtained prior to the OTE Day 1 visit.
Randomization / Treatment Assignment	X							When entering the OTE, participants that were assigned to placebo and had not had dose reduction will be randomized to 30 mg or 60 mg BMS-986278 BID.
Weight measurement				X		X		
Laboratory/Safety Assessments								
12-lead ECG				X		X		All ECGs must be performed prior to bronchodilator administration OR at least 20 hours after bronchodilator administration. ECG at Week 4 to be collected before morning dosing. See Section 9.4.3 for further details.
Clinical laboratory samples	X		X	X	X	X	X	Hematology, chemistry, and urinalysis. A clinical laboratory sample will be collected at the OTE Day 1 visit. Collection of Day 1 clinical laboratory samples is not required if the Week 26 clinical laboratory sampling in the main study is completed within 3 days prior to the OTE Day 1 visit.
Physical examination	X			X		X	X	
Vital signs	X[c]	X	X	X	X	X	X	Predose vital signs include body temperature, respiration rate, and orthostatic BP and HR. Refer to Section 9.4.2 for further details on vital signs.

Table 2: Schedule of Activities for Study IM027040 (Optional Treatment Extension)

	Treatment (Day 1 to Week 26)[a]						Post OTE treatment follow-up (28 ± 7 days after OTE Week 26)	Notes
	OTE Day 1	OTE Day 2[b]	OTE Day 8 Week 1 (± 3 days)	OTE Day 29 Week 4 (± 3 days)	OTE Day 113 Week 16 (± 5 days)	OTE Day 183 Week 26 (+ 5 days)		
								During post-Day 1 visits, additional BP monitoring is required (similar to Day 2 visit) if either *asymptomatic* or *symptomatic* low BP criteria are met, as specified in section 5.1.2.1.
Orthostatic evaluations	See notes.							At every visit, symptoms that could indicate the presence of orthostatic intolerance, orthostatic hypotension, and orthostatic tachycardia will be gathered. Refer to section 9.4.2 and section 5.1.2.1 further details on orthostatic evaluations.
Pharmacokinetic and Biomarker Assessments								
Blood samples for sparse PK profiling	See notes.							According to schedule in Table 8.
Blood samples for biomarkers						X		See Section 9.6 for further details.
Efficacy-related Assessments								
HRCT						X		See Section 9.1.3 for further details.
Spirometry[d]				X	X	X		See Section 9.1.1 for further details.
DLCO SB				X	X	X		See Section 9.1.2 for further details.
Clinical Outcome Assessments (COAs)								
L-PF	X					X		
PGI-S	X					X		

Table 2: Schedule of Activities for Study IM027040 (Optional Treatment Extension)

	Treatment (Day 1 to Week 26)[a]						Post OTE treatment follow-up (28 ± 7 days after OTE Week 26)	Notes
	OTE Day 1	OTE Day 2[b]	OTE Day 8 Week 1 (± 3 days)	OTE Day 29 Week 4 (± 3 days)	OTE Day 113 Week 16 (± 5 days)	OTE Day 183 Week 26 (+ 5 days)		
PGI-C	X					X		If possible, eCOAs should be administered using the electronic device prior to other study related procedures.
6MWT						X		If possible, to be administered after eCOAs. Separate instructions on the 6MWT will be provided. See Section 9.1.4.6 for further details.
Study Treatment/Concomitant Medication								
Dispense study treatment	Participants will receive study treatment twice daily for a total of 26 weeks (from OTE Day 1 to OTE Day 182 of Week 25). At every study visit, morning administration of study treatment will occur at the clinical research site. Fed/fasted status and time of meal (if fed) at every visit must be recorded on the case report form. A sufficient study treatment supply will be dispensed to each participant during the study. New study treatment supplies will be provided to those participants whose dose is reduced (see Section 7).							Any leftover study treatment should be returned to the site for the drug accountability. Treatment compliance should be performed at each study visit between Day 29 (Week 4) and Week 26. Treatment compliance will also be performed at the time of dose reduction or dose discontinuation (if applicable).
Concomitant medications	X	X	X	X	X	X	X	Collected throughout the study.
Adverse Events								
Adverse events	See notes.							Collected throughout the study.
Serious adverse events	See notes.							Serious adverse events will continue to be recorded throughout the entire study until 30 days from last visit.

6MWT = 6-Minute Walk Test; BID = twice daily; BP = blood pressure; DLCO SB = single-breath diffusing capacity of carbon monoxide; ECG = electrocardiogram; HR = heart rate; HRCT = high-resolution computed tomography; L-PF = Living with Pulmonary Fibrosis Questionnaire; OTE = optional

treatment extension; PGI-C = patient global impression of lung fibrosis symptom severity change; PGI-S = patient global impression of lung fibrosis symptom severity

[a] Visit windows may be extended to accommodate participants' schedules on a case-by-case after consultation with the Medical Monitor.

[b] Participants will only attend the Day 2 visit if required due to defined low BP criteria being met on Day 1. If dose reduction is decided on or after the Day 8 visit, the participant is required to follow the Day 2 BP monitoring instructions at the site (see Section 5.1.2.1).

[c] In addition to the predose measurements, orthostatic BP and HR will be performed at 1.5, 2, and 4 hours post dose on OTE Day 1 for all participants. Refer to BP monitoring in Section 5.1.2.1.

[d] Measurements must be performed more than 6 hours after administration of short-acting β-agonists or anticholinergics, at least 12 hours after administration of a long-acting bronchodilator, and at least 24 hours after administration of longer-acting agents.

3 INTRODUCTION

3.1 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease of unknown cause that is characterized by worsening dyspnea, cough, and progressive loss of lung function due to scar formation in the lung.[1] IPF belongs to a family of lung disorders known as interstitial lung diseases (ILDs) and is characterized by the pathological and radiographic pattern known as usual interstitial pneumonia (UIP). A diagnosis of IPF is diagnosis of exclusion, as it is reserved to those individuals with the UIP pattern of lung injury without any identifiable cause such as connective tissue disease or environmental exposure. It is a progressive disease in which scarring and lack of elasticity in the lung continues to increase until the majority of patients die from respiratory failure. Non-drug treatments include supplemental oxygen, pulmonary rehabilitation, and lung transplant.

To date, 2 drugs have been approved for treatment of IPF in several countries globally: pirfenidone, a small-molecule inhibitor of fibrosis (precise mechanism of action is unknown), and nintedanib, a triple tyrosine kinase inhibitor, that blocks signaling from vascular endothelial growth factor, fibroblast growth factor-, and platelet-derived growth factor receptors. In separate Phase 3 trials in IPF patients, both pirfenidone and nintedanib slowed the rate of decline in forced vital capacity (FVC). In addition, nintedanib significantly improved respiratory related quality of life. Both drugs have significant gastrointestinal side effects, many patients progress despite treatment and as such, there remains a significant unmet need based on the benefits and risks of the approved treatments.

3.1.1 Non-IPF, Progressive Fibrotic ILD (PF-ILD)

Beyond IPF, some patients with other chronic forms of fibrotic ILD develop a progressive phenotype characterized by worsening respiratory symptoms, lung function, progressive fibrosis on imaging and early mortality. There is a high unmet need for effective and tolerable treatments for patients with PF-ILD that exhibit disease progression.[2, 3, 4] Because of the clinical and pathophysiological similarities among these diseases, it has been suggested that such disorders have a common pathobiologic mechanism regardless of the cause – with resultant progressive lung fibrosis – and thus could have a response to similar treatment as IPF.[2, 3, 4] Indeed, in the recently published INBUILD trial, patients with PF-ILD with diverse etiologies were treated with nintedanib vs placebo. Those treated with nintedanib had slower progression of lung fibrosis than those who received placebo, as demonstrated by a lower annual rate of decline in FVC over the 52-week study period. The absolute treatment effects in this PF-ILD cohort were similar in magnitude to those observed in the pivotal INPULSIS trials that led to approval of nintedanib for treatment of IPF and based on data from the INBUILD trial, a number of health authorities have also approved nintedanib for patients with PF-ILD.[5]

3.2 Lysophosphatidic Acid Receptor Pathway

Aberrant wound healing responses to lung injury are widely assumed to contribute to the pathogenesis of fibrotic lung diseases, such as IPF. Lysophosphatidic acid (LPA), by virtue of its ability to mediate many basic cellular functions in several cell types associated with wound healing

(survival/apoptosis, proliferation, migration, and contraction), can regulate the transition from normal scar formation to aberrant wound repair (fibrosis), which is characterized by excessive deposition of extracellular matrix. LPA mediates its physiological effects by binding to and activating a family of G protein-coupled receptors (LPA_{1-6}).

Several lines of published evidence support targeting the LPA/lysophosphatidic acid receptor subtype 1 (LPA_1) receptor pathway in fibrotic diseases and for the treatment of IPF.[6, 7] Increased LPA concentrations have been reported in the alveolar space of both IPF patients and the corresponding bleomycin (BLEO) mouse lung model, in which genetic deletion[6, 8] or pharmacological inhibition[9] of LPA_1 attenuated the development of the modeled disease, suggesting a direct involvement of LPA and LPA_1 in disease pathogenesis. Increased epithelial cell apoptosis in response to lung injury has also been implicated in the development of IPF and linked to LPA. LPA signaling through LPA_1 has been reported to promote epithelial cell apoptosis induced by BLEO injury in mice.[8] The number of apoptotic cells present in the alveolar and bronchial epithelia of LPA_1-deficient mice was significantly reduced compared with wild-type mice after BLEO challenge.[8]

Consistent with these in vivo rodent results, increases in LPA levels and LPA signaling through LPA_1 have been observed in individuals with fibrotic diseases. LPA levels are elevated in the bronchoalveolar lavage (BAL) of patients with IPF.[6] Increased concentrations of autotaxin, the enzyme largely responsible for extracellular LPA production, have been found to be elevated in both murine and human fibrotic lungs.[10] Together these data suggest that antagonizing the LPA_1 receptor may be beneficial in treating patients with IPF. Furthermore, a previous Phase 2 study demonstrated improvements in the rate of decline in lung function (as measured by FVC) in IPF patients treated with the LPA_1 antagonist BMS-986020 compared to placebo.[11]

BMS-986278 is a potent full antagonist at LPA_1 that has been shown to potently inhibit LPA-stimulated activation of multiple signal transduction pathways. BMS-986278 is being developed as a potential treatment for IPF (see the Investigator's Brochure for additional details).

3.3 Study Rationale

A clinical need exists for more effective treatment of pulmonary fibrosis. Nonclinical studies support the development of BMS-986278 as a potential treatment for IPF by its antagonistic effect on LPA_1. The overall objective of the clinical development program is to demonstrate that BMS-986278 is effective and safe for the treatment of IPF.

A separate cohort of PF-ILD, will also be enrolled to evaluate whether BMS-986278 is safe and efficacious for the treatment in PF-ILD.

In order to augment knowledge about safety, tolerability, and efficacy of BMS-986278, an optional treatment extension (OTE) will be offered to those participants that complete the 26-week main study.

The proof of concept for antifibrotic activity with an LPA_1 antagonist was demonstrated in a randomized, double-blind, placebo-controlled Phase 2 study with BMS-986020, another selective,

small-molecule LPA_1 antagonist (Study IM136003) discussed below in Section 3.4.4.1. The present study is designed to provide an initial evaluation of the efficacy of BMS-986278, further demonstrate the safety and the tolerability of BMS-986278 and provide information on the pharmacokinetics of BMS-986278 in participants with IPF and in those with PF-ILD. In this study, it is anticipated that the average rate of decline in percent predicted forced vital capacity (ppFVC) between baseline and Week 26 will be smaller among participants taking 1 of the 2 different doses of BMS-986278 than among those taking placebo.

3.4 Background

Details on the nonclinical pharmacology, pharmacokinetics (PK), and toxicology of BMS-986278 are in the Investigator's Brochure.

3.4.1 Nonclinical Pharmacology

See the Investigator's Brochure for additional details on nonclinical pharmacology studies.

BMS-986278 is a potent full antagonist of LPA_1 (Kb = 6.9 nM). BMS-986278 potently inhibited LPA-stimulated activation of multiple signal transduction pathways mediated by G protein-coupled receptors Gq, Gi, and G_{12}, as well as β-arrestin recruitment in heterologous cells and endogenous cells expressing human LPA_1 ($hLPA_1$), exhibiting 3.9 to 25 nM affinity in all assays. BMS-986278 also acts as a potent but partial inhibitor of LPA_3 (Kb = 2.1 nM, maximal inhibition (Imax) = 36%); however, was inactive at other LPA receptor isoforms tested, including LPA_2, LPA_4, and LPA_5. BMS-986278 is also a potent inhibitor of the mouse and rat LPA_1 receptor (Kb = 4 nM), indicating the suitability of these animal species for preclinical efficacy testing. LPA_1 signaling has been shown in preclinical studies to contribute to the development of lung fibrosis, in part, through the stimulation of Gq-mediated Ca^{2+} flux and fibroblast proliferation. BMS-986278 was a potent inhibitor of LPA-stimulated proliferation of human lung fibroblasts with IC50 of 25 nM.

In vivo, BMS-986278 demonstrated antifibrotic efficacy in both the murine subcutaneous bleomycin systemic model as well as in the intratracheal BLEO rat model of lung fibrosis. BMS-986278 administered orally at 10 mg/kg (twice daily [BID] for 14 days, administered starting on Day 7 after BLEO treatment) decreased BLEO-induced fibrosis, as measured by quantitative histological analysis, by 55% ($P < 0.01$; plasma trough concentration 244 nM; calculated occupancy 87%) in the rat model and by 58% ($P < 0.01$; plasma trough concentration 239 nM; calculated occupancy 95%) in the mouse model.

Taken together these data suggest that antagonizing the LPA_1 receptor with BMS-986278 may be beneficial in treating patients with IPF and with PF-ILD in general.

3.4.2 Nonclinical Pharmacokinetics

See the Investigator's Brochure for additional details on nonclinical PK studies.

The nonclinical PK of BMS-986278 following a single intravenous (IV) or oral dose were characterized in mice, rats, dogs, and monkeys. After IV administration, the apparent elimination half-life (T-HALF) of BMS-986278 was 2.5, 4.5, 5.7 and 11 hours in mice, rats, dogs, and monkeys, respectively. Total plasma clearance was low in monkeys and moderate in other

preclinical species (37, 15, 29, and 2 mL/min/kg in mice, rats, dogs, and monkeys, respectively). The steady-state volume of distribution (Vss), ranging from 1.6 L/kg to 5.5 L/kg in mice, rats, dogs, and monkeys, indicated extensive extravascular distribution of BMS-986278. The absolute oral bioavailability was 70%, > 100%, 35%, and 79% in mice, rats, dogs, and monkeys, respectively.

BMS-986278 showed significant metabolic turnover in hepatocytes across species (mouse, rat, dog, monkey, and human). Direct glucuronidation of the carboxylic acid moiety to form an acylglucuronide (BMT-332415) was predominant in dog and monkey hepatocytes, and major in hepatocytes of other species. N-demethylation (BMT-323719) was another major metabolic pathway in human, monkey, and rodent hepatocytes. Oxidation, dealkylation, and epimerization were minor in human hepatocytes.

3.4.3 Nonclinical Toxicology

See the Investigator's Brochure for additional details on nonclinical toxicology studies.

3.4.3.1 Genotoxicity, Phototoxicity, Safety Pharmacology

Briefly, BMS-986278 is neither genotoxic nor phototoxic. Moreover, the compound has displayed no safety pharmacology concerns based on off-target, central nervous system, respiratory, or electrocardiogram (ECG) assessments. In telemeterized monkeys (Good Laboratory Practice [GLP] study), a single 20 mg/kg dose (highest dose tested), produced transient and minimal decreases in systolic blood pressure (SBP) and mean arterial blood pressure (BP) (7 to 9 mmHg) from approximately 4.5 to 8 hours post dose, a transient increase in heart rate (HR) (6 beats per minute [bpm]) from 2 to 2.5 hours post dose, and a minimal decrease in HR (-14 bpm) from 4.5 to 6.5 hours post dose. These effects were not replicated in a subsequent telemeterized monkey study (non-GLP) at higher doses, 50 and 100 mg/kg. There were no effects noted in any of the cardiovascular parameters (hemodynamics, ECG, rate, rhythm, or waveform morphology). Based on these studies, the monkey may not be predictive of the BP changes observed in humans.

3.4.3.2 Repeat-dose Toxicity

In the 1-month oral rat toxicity study, BMS-986278 was well tolerated up to the highest dose tested (300 mg/kg/day) with no BMS-986278-related adverse findings. Therefore, the no-observed adverse effect level (NOAEL) was considered to be 300 mg/kg/day.

In the 6-month oral toxicity study in rats with a 3-month recovery period, BMS-986278 was well tolerated up to the highest dose tested, 300 mg/kg/day (area under the plasma concentration-time curve from time 0 to 24 hours post dose [AUC(0-24h)] = 2,400 µg•h/mL in males and AUC[0-24h] = 3,120 µg•h/mL in females). The only adverse finding was increased incidence/severity (minimal to moderate) of degenerative joint disease at the femorotibial joint (common age-related spontaneous background change in rats, characterized by articular cartilage fibrillation, clefting, erosion and/or chondrocyte loss/cloning, synovial inflammation, capsular fibrosis without bone changes) in males at ≥ 100 mg/kg/day (≥ AUC[0-24h] = 615 µg•h/mL). Therefore, the NOAEL was considered to be 30 mg/kg/day (AUC[0-24h] = 45.2 µg•h/mL; males and AUC[0-24h] =

106 µg•h/mL females). Similar findings were not observed in sexually mature monkeys dosed for 9 months up to 150 mg/kg/day (see below).

In the 1-month oral toxicity study in sexually immature monkeys, BMS-986278 was well tolerated up to the highest dose tested (100 mg/kg/day). At 100 mg/kg/day the only noteworthy BMS-986278-related finding was moderate physeal dysplasia, segmented at the caudal aspect of the distal femur in 1 of 5 monkeys assessed with no associated changes in bone biomarkers. The bone change was considered adverse because, in sexually immature monkeys with a continuously growing growth plate, it could potentially result in malalignment of the adjacent articular surfaces before attainment of full sexual maturity. The bone finding is consistent with the role of LPA_1 in development of the growth plate and chondrocyte proliferation and positioning to promote cartilage formation. No bone findings were evident in recovery monkeys. Based on the bone findings at 100 mg/kg/day, the NOAEL in sexually immature monkeys was considered to be 50 mg/kg/day (mean sex-combined AUC(0-24h) = 251 µg•h/mL).

In the 9-month oral toxicity study in sexually mature monkeys with a 3-month recovery period, doses tested were 0 (vehicle), 20, 50, or 150 mg/kg/day. BMS-986278 was well tolerated by monkeys up to the highest dose tested with no adverse BMS-986278-related findings. Moderate physeal dysplasia noted in 1/5 females in sexually immature monkeys at 100 mg/kg/day in the 1-month toxicity study did not recapitulate in sexually mature monkeys (with closed growth plates). Therefore, the NOAEL was considered 150 mg/kg/day (mean sex-combined AUC[0-24h] = 1,140•µg·h/mL).

3.4.3.3 Embryo-fetal Development Studies

Embryo-fetal development studies in rat and rabbit indicated that BMS-986278 is a selective developmental toxicant. In pregnant rats, BMS-986278 was administered orally at 0, 15, 45, and 75 mg/kg/day during the period of organogenesis (Gestation Day [GD] 6 to 16). Fetal external, visceral, and skeletal malformations, predominantly localized to the craniofacial and thoracic/rib regions were noted starting at the lowest dose tested (15 mg/kg/day; mean AUC[0-24h] = 16 µg•h/mL). The malformations occurred in the absence of any apparent maternal toxicity. In rabbits, BMS-986278 was administered orally at 0, 20, 75, and 200 mg/kg/day during the period of organogenesis (GD 7 to 19). BMS-986278-related effects on maternal survival, body weight (including body weight loss), food consumption (inappetence), and fetal viability (increased postimplantation loss) were observed at 200 mg/kg/day. An increased incidence of fetal skeletal malformations (ribs, sternebrae, cranium/skull) was noted at ≥ 75 mg/kg/day (absence of maternal toxicity at 75 mg/kg/day). In light of these findings, the developmental NOAEL was considered to be 20 mg/kg/day (mean AUC[0-24h] = 32.1 µg•h/mL).

In an oral study of fertility and early embryonic development, BMS-986278 was well tolerated by male and female rats, with no effects noted on fertility or early embryonic development up to doses of 300 mg/kg/day. Therefore, 300 mg/kg/day (BMS-986278 AUC[0-24h] = 1,870 µg•h/mL male and 1,390 µg•h/mL female) was considered the reproductive NOAEL.

Overall, based on data available to date, the nonclinical safety assessments support continued development of BMS-986278. Evidence for teratogenicity in rats and rabbits highlights the need

for special precautions when enrolling women of childbearing potential (WOCBP) in clinical studies.

3.4.3.4 Nonclinical Combination Toxicology

The objective of the clinical development program is to demonstrate that BMS-986278 is safe and effective for the treatment of IPF when used alone or concomitantly with approved IPF treatments. To date, 2 drugs have been approved for treatment of IPF in several countries globally: pirfenidone, a small-molecule inhibitor of fibrosis (precise mechanism of action unknown) and nintedanib (a multiple tyrosine kinase inhibitor).

BMS conducted a definitive 3-month combination toxicity study in rats with BMS-986278 and pirfenidone or nintedanib to determine the potential toxicokinetic and toxicological interactions between the compounds and to support the Phase 2 clinical study. To support the definitive 3-month combination toxicity study dose selection and study design, 2 preceding 7-day dose range-finding studies for BMS-986278 were conducted. Pirfenidone and nintedanib doses were equivalent to the area under the plasma concentration-time curve (AUC) at the maximum recommended human dose (MRHD); pirfenidone 500 mg/kg/day and nintedanib 20 mg/kg/day.

The two 7-day range-finding studies in rats suggested that BMS-986278 exacerbated pirfenidone-induced clinical signs (decreased activity, ataxia, eyelids partially closed, abnormal posture/gait, piloerection, increased/labored breathing, and/or cold to touch). Female animals were more sensitive to the combination effect than the males, resulting in some moribundity at BMS-986278 doses ≥ 15 mg/kg/day in both range-finding studies. The clinical signs/moribundity were partially attributed to observed higher pirfenidone exposures on Day 1. As previously described, rats generally developed tolerability to pirfenidone within 2 to 3 days. Systemic exposure to BMS-986278 was generally lower (< 2×) when coadministered with pirfenidone. Based on range-finding studies, doses in the 3-month study for BMS-986278 doses were decreased to 15/7.5 mg/kg/day (male/female) and pirfenidone dosing was initiated a week prior to BMS-986278 to enable development of tolerance.

Nintedanib and BMS-986278, in combination, was well tolerated in two range-finding studies. In one range-finding study, the observed decrease in nintedanib exposure was attributed to the vehicle. BMS-986278 doses selected for the definitive 3-month combination toxicology study in rat were 30/15 mg/kg/day (male/female) and dosing was initiated concurrently. No PK or toxicological interaction were noted between BMS-986278 and nintedanib.

In a definitive 3-month combination toxicology study, BMS-986278 doses in the pirfenidone combination part of the study were 15 mg/kg/day in males and 7.5 mg/kg/day females (1 to 3× projected high/low human efficacious AUC) and that of pirfenidone was 500 mg/kg/day (1× MRHD). There were no unique clinical pathology or anatomic pathology findings when BMS-986278 was administered in combination with pirfenidone at doses providing clinically relevant exposures. All findings were consistent with those reported previously for each drug alone.[12, 13, 14] There was a slight increase in alanine aminotransferase (ALT) levels in animals receiving the combination (1.41 to 1.45×). When administered in combination with pirfenidone, BMS-986278 systemic exposures (maximum concentration [Cmax] and AUC[0-24h]) were 0.2 to

0.5× those when administered alone, indicating a possible toxicokinetic interaction in rat. Although initiation of pirfenidone dosing 1 week ahead of BMS-986278 enabled development of tolerance to the central nervous system-related signs caused by pirfenidone, clinical signs were observed sporadically in a small number of rats after BMS-986278 administration was initiated on Day 8 in a small number of rats. Additionally, 4 rats were euthanized or found dead on or after Day 45 (3 in the combination group compared to 1 in the pirfenidone alone group). However, when accounting for the different group sizes, there was a similar incidence [5% to 8%] in the combination and pirfenidone-only treatment groups. Nevertheless, the clinical signs and mortality suggested a possible toxicologic interaction between BMS-986278 and pirfenidone.

BMS-986278 doses in the nintedanib combination part of the study were 30 mg/kg/day in males and 15 mg/kg/day females and that of nintedanib was 20 mg/kg/day. There was no toxicokinetic or toxicologic interaction between BMS-986278 and nintedanib when coadministered at doses providing clinically relevant exposures. All findings were consistent with those reported previously for each drug alone.

3.4.4 Clinical Experience

3.4.4.1 Efficacy of Previous LPA_1 Antagonist (BMS-986020)

The proof of concept for antifibrotic activity with an LPA_1 antagonist was demonstrated in a randomized, double-blind, placebo-controlled Phase 2 study with BMS-986020, another selective, small-molecule LPA_1 antagonist (Study IM136003). Study IM136003 was a 26-week study comparing BMS-986020 600 mg (n=96) to placebo (n=47) in 143 patients with IPF. Study drug was administered either once daily (QD) or BID. The primary endpoint was the rate of change in absolute FVC from baseline to study end, measured at 26 weeks.

For the higher-dose regimen of BMS-986020 600 mg twice daily, the primary treatment comparison, active treatment versus placebo, showed a significant difference in the primary endpoint, change in FVC (liters) from baseline to Week 26. The estimate (95% CI) of the slope of decline in FVC was -0.042 liters (-0.106, 0.022) in the BID group, compared with -0.134 liters (-0.201-0.068) in the placebo group and the difference in estimates of rate of change in FVC from baseline to 26 weeks was 0.093 liters per 26 weeks (0.000, 0.185) (P=0.049). There was no statistically significant difference in slope of FVC decline between BMS-986020 600 mg QD and placebo. The estimate (95% CI) of the slope of decline (liters per 26 weeks) in FVC at Week 26 was -0.073 liters (-0.138,-0.007) in the QD group, compared with -0.134 liters (-0.201,-0.068) in the placebo group and the difference in estimates of rate of change in FVC from baseline to 26 weeks was 0.062 liters per 26 weeks (-0.032, 0.155) (P=0.194).

In Study IM136003, there were 3 drug-associated events of cholecystitis leading to cholecystectomy, and the decision was made to discontinue development of BMS-986020 due to these events. Nonclinical and clinical studies to date with BMS-986278 do not show physiologically significant hepatobiliary effects.

3.4.4.2 First-in-Human Study (Study IM027009)

The first-in-human (FIH) study for BMS-986278, Study IM027009, was a double-blind, placebo-controlled, randomized single-ascending-dose and multiple-ascending-dose study.

The primary objective of the study was to evaluate the safety and tolerability of single and multiple ascending oral doses of BMS-986278 in healthy participants. Secondary objectives included:

- To evaluate the plasma PK of single and multiple ascending oral doses of BMS-986278 in healthy participants.
- To evaluate the effect of a high-fat meal and of a modified gastric pH on the plasma PK of a single dose of BM-986278 in healthy participants.
- To compare the plasma PK of multiple ascending oral doses of BMS-986278 in Japanese and non-Japanese healthy participants.

Following both single and repeat administrations of BMS-986278, plasma concentrations of the parent compound peaked rapidly each day approximately 1.5 hours after dosing. A similar second peak, presumably due to enterohepatic recycling, was observed each day approximately 4.5 hours after dosing, followed by a log-linear decline. BMS-986278 area under the plasma concentration-time curve from time 0 extrapolated to infinite time (AUC[INF]) and Cmax increased proportionally with dose with both single and repeat administrations; oral clearance was independent of dose. Steady-state plasma concentrations of the compound were reached at approximately 6 days after the first administration of the compound. There was minimal plasma accumulation of BMS-986278 and its metabolites.

BMS-986278 was generally well tolerated at single doses up to 150 mg and at multiple doses of up to 125 mg BID for 14 days. No deaths or serious treatment-emergent adverse events (TEAEs) were reported, and no participant discontinued dosing due to TEAEs. There were no clinically significant laboratory findings. The maximum tolerated single dose was determined to be 150 mg. Dose-limiting toxicity was not observed up to 125 mg BID for 14 days.

BMS-986278 was associated with reversible, generally dose-dependent reductions in BP that generally reached a maximum 4 to 8 hours after dosing, returned to baseline within 24 hours, and were not associated with meaningful changes in HR. Orthostasis was infrequently observed in both placebo and active dose groups, with no clear association with BMS-986278. BP reductions were mostly asymptomatic.

3.4.4.3 BMS-986278 in Combination with Rifampin (Study IM027017)

Study IM027017 was an open-label, 2-period drug-drug interaction study in a planned total of 15 participants (healthy male and female [non-childbearing potential] participants). The primary objective of the study was to assess the effect of rifampin, a potent inhibitor of organic anion transport protein (OATP)1B1 and OATP1B3, on the single-dose PK of BMS-986278 in healthy participants. In Period 1 BMS-986278 was administered alone and in Period 2 BMS-986278 was administered immediately following a single oral dose of 600 mg rifampin.

[redacted]

BMS-986278 was generally well tolerated both alone and when coadministered with rifampin. Only 4 TEAEs were reported in the study. No deaths, serious adverse events (SAEs), or treatment-related TEAEs were reported and no participant discontinued treatment due to a TEAE. As in Study IM027009, asymptomatic BP reductions were observed, but the mean changes in SBP- and diastolic blood pressure (DBP)-time profiles were similar between the 2 treatments, indicating that elevated exposures to BMS-986278, when coadministered with rifampin, did not result in larger BP reductions.

3.4.4.4 BMS-986278 in Combination with Pirfenidone (Study IM027041)

Study IM027041 was an open-label, three-period, randomized crossover study in 22 healthy, male and female participants (in order to achieve 18 participants who complete the study) who are not users of nicotine; female participants must not be of childbearing potential. The primary objective of the study was to characterize the PK of BMS-986278 after administration of a single dose of BMS-986278 alone or in combination with pirfenidone.

[redacted]

3.5 Benefit/Risk Assessment

The known benefit of participation in this study is limited to a baseline assessment of health being provided for all participants in this study. The overall risk for participation is considered low based on safety and tolerability data from the FIH study with BMS-986278. Transient, mostly asymptomatic decreases in BP were reported in the IM027009 study, but in all cases BP returned to baseline with no intervention. Vital signs assessments will be in place to monitor the potential occurrence of BP reductions, and participants will be monitored closely at the study site for the first 4 hours following the first dose of study treatment. Participants may undergo BMS-986278 dose reduction if BP reduction criteria (described in Section 5.1.2.1) are observed.

In nonclinical studies, physeal dysplasia of the bone was observed, but the risk for similar bone effects in this study is considered low. Moreover, bone growth plates are expected to be closed in

the participant population eligible for the study (40 years and above for the IPF cohort and 21 years and above for the PF-ILD cohort). BMS-986278 was not genotoxic in the Ames assay, but BMS-986278 has demonstrated reproductive and developmental toxicities in rats and rabbits, thus WOCBP will not be included in the study.

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of BMS-986278 may be found in the Investigator's Brochure.

3.5.1 COVID-19-related Benefit/Risk Assessment

The ongoing Coronavirus Disease 2019 (COVID-19) pandemic is a risk that needs to be considered by the site investigator, particularly as lung fibrosis patients are at increased risk for respiratory infections in general. Similar to other infections, participants with recent acute infection with SARS-CoV-2 are excluded. Evaluation and management of SARS-CoV-2 infection arising during the course of the trial are left to the discretion and expertise of the site investigator. Importantly, as BMS-986278 is not immunosuppressive in nature, there is no known additional risk for SARS-CoV-2 infection associated with administration of the investigational medicinal product (IMP) in this clinical trial.

- In the event participants are unable or not permitted to attend an onsite visit due to the COVID-19 pandemic, the study site should contact the Study Director or Medical Monitor and each instance will be addressed on a case by case basis.

4 OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Objectives	Endpoint(s)
• **Primary**	
• To evaluate the rate of change in ppFVC from baseline to Week 26 in IPF participants randomized to receive BMS-986278 at 30 mg or 60 mg BID compared to those randomized to receive placebo.	• Rate of change in ppFVC (%) from baseline to Week 26 in IPF participants
• **Secondary**	
• To evaluate the safety and tolerability of BMS-986278 through 26 weeks of treatment by comparing results observed in participants with IPF and PF-ILD randomized to receive BMS-986278 at 30 mg or 60 mg BID with those who receive placebo. The IPF and PF-ILD cohorts will be analyzed separately.	• AEs • SAEs • AEs leading to early discontinuation of study treatment • Treatment-emergent deaths • Clinical laboratory findings and ECGs • Vital signs • Physical exam findings
• To evaluate the rate of change in ppFVC from baseline to Week 26 in PF-ILD participants randomized to receive	• Rate of change in ppFVC (%) from baseline to Week 26 in PF-ILD participants

Table 3: Objectives and Endpoints

Objectives	Endpoint(s)
BMS-986278 at 30 mg or 60 mg BID compared to those randomized to receive placebo.	
• To evaluate the effect of treatment with BMS-986278 on clinical assessments of lung fibrosis in participants with IPF and PF-ILD randomized to receive BMS-986278 at 30 mg or 60 mg BID compared with participants randomized to receive placebo through Week 26. The IPF and PF-ILD cohorts will be analyzed separately.	• Proportion of participants with ≥ 10% absolute decline in ppFVC (%) at Weeks 4, 8, 12, 16, 20, and 26 • Proportion of participants with > 0% change in ppFVC at Weeks 4, 8, 12, 16, 20, and 26 • Time to first acute exacerbation • Time to first ≥ 10% absolute decline in ppFVC (%) • Absolute change in FVC (mL) from baseline to Week 26 • Absolute change in ppFVC (%) from baseline to Week 26 • Absolute change in DLCO SB (mL/min/mmHg) (corrected for hemoglobin) from baseline to Week 26 • Absolute change in ppDLCO SB (%) (corrected for hemoglobin) from baseline to Week 26 • Change in walking endurance/distance from baseline at Week 26 as measured using the 6MWT • Proportion of participants with acute exacerbations of lung fibrosis defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality, as follows:[15] 1. Acute worsening or development of dyspnea (< 1 month duration) 2. Imaging with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern of lung fibrosis 3. Respiratory deterioration not fully explained by cardiac failure or fluid overload
• To characterize the PK of BMS-986278 in IPF participants.	• Cmax, Tmax, and AUC(0-8) on Day 1 and Week 4 and Ctrough on Week 4 and Week 12 of intensive PK substudy

Table 3: Objectives and Endpoints

Objectives	Endpoint(s)
Exploratory	
• To characterize the PK of BMS-986278 in PF-ILD participants, if applicable	• Cmax, Tmax, and AUC(0-8) on Day 1 and Week 4 and Ctrough on Week 4 and Week 12 of intensive PK substudy
• To characterize PK of the inactive metabolite BMT-323719.	• Exposure parameters, including but not limited to AUC(0-8), Ctrough, Cmax, and Tmax of intensive PK study
• To explore potential interactions between nintedanib or pirfenidone and BMS-986278 using population pharmacokinetics.	• Plasma concentrations of nintedanib and pirfenidone in participants who receive nintedanib or pirfenidone alone and co-administered with BMS-986278
• To evaluate the effect of treatment on the rate of change in lung fibrosis in IPF and PF-ILD as measured by HRCT through 26 weeks of treatment in participants randomized to BMS-986278 at 30 mg or 60 mg BID compared with participants randomized to receive placebo. The IPF and PF-ILD cohorts will be analyzed separately.	• Change in quantitative lung fibrosis using the Quantitative HRCT Fibrosis Score from baseline to Week 26
• To assess the effect of treatment in participants with IPF and PF-ILD randomized to BMS-986278 at 30 mg or 60 mg BID to that of placebo on assessments of disease outcomes through 26 weeks of treatment. The IPF and PF-ILD cohorts will be analyzed separately.	• Composite endpoint of time to first all-cause hospitalization or overall survival • Pulmonary fibrosis progression-free survival: Progression of pulmonary fibrosis is defined as ≥ 10% decline in ppFVC relative to baseline, ≥ 50 m decline in 6MWT relative to baseline, lung transplantation, or death
• To assess changes in COAs during treatment in participants with IPF and PF-ILD randomized to BMS-986278 at 30 mg or 60 mg BID compared with participants randomized to placebo. The IPF and PF-ILD cohorts will be analyzed separately.	• Change in HRQoL from baseline at each assessment timepoint during treatment as measured by the L-PF • Change in HRQoL from baseline at each assessment timepoint during treatment as measured by the SGRQ • Change in dyspnea from baseline at each assessment timepoint during treatment as measured by the UCSD SOBQ • Change in cough severity from baseline at each assessment timepoint during treatment as measured using a VAS • Change in walking endurance/distance from baseline at each assessment timepoint during treatment as measured using the 6MWT

Table 3: Objectives and Endpoints

Objectives	Endpoint(s)
• To assess the effect of treatment in participants with IPF and PF-ILD randomized with BMS-986278 at 30 mg or 60 mg BID to that of placebo on additional categorical clinical assessments of disease through 26 weeks of treatment. The IPF and PF-ILD cohorts will be analyzed separately.	• Proportion of participants with > 5% decline in FVC (mL) relative to baseline • Proportion of participants with > 10% decline in FVC (mL) relative to baseline • Proportion of participants with > 5% absolute decline in ppFVC (%) • Proportion of participants with > 5% decline in ppFVC (%) relative to baseline • Proportion of participants with > 10% decline in ppFVC (%) relative to baseline • Time to first > 5% absolute decline in ppFVC (%) • Time to first > 5% decline in ppFVC relative to baseline (%) • Time to first > 10% decline in ppFVC relative to baseline (%) • Time to first > 5% decline in FVC (mL) relative to baseline • Time to first > 10% decline in FVC (mL) relative to baseline
• To assess the effect of BMS-986278 on blood-based biomarkers.	• Change from baseline of blood-based biomarkers of lung fibrosis and inflammation; including gene expression profiles
• To assess the effects of IPF-related genes on drug response. • To assess the effect of genetic variations in genes associated with drug absorption, distribution, metabolism, excretion, and transport on the PK of BMS-986278.	• Presence or absence of single nucleotide variants in genes associated with lung fibrosis • Presence or absence of single nucleotide polymorphism variants in genes encoding organic anion transporting polypeptides, cytochrome P450 (CYP)2C8, and breast cancer resistance protein
• To assess the impact of SARS-CoV-2 serologic status on participants with IPF or PF-ILD receiving BMS-986278.	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) from serum samples collected at baseline and end of the main study.
Exploratory - Optional Treatment Extension	
• To further evaluate the safety and tolerability of BMS-986278 in participants with IPF or PF-ILD that participate in the optional treatment extension (OTE).	• AEs • SAEs • Treatment-emergent deaths • Clinical laboratory findings, PK

Table 3: Objectives and Endpoints

Objectives	Endpoint(s)
• To further evaluate the efficacy of BMS-986278 in participants with IPF or PF-ILD that participate in the OTE.	• FVC trajectory (eg, rate of change of ppFVC [%] and FVC [mL] from Week 26 in the main study to Week 26 in the OTE and from baseline in the main study to Week 26 in the OTE) • DLCO trajectory (eg, rate of change of ppDLCO SB [%] and DLCO SB [mL/min/mmHg] from Week 26 in the main study to Week 26 in the OTE and from baseline in the main study to Week 26 in the OTE) • Changes in quantitative lung fibrosis using the Quantitative HRCT Fibrosis Score • Changes in HRQoL as measured by the L-PF • Changes in walking endurance/distance as measured using the 6MWT • Blood-based biomarkers of lung fibrosis and inflammation; including gene expression profiles
• To assess the impact of SARS-CoV-2 serologic status on participants with IPF or PF-ILD receiving BMS-986278.	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) from serum samples collected at the end of the OTE.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2 randomized, double-blind, placebo-controlled clinical study investigating the efficacy and the safety and tolerability of BMS-986278 in participants with pulmonary fibrosis. In the primary cohort, a total of approximately 240 participants with IPF will be randomized to receive 30 mg or 60 mg BMS-986278 BID or placebo BID at a ratio of 1:1:1 for 26 weeks in the main study. Stable standard of care (SOC) background therapy for IPF with either nintedanib or pirfenidone will be allowed.

In a secondary cohort, a total of approximately 120 participants with PF-ILD will be randomized to receive 30 mg or 60 mg BMS-986278 BID or placebo BID at a ratio of 1:1:1 for 26 weeks. Participants with PF-ILD will be allowed to remain on stable background therapies commonly used as part of their usual care, including nintedanib, pirfenidone, and/or select immunosuppressive medications (ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus).

IPF and PF-ILD participants receiving 30 mg or 60 mg (or placebo) BMS-986278 BID in the main study who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID (or placebo for 10 mg BID) (refer to Section 5.1.2.1).

An optional treatment extension (OTE) that will last 26 weeks will be offered to IPF and PF-ILD participants that complete the 26-week main study. All participants will receive active treatment in the OTE. Participants who received 30 mg placebo tablets in the main study will be randomized to receive 30 mg or 60 mg BMS-986278 BID, and participants who received 30 mg or 60 mg BMS-986278 BID in the main study will continue with the assigned doses. Participants receiving 30 mg or 60 mg BMS-986278 BID in the OTE will remain blinded to study treatment until the database lock for analyses of the 26-week main study in IPF and PF-ILD cohorts, respectively. At the time of main study database lock in each cohort, the OTE will be unblinded for that cohort. Participants who dose reduced and received 10 mg BMS-986278 BID or placebo for 10 mg BMS-986278 BID in the main study will receive 10 mg BMS-986278 BID unblinded in the OTE. Participants receiving 30 mg or 60 mg BMS-986278 BID in the OTE who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID (refer to Section 5.1.2.1).

The study includes:

- A screening period of up to 42 days
- A 26-week, double-blind treatment period, during which participants will receive 1 of the following 3 treatments: 30 mg BMS-986278 oral tablets BID, 60 mg BMS-986278 oral tablets BID, or matching placebo tablets
- A 4-week posttreatment follow-up period for those participants that do not elect to continue in the OTE
- A 26-week OTE phase in which IPF and PF-ILD participants that choose to participate will receive one of 3 doses of BMS-986278 (30 mg BID, 60 mg BID, or 10 mg BID)
- A 4-week post OTE treatment follow-up period
- The study design schematics for the main study are presented in Figure 1 for the IPF cohort and Figure 2 for the PF-ILD cohort. Refer to Table 1 for the Schedule of Activities for the main study.
- The study design schematic for the OTE is presented in Figure 3. Refer to Table 2 for the Schedule of Activities for the OTE.

5.1.1 Screening Period

Eligibility will be based on specified inclusion and exclusion criteria (Section 6), including medical history, disease activity, and safety assessments. Eligibility criteria for this study have been carefully considered to ensure the safety of the participants and that the results of the study can be analyzed properly. It is imperative that participants fully meet all eligibility criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Certain procedures conducted as part of the participant's routine clinical management and obtained before signing of informed consent may be utilized for screening purposes provided the procedure meets the

protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

5.1.2 Treatment Period

In the primary cohort of IPF participants, eligible participants will be randomized to receive 1 of 2 dose levels of BMS-986278 (30 mg or 60 mg BID) or placebo for 26 weeks. Randomization will be stratified by country (non-Japan versus Japan), and concomitant use of approved IPF therapy (pirfenidone versus nintedanib versus none).

In the secondary cohort of PF-ILD participants, eligible participants will be randomized to receive 1 of 2 dose levels of BMS-986278 (30 mg or 60 mg BID) or placebo for 26 weeks. Randomization will be stratified by UIP pattern (present vs absent) of lung injury and by category of background therapy (ILD-targeted immunosuppression [ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus] alone versus anti-fibrotics [nintedanib, pirfenidone] with or without ILD-targeted immunosuppression versus no ILD-targeted immunosuppression or anti-fibrotics).

All participants randomized will undergo functional, quality-of-life, PK and biomarker assessments according to the Schedule of Activities (Table 1).

In addition, physical examinations, vital sign measurements (including orthostatic assessments), 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for AEs throughout the study.

For all study participants, blood samples will be collected for up to 4 hours after study treatment administration for PK analysis on Day 1. Predose blood samples will be collected at Week 12 and Week 26. Additional samples will be collected from IPF and PF-ILD participants in the intensive PK substudy (see Section 9.5.2).

After completing the 26-week main study, participants will have the opportunity to continue study treatment in the OTE for another 26 weeks. Refer to the assessments in the Schedule of Activities (Table 2) and Sections 7.1 and 7.2 for treatments administered and treatment assignments, respectively.

5.1.2.1 Blood Pressure Monitoring

Symptoms that could indicate the presence of orthostatic intolerance, orthostatic hypotension, and orthostatic tachycardia (defined below, per the ACC/AHA/HRS guideline[16]) will be gathered at all study visits, including the screening visit.

Orthostatic intolerance: defined as a syndrome consisting of a constellation of symptoms that include frequent, recurrent, or persistent lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue upon standing. These symptoms can occur with or without orthostatic tachycardia, orthostatic hypotension, or syncope. Individuals with orthostatic intolerance have at least 1 of these symptoms associated with reduced ability to maintain upright posture.

Orthostatic hypotension: defined as a drop in SBP of ≥ 20 mmHg or DBP of ≥ 10 mmHg with assumption of an upright posture from either supine or seated to upright position.

Orthostatic tachycardia: defined as a sustained increase in HR of ≥ 30 bpm within approximately 10 minutes of moving from a recumbent to a quiet (nonexertional) standing position; defined as the difference in HR from either supine or seated to upright position.

Day 1 blood pressure monitoring:

On Day 1, participants will remain at the site for at least 4 hours post dose. Orthostatic BP and HR will be performed predose and 1.5, 2, and 4 hours post dose.

During orthostatic assessments, participants will be queried for any of the following symptoms suggestive of orthostatic intolerance: lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue upon standing.

Participants will take the Day 1 evening dose at home and will return to the study site on Day 8 if neither *asymptomatic* nor *symptomatic* low BP criteria are met.

Participants will not receive the Day 1 evening dose if either *asymptomatic* or *symptomatic* low BP criteria are met.

Asymptomatic low BP criteria:

a) Seated SBP < 85 mmHg (confirmed by retest within 15 minutes)
b) Seated DBP < 55 mmHg (confirmed by retest within 15 minutes)
c) Orthostatic hypotension (confirmed by retest within 15 minutes)

Symptomatic low BP criteria:

a) The participant is experiencing symptoms that, in the opinion of the investigator, could be associated with low BP (eg, confusion, lightheadedness, dizziness, palpitations, falls, tremulousness, generalized weakness, blurred vision, exercise intolerance [if different from baseline], fatigue upon standing [if different from baseline], angina, transient ischemic attack, pre-syncope, or syncope) AND at least one of the following BP thresholds:
    i. Seated SBP < 100 mmHg (confirmed by retest within 15 minutes) or seated DPB < 60 mmHg (confirmed by retest within 15 minutes)
    ii. Decrease of seated SBP of ≥ 20 mmHg (confirmed by retest within 15 minutes) from previous visit or decrease of seated DBP of ≥ 10 mmHg (confirmed by retest within 15 minutes) from previous visit
    iii. Orthostatic hypotension (confirmed by retest within 15 minutes)
    iv. Orthostatic tachycardia (confirmed by retest within 15 minutes)

If either *asymptomatic* or *symptomatic* low BP criteria are met, participants will not receive the Day 1 evening dose and will remain at the site until BP resolution criteria are met:

a) Participants provide 2 consecutive seated BP measurements (at least 30 minutes apart) showing SBP > 85 mmHg and DBP > 55 mmHg

b) Participants do not demonstrate orthostatic hypotension

c) Potential symptoms of decreased BP (as described above) have not been present for at least 30 minutes

Participants will return to the site on Day 2 prior to receipt of the morning dose.

Day 2 blood pressure monitoring (for participants that were unable to receive evening dose on Day 1 due to having met either *asymptomatic* or *symptomatic* low BP criteria):

At the Day 2 visit, participants will receive a reduced dose of BMS-986278 (10 mg BID) while those randomized to placebo will be administered placebo for 10 mg BMS-986278 BID. Dose reduction should be appropriately noted in the case report form.

On Day 2, participants will remain at the site for at least 4 hours post dose. Orthostatic BP and HR will be performed predose and 1.5, 2, and 4 hours post dose. Participants will be carefully monitored for symptoms associated with low BP.

Participants will remain on reduced dose (10 mg BMS-986278 BID or matching placebo for 10 mg BMS-986278 BID) and will take the Day 2 evening dose at home and return to the study site on Day 8 if neither *asymptomatic* nor *symptomatic* low BP criteria are met.

If either *asymptomatic* or *symptomatic* low BP criteria, as described for Day 1, are met on Day 2, participants will be discontinued from study treatment (but continue in the study).

Blood pressure monitoring at post-Day 1 study visits:

At every post-Day 1 study visit, vital signs, including orthostatic assessments, will be performed.

Participants will take the evening dose at home and will return for their next scheduled study visit, as indicated in the Schedule of Activities (Section 2), if neither *asymptomatic* nor *symptomatic* low BP criteria are met during any post-Day 1 study visit.

If either *asymptomatic* or *symptomatic* low BP criteria, as described for Day 1, are met on any post-Day 1 visit (predose), participants will remain at the site for at least 4 hours. Orthostatic BP and HR will be performed 1.5, 2, and 4 hours after the low BP criteria at predose are detected.

Participants will not receive the evening dose and will remain at the site until BP resolution criteria are met:

a) The participant provides 2 consecutive seated BP measurements (at least 30 minutes apart) showing SBP > 85 mmHg and DBP > 55 mmHg

b) The participant does not demonstrate orthostatic hypotension

c) Potential symptoms of decreased BP (as described under Day 1) have not been present for at least 30 minutes

If a decision is made to reduce to 10 mg BMS-986278 BID (or placebo for 10 mg BMS-986278 BID), the participant will return to the site the following day prior to receipt of the morning dose and will follow the Day 2 BP monitoring instructions. Dose reduction should be appropriately noted in the case report form.

Identifiable causes of low BP at any study visit, unrelated to study treatment, will be managed as clinically indicated. The management of initial low BP without an identifiable cause will include BP monitoring consistent with that described for Day 1 and Day 2.

At every post-Day 1 study visit, if any predose BP and/or HR measurements meet *asymptomatic* or *symptomatic* low BP criteria, participants will not receive study treatment during that visit.

Blood pressure monitoring criteria described above will apply to the OTE.

5.1.3 Main Study Posttreatment Follow-up Period

Participants in the main study that do not enter the OTE will undergo a posttreatment follow-up visit 28 days (± 7 days) after the Week 26 visit. During the follow-up period, participants will not receive either active treatment or placebo.

Participants in the main study that discontinue study treatment with BMS-986278 or matching placebo before Week 26 will complete the remaining study visits according to the Schedule of Activities (Table 1), including the posttreatment follow-up visit.

5.1.4 Optional Treatment Extension

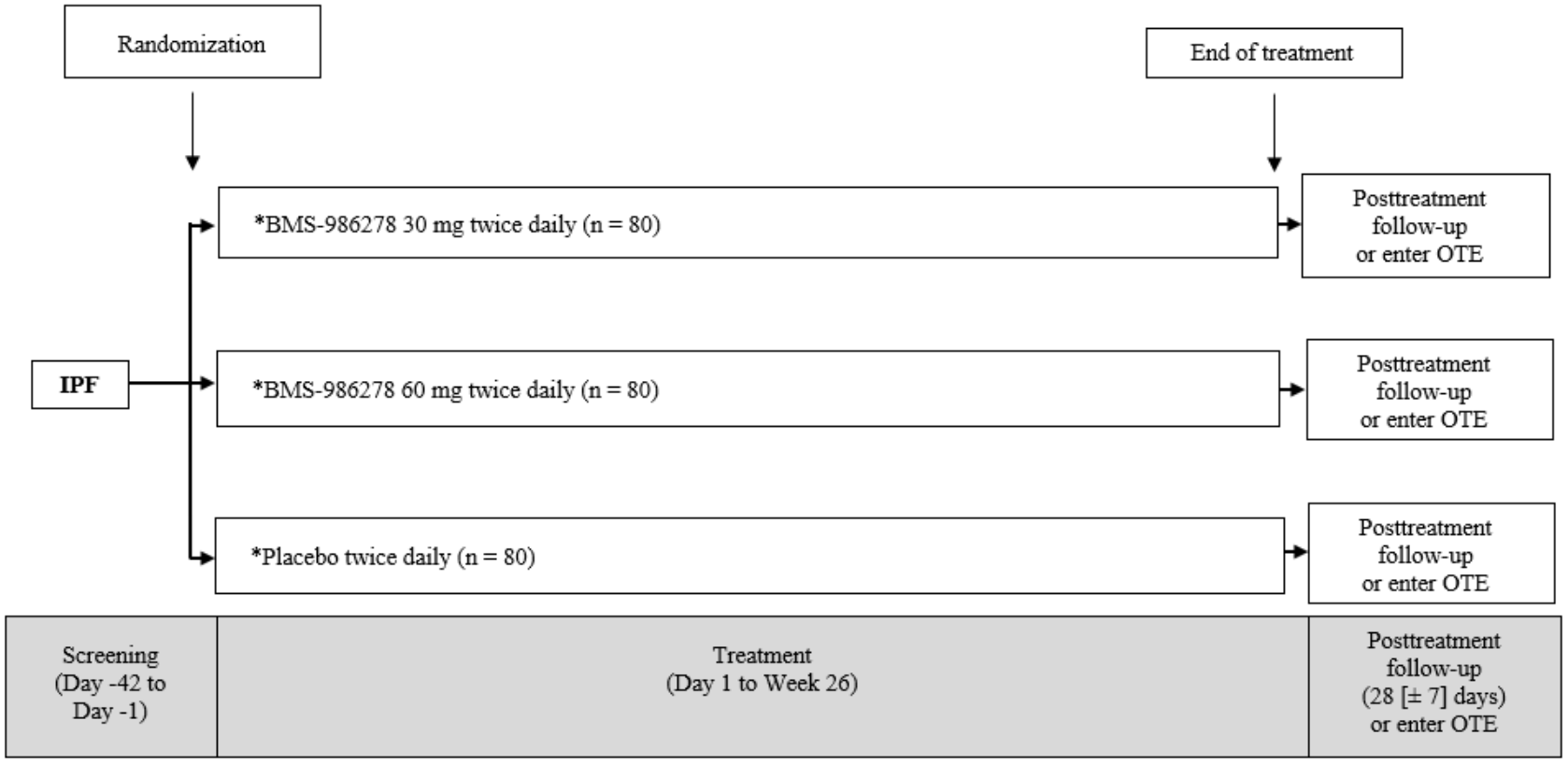
At the end of the main study treatment period, participants will have the opportunity to participate in an additional 26-week OTE.

Participants that elect to enter the OTE will receive active treatment within 1 to 15 days from completing the Week 26 visit in the main study. Study visits and procedures during the OTE are described in the study design schematic (Figure 3) and the Schedule of Activities (Table 2).

Participants in the OTE that discontinue study treatment with BMS-986278 before Week 26 will complete the remaining study visits according to the Schedule of Activities (Table 2), including the post OTE treatment follow-up visit.

During the OTE, BP monitoring should follow the requirements in Section 5.1.2.1 for every study visit, including OTE Day 1.

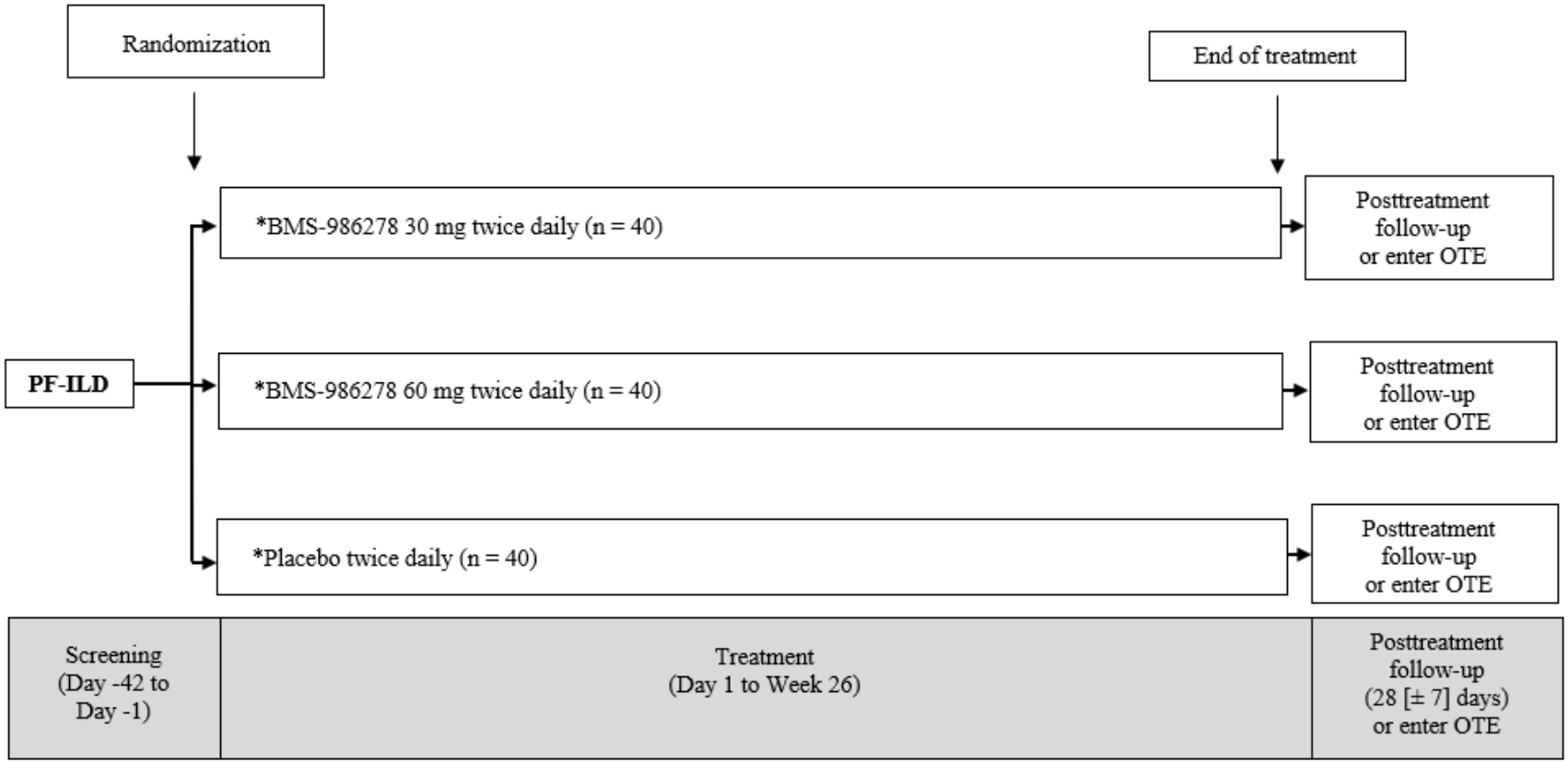
Figure 1: Study Design Schematic of the IPF Cohort (Main Study)



BID = twice daily; BP = blood pressure; IPF = idiopathic pulmonary fibrosis; OTE = optional treatment extension

* Participants receiving 30 mg or 60 mg (or placebo) BMS-986278 BID in the main study who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID (or placebo for 10 mg BID)

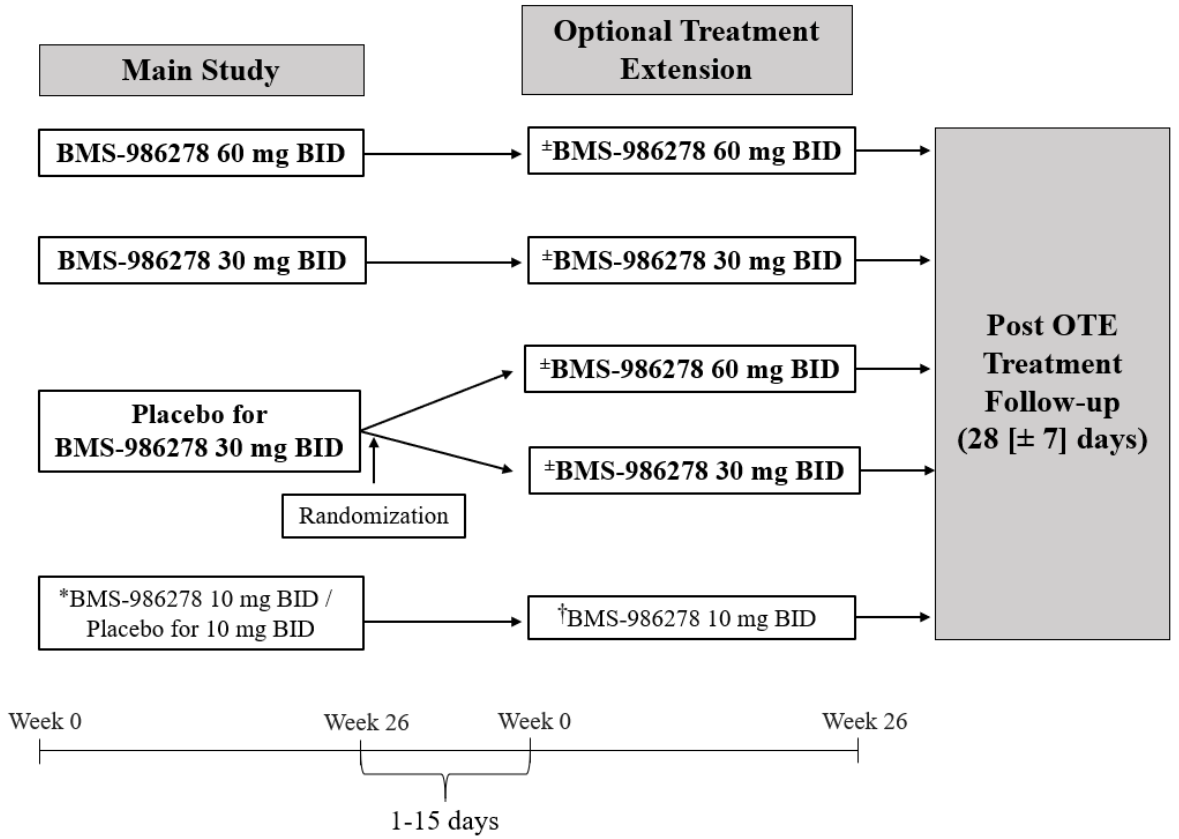
Figure 2: Study Design Schematic of the PF-ILD Cohort (Main Study)



BID = twice daily; BP = blood pressure; OTE = optional treatment extension; PF-ILD = non-IPF, progressive fibrotic interstitial lung disease

* Participants receiving 30 mg or 60 mg (or placebo) BMS-986278 BID in the main study who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID (or placebo for 10 mg BID)

Figure 3: Study Design Schematic for the OTE (for each of the separate IPF and PF-ILD Cohorts)



BID = twice daily; IPF = idiopathic pulmonary fibrosis; OTE = optional treatment extension; PF-ILD = non-IPF, progressive fibrotic interstitial lung disease

* Participants that were dose reduced in the main study

† Participants on 10 mg BMS-986278 BID are unblinded in the OTE

± Participants receiving 30 mg or 60 mg BMS-986278 BID in the OTE who meet low BP criteria may be dose reduced to 10 mg BMS-986278 BID

5.1.5 Data Monitoring Committee and Other External Committees

Study results will be monitored by an Independent Data Monitoring Committee (DMC); the scope of responsibility of the DMC will be outlined in the DMC Charter. Safety results will be reviewed by the DMC after approximately 30 randomized participants from either the IPF or PF-ILD cohort have completed at least 4 weeks after the first dose and at subsequent points outlined in the DMC Charter. Based on their reviews, the DMC will make recommendations to the sponsor on whether the study should be allowed to continue or be modified or terminated. Additional DMC meetings may also be scheduled to review the study data during the treatment period, as described in the DMC Charter.

Based on their overall benefit/risk evaluation, the DMC recommendations may include proceeding with the study without modification, proceeding with the study with modification, or study suspension. The scope, conduct, membership, processes, and accountabilities of the DMC are specified in the DMC Charter.

5.2 Number of Participants

This study will randomize approximately 360 participants in total.

Approximately 240 participants with IPF will be randomized to receive 30 mg BMS-986278 BID, 60 mg BMS-986278 BID, or placebo BID at a ratio of 1:1:1 for 26 weeks in the main study.

In addition, a secondary cohort of approximately 120 PF-ILD participants will be randomized to receive 30 mg or 60 mg BMS-986278 BID or placebo BID at a ratio of 1:1:1 for 26 weeks in the main study.

Following the 26-week main study, participants from both IPF and PF-ILD cohorts will have the opportunity to participate in an additional 26-week OTE. All participants in the OTE will receive an active dose of BMS-986278 (30 mg BID, 60 mg BID, or 10 mg BID).

5.3 End of Study Definitions

The start of the study is defined as the visit for first participant screening.

The last day of the main study will occur when the last participant has completed the follow-up visit (28 ± 7 days after the Week 26 visit). Primary study completion is defined as the final date on which data for the primary endpoint of the 26-week main study was or is expected to be collected. Participants will be considered to have completed the main study if they complete 26 weeks of evaluation.

The last participant visit of the OTE is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Table 2) for the last participant, whichever occurs last. This last participant visit will be the last visit for the entire study.

End of study is defined as the date of the last visit of the last participant.

5.4 Scientific Rationale for Study Design

Several lines of published evidence support targeting the LPA/LPA_1 receptor pathway in fibrotic diseases and for the treatment of IPF.[6, 7] Increased LPA concentrations have been reported in the

alveolar space of both IPF patients and the corresponding BLEO mouse lung model, in which genetic deletion[6, 8] or pharmacological inhibition[9] of LPA_1 attenuated the development of the modeled disease, suggesting a direct involvement of LPA and LPA_1 in disease pathogenesis. Increased epithelial cell apoptosis in response to lung injury has also been implicated in the development of IPF and linked to LPA. LPA signaling through LPA_1 has been reported to promote epithelial cell apoptosis induced by BLEO injury in mice.[8] The number of apoptotic cells present in the alveolar and bronchial epithelia of LPA_1-deficient mice was significantly reduced compared with wild-type mice after BLEO challenge.[8]

Consistent with these in vivo rodent results, increases in LPA levels and LPA signaling through LPA_1 have been observed in individuals with fibrotic diseases. LPA levels are elevated in the bronchoalveolar lavage (BAL) of patients with IPF[6] and were also found to be higher in patients with systemic sclerosis versus normal healthy volunteers.[17] Increased concentrations of autotaxin, the enzyme largely responsible for extracellular LPA production, were elevated in both murine and human fibrotic lungs.[10] Together these data suggest that antagonizing the LPA_1 receptor may be beneficial in treating patients with IPF. Furthermore, the proof of concept for antifibrotic activity with an LPA_1 antagonist was demonstrated in a randomized, double-blind, placebo-controlled Phase 2 study with BMS-986020, another selective, small-molecule LPA_1 antagonist (Study IM136003) discussed above in Section 3.4.4.1.[11]

BMS-986278 is a potent full antagonist at LPA_1 that has been shown to potently inhibit LPA-stimulated activation of multiple signal transduction pathways. BMS-986278 is being developed as a potential treatment for IPF (see the Investigator's Brochure for additional details).

Beyond IPF, some patients with other chronic forms of fibrotic ILD develop a progressive phenotype characterized by worsening respiratory symptoms, lung function, progressive fibrosis on imaging and early mortality. There is a high unmet need for effective and tolerable treatments for patients with non-IPF, fibrotic ILD that exhibit disease progression.[2, 3, 4] Because of the clinical and pathophysiological similarities among these diseases, it has been suggested that such disorders have a common pathobiologic mechanism regardless of the cause – with resultant progressive lung fibrosis – and thus could have a response to similar treatment as IPF.[2, 3, 4] Indeed, in the recently published INBUILD trial, patients with PF-ILD with diverse etiologies were treated with nintedanib vs placebo. Those treated with nintedanib had slower progression of lung fibrosis than those who received placebo, as demonstrated by a lower annual rate of decline in FVC over the 52-week study period. The absolute treatment effects in this PF-ILD cohort were similar in magnitude to those observed in the pivotal INPULSIS trials that led to approval of nintedanib for treatment of IPF and based on data from the INBUILD trial, a number of health authorities have also approved nintedanib for patients with PF-ILD.[5] In this study, it is anticipated that the average rate of decline in ppFVC between baseline and Week 26 will be smaller among participants taking 2 different doses of BMS-986278 than among those taking placebo. It is also anticipated that the rate of decline in ppFVC between baseline and Week 26 will be smaller among participants taking each individual dose than among those taking placebo.

This study is the first evaluation of BMS-986278 in participants with pulmonary fibrosis. This study is designed to provide an initial evaluation of the efficacy of BMS-986278 in participants with IPF, further demonstrate the safety of BMS-986278, and provide information on the PK of BMS-986278 in participants with IPF. In addition, a secondary cohort consisting of PF-ILD participants will be enrolled in order to assess safety, tolerability, and efficacy of BMS-986278 in PF-ILD. The PF-ILD cohort will be analyzed separately from the IPF cohort, but with the same schedule of activities and endpoints.

In order to augment knowledge about the safety, tolerability, and efficacy of BMS-986278, an OTE will be offered to all participants that complete the 26-week main study.

5.4.1 Rationale for Optional Treatment Extension (OTE)

An optional treatment extension of an additional 26 weeks of IP is being offered to participants who complete the 26-week main study. Decisions about whether to continue in the OTE are left to the discretion of the clinical investigator and the willingness of the participant. Many factors will be taken into consideration by the investigator and participant, including a clinical assessment of disease status (ie, whether the enrolled participant is benefiting from ongoing treatment) along with assessments of tolerability and safety considerations.

A chief focus of the OTE is to augment knowledge regarding safety and tolerability of BMS-986278 in participants with IPF and PF-ILD. As such, vigilant safety and tolerability monitoring are the primary focus of the frequent visits during the OTE.

Finally, during the OTE, management decisions regarding concomitant background antifibrotic or immunosuppressive medications are left to the discretion of the clinical investigator and participant preference. There are no known contraindications to the combination of BMS-986278 with antifibrotic (eg, pirfenidone, nintedanib) medications or any of the immunosuppressive medications other than cyclosporine. (Cyclosporine use is contraindicated in the main study and OTE because it is a potent inhibitor of OATPs [APPENDIX 5].)

5.5 Justification for Dose

The expected therapeutic dose range for BMS-986278 is 26 mg to 100 mg based on in vitro and animal models.[6, 7, 8, 9, 18, 19] In the FIH study (Study IM027009), single BMS-986278 doses of up to 150 mg and daily doses of up to 125 mg BID for 14 days were generally well tolerated, and the events of decrease in BP observed in the study were generally asymptomatic and are monitorable. The doses selected for this study (30 mg BID and 60 mg BID) were informed by the safety and tolerability of BMS-986278 observed in the FIH study of BMS-986278 (Study IM027009), as well as the results of a prior exposure-response analysis for BMS-986020, another LPA1 antagonist that was studied in a Phase 2 study in patients with IPF (Study IM036003). 30 mg BID and 60 mg BID were selected such that both dose levels are likely to achieve a profile of halting disease progression based on ppFVC, thus enabling the achievement of a compelling efficacy as well as safety profile. Both doses are expected to be safe and well tolerated based on the overall clinical experience in healthy volunteers at doses as high as 125 mg BID in Study IM027009. Studying at least a 2× difference in exposure is expected to allow delineation of any potential differences in safety profile, as well as any potential differences in BP response. Data on a lower dose level (ie,

10 mg BID) may be collected in case one of the 2 dose levels is not well tolerated (eg, due to significant BP lowering following the first few hours after dosing), allowing further delineation of exposure-efficacy and exposure-safety relationships.

6 STUDY POPULATION

The section below outlines the inclusion and exclusion criteria for the IPF and PF-ILD cohorts.

These criteria specify which concomitant therapies (eg, antifibrotic or immunosuppressive therapies) are permitted for IPF and PF-ILD during the main study. Decisions about whether a patient with IPF or PF-ILD will choose to consider participation in this clinical study are left to the discretion of the clinical investigator, as well as the patient himself/herself, after due consideration of the inclusion criteria, study design, and numerous other variables. Factoring in the background therapies permitted during the 26-week main study may impact such consideration. Potential decisions to modify or discontinue background therapies to enable potential enrollment in this clinical study are not recommended, determined, or mandated by the study sponsor; rather, any such decision is left strictly to the discretion of the clinical investigator and the willingness of the potential patient.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) **Not applicable per Revised Protocol 03**. Willing to participate in the study and sign the informed consent form (ICF) by participants or their legal authorized representative.

b) Willing and able to complete all study-specific procedures and visits.

c) Willing to participate in the study and sign the informed consent form (ICF) by participants.

2) Type of Participant and Target Disease Characteristics:

a) <u>For the IPF cohort:</u>

i) **Not applicable per Protocol Amendment 04; refer to Inclusion Criterion 2)a)v**. Diagnosis of IPF within 7 years of screening (including screening period).

ii) Centrally read chest high-resolution computed tomography (HRCT) obtained at screening:

(1) HRCT interpretation as consistent with UIP or probable UIP.

(2) If the HRCT interpretation on central reading is inconsistent with UIP, there must be verification that surgical lung biopsy histopathology is consistent with UIP. UIP pattern identification via cryobiopsy will be considered on a case-by-case basis.

iii) If not currently on pirfenidone or nintedanib, participants must be naïve to either medication or have not received either of these medications within 4 weeks prior to Day 1. See Section 7.7.1 for OTE guidance.

iv) If on pirfenidone or nintedanib, participants must have been receiving a stable dose for at least 3 months prior to screening and during the screening period. Pirfenidone or

nintedanib concomitant treatment should be used as per usual prescribing information approved by local regulatory agencies but patients on stable reduced dose can be included. See Section 7.7.1 for OTE guidance.

v) Diagnosis of IPF within 7 years of screening.

b) <u>For the PF-ILD cohort:</u>

i) **Not applicable per Revised Protocol 03.** Diagnosis of ILD within 7 years of screening (including screening period).

ii) Evidence of progressive ILD within the 24 months before screening, defined as either:

(1) a decline in the relative ppFVC of ≥ 10%, or

(2) a decline in the relative ppFVC of ≥ 5% to < 10% along with an increased extent of fibrosis on pre-screening thoracic computed tomography compared with prior imaging, or

(3) symptoms associated with progression of ILD along with an increased extent of fibrosis on pre-screening thoracic computed tomography compared with prior imaging.

iii) Centrally read HRCT obtained at screening demonstrating evidence of > 10% parenchymal fibrosis within the whole lung.

iv) If not currently on pirfenidone or nintedanib, participants must be naïve to either medication or have not received either of these medications within 4 weeks prior to Day 1. See Section 7.7.1 for OTE guidance.

v) If on pirfenidone or nintedanib, participants must have been receiving a stable dose for at least 3 months prior to screening and during the screening period. Pirfenidone or nintedanib concomitant treatment should be used as per usual prescribing information approved by local regulatory agencies but participants on stable reduced dose can be included. See Section 7.7.1 for OTE guidance.

vi) Mycophenolate mofetil, mycophenolic acid, azathioprine or and/or tacrolimus are permitted only if the participant is on a stable dose at least 6 months prior to screening. These immunosuppressive medications cannot be initiated during the course of the main study.

3) Target Disease Characteristics

a) ppFVC ≥ 40%

b) Forced expiratory volume in 1 second (FEV_1)/FVC ≥ 0.7, based on prebronchodilator spirometry.

c) ppDLCO SB (percent predicted single-breath carbon monoxide diffusing capacity, corrected for hemoglobin) ≥ 25%.

4) Age and Reproductive Status

a) Female Participants:

i) Women not of childbearing potential ≥ 40 years of age for the IPF cohort and ≥ 21 years of age for the PF-ILD cohort.

ii) Women participants must have documented proof that they are not of childbearing potential (refer to APPENDIX 4).

iii) A female participant is eligible to participate if she is not pregnant or breastfeeding, and is not a WOCBP.

b) Male Participants:

i) Male ≥ 40 years of age for the IPF cohort and ≥ 21 years of age for the PF-ILD cohort.

ii) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP even if the participant has undergone a successful vasectomy or if the partner is pregnant.

iii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (APPENDIX 4) for the duration of treatment with BMS-986278 and for at least 3 days after treatment completion.

iv) Male participants must refrain from sperm donation during the duration of treatment with BMS-986278 and for at least 3 days after dosing has been completed.

v) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the duration of treatment with BMS-986278 and for at least 3 days after dosing has been completed.

vi) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, during the treatment and for at least 3 days after the end of treatment.

vii) Female partners of males participating in the study should be advised to use highly effective methods of contraception until the end of relevant systemic exposure, defined as 3 days after the end of treatment in the male participant.

viii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

Investigators shall counsel male participants who are sexually active with WOCBP on the importance of pregnancy prevention, the implications of an unexpected pregnancy and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Medical Conditions

a) Women who are of childbearing potential

b) Women who are breastfeeding

c) For the <u>IPF cohort</u>:

i) ILD associated with known primary causes.

ii) Diagnosis of any systemic autoimmune disease (also known as "connective tissue disease") (including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis).

d) For the <u>PF-ILD cohort</u>:

i) A diagnosis of IPF, along with UIP pattern on central reading of HRCT, surgical lung biopsy, or cryobiopsy.

ii) **Not applicable per Revised Protocol 03.** A diagnosis of sarcoidosis or any systemic autoimmune disease (also known as "connective tissue disease") *other than rheumatoid arthritis* (including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus) as confirmed by the principal investigator. (Rheumatoid arthritis-ILD is the lone systemic autoimmune disease eligible for the PF-ILD cohort. Furthermore, participants that are considered as having "interstitial pneumonia with autoimmune features" are eligible for the PF-ILD cohort.)

iii) **Not applicable per Revised Protocol 03.** Use of either pirfenidone and nintedanib within 4 weeks of Day 1. Neither pirfenidone nor nintedanib are allowed during this study for the PF-ILD cohort. See Section 7.7.1 for guidance in the OTE.

iv) A diagnosis of sarcoidosis or any systemic autoimmune disease (also known as "connective tissue disease") *other than rheumatoid arthritis* (including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and systemic vasculitis) as confirmed by the principal investigator. (Rheumatoid arthritis-ILD is eligible for the PF-ILD cohort. Furthermore, participants that are considered as having "interstitial pneumonia with autoimmune features" are eligible for the PF-ILD cohort.)

e) Clinically significant (in the opinion of the investigator) non-parenchymal lung disease, (eg, asthma, chronic obstructive pulmonary disease, cavitary or pleural diseases) at screening.

f) Known significant pulmonary arterial hypertension (PAH) (ie, previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization showing a cardiac index < 2 L/min/m^2, or PAH requiring combination of PAH-specific therapies or any PAH parenteral therapy).

g) Emphysema ≥ 50% on HRCT assessed by a central reader, or the extent of emphysema is greater than the extent of fibrosis according to reported results from the most recent HRCT.

h) Acute IPF/ILD exacerbation within 6 weeks before or during screening, defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality, as follows:[15]

   1. Acute worsening or development of dyspnea (< 1 month duration).
   2. Imaging with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrotic lung disease.
   3. Respiratory deterioration not fully explained by cardiac failure or fluid overload.

i) **Not applicable per Revised Protocol 03.** Clinically significant respiratory tract infection (in the opinion of the investigator) (eg, active tuberculosis, infectious pneumonia) within 4 weeks prior to screening or during screening.

j) Significant cardiac disease (eg, hospitalization for congestive heart failure; myocardial infarction, unstable angina, coronary angioplasty or coronary artery bypass graft within 6 months of screening) or uncontrolled atrial or ventricular cardiac arrhythmias.

k) Known presence of significant left-ventricular dysfunction (ie, echocardiography with ejection fraction of < 40%).

l) History, within the last 2 years, of alcohol or frequent nonprescription drug abuse (in the opinion of the investigator), significant mental illness, or physical dependence on any opioid.

m) Positive urine test during screening for illegal drugs of abuse (with the exception of marijuana), unless these drugs are prescribed by the treating physician (prescription must be documented by the investigator or the designee in source documents).

n) Participants who have: 1) current malignancy or 2) a previous malignancy up to 5 years prior to screening are excluded except for those with a documented history of cured nonmetastatic squamous cell skin carcinoma, basal cell skin carcinoma, or cervical carcinoma in situ. Participants who have a biopsy that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations, are also excluded.

o) History of stroke or transient ischemic attack within 6 months prior to screening.

p) **Not applicable per Protocol Amendment 04; refer to Exclusion Criterion 1)y.** History of lung reduction surgery or transplant, or is awaiting lung transplant, or plans to undergo lung reduction surgery or transplant during the study.

q) Positive for hepatitis C antibody (unless documented hepatitis C virus RNA negative), positive hepatitis B surface antigen (HBsAg) or positive hepatitis B core antibody (HBcAb) (unless documented hepatitis B virus DNA negative), human immunodeficiency virus (HIV)-1 antibody, or HIV-2 antibody.

r) Cigarette smoking (including e-cigarettes) within 3 months before screening or unwilling to avoid smoking throughout the study.

s) Inability to tolerate oral medication.

t) Inability to be venipunctured and/or tolerate venous access.

u) **Not applicable per Revised Protocol 03.** Any other sound medical, psychiatric, and/or social reason as determined by the investigator.

v) Positive pregnancy test prior to Day 1 study treatment administration.

w) Clinically significant respiratory tract infection (in the opinion of the investigator) (eg, active tuberculosis, infectious pneumonia) within 4 weeks prior to screening or during screening. Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the medical monitor or study director, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

x) Any other sound medical, psychiatric, and/or social reason as determined by the investigator. Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the medical monitor or study director, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

y) History of lung reduction surgery or lung transplantation, or is on an active transplant list, or plans to undergo lung reduction surgery or lung transplantation during the study.

2) Prior Therapy

a) Use of systemic corticosteroids equivalent to prednisone > 15 mg/day within 2 weeks of Day 1. See Section 7.7.1 for guidance in the OTE.

b) **Not applicable per Revised Protocol 03**. Use of azathioprine, cyclophosphamide, cyclosporine, methotrexate, leflunomide, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus within 4 weeks of Day 1. Additionally, use of rituximab or other specific B-cell depleting therapies within 6 months of Day 1. Disease modifying anti-rheumatic drugs (DMARDs), including but not limited to hydroxychloroquine, sulfasalazine, anti-TNF alpha antagonists, interleukin antagonists, abatacept, tofacitinib, and baricitinib, will be permitted as long as these agents have been in place and stable for at least 6 months prior to screening (refer to Section 7.7). See Section 7.7.1 for guidance in the OTE.

c) Use of potent inhibitors of OATPs, defined as inhibitors expected to increase exposures of OATP substrates by more than 2× within 4 weeks of Day 1 (see APPENDIX 5).

d) Use of potent inhibitors or inducers of cytochrome P450 CYP3A4 or CYP2C8 (see APPENDIX 6 and APPENDIX 7, respectively) within 4 weeks of Day 1.

e) Received experimental IPF or other experimental ILD therapy within 4 weeks before screening.

f) **Not applicable per Protocol Amendment 04; refer to Exclusion Criterion 2)i**. Long-acting phosphodiesterase 5 inhibitors (eg, tadalafil, vardenafil). Daily use of short-acting phosphodiesterase 5 inhibitors (eg, sildenafil) taken as needed for erectile dysfunction is allowed during the study, but is not allowed within 7 days pre or post Day 1. Short-acting phosphodiesterase 5 inhibitors taken daily for treatment of pulmonary arterial hypertension are not allowed during the study.

g) Simultaneous use of pirfenidone and nintedanib at screening.

h) Use of, cyclophosphamide, cyclosporine, methotrexate, and/or leflunomide within 4 weeks of Day 1. Additionally, use of rituximab or other specific B-cell depleting therapies within 6 months of Day 1. Mycophenolate mofetil, mycophenolic acid, azathioprine or and/or tacrolimus are permitted only if the participant is on a stable dose at least 6 months prior to screening. These immunosuppressive medications cannot be initiated during the course of the main study. Disease modifying anti-rheumatic drugs (DMARDs), including but not limited to hydroxychloroquine, sulfasalazine, anti-TNF alpha antagonists, interleukin antagonists, abatacept, tofacitinib, and baricitinib, will be permitted as long as these agents have been in place and stable for at least 6 months prior to screening (refer to Section 7.7). See Section 7.7.1 for guidance in the OTE.

i) Long-acting phosphodiesterase 5 inhibitors (eg, tadalafil, vardenafil) and chronic use of short-acting phosphodiesterase 5 inhibitors (eg, sildenafil). Short-acting phosphodiesterase 5 inhibitors taken as needed for erectile dysfunction is allowed during the study, but is not allowed within 7 days pre or post Day 1.

3) Physical and Laboratory Test Findings

a) Participants with a seated SBP of < 100 mmHg (confirmed by retest within 15 minutes) or seated DBP of < 60 mmHg (confirmed by retest within 15 minutes) at screening or prior to Day 1 study treatment will be excluded from participation in this study.

b) **Not applicable per Revised Protocol 03.** Participants with orthostatic intolerance, orthostatic hypotension or orthostatic tachycardia (as defined in Section 5.1.2.1) at screening or prior to Day 1 study treatment will be excluded from participation in this study.

c) **Not applicable per Protocol Amendment 04; refer to Exclusion Criterion 3)i.** Uncontrolled hypertension, defined as SBP > 160 mmHg or DBP > 100mmHg at screening or prior to the first dose of study treatment. BP may be rechecked no more than twice as clinically indicated.

d) ALT or aspartate aminotransferase (AST) ≥ 2× the upper limit of normal (ULN) at screening.

e) Estimated glomerular filtration rate < 30 mL/min at screening.

f) Any of the following on ECG prior to study treatment administration, confirmed by repeat:

i) **Not applicable per Revised Protocol 03.** PR ≥ 210 msec

ii) **Not applicable per Revised Protocol 03.** QRS ≥ 120 msec

iii) QT ≥ 500 msec

iv) QTcF ≥ 450 msec

g) **Not applicable per Protocol Amendment 04; refer to Exclusion Criterion 3)j.** Baseline total bilirubin > 1.5× ULN unless the participant has Gilbert's syndrome. Participants with Gilbert's syndrome must have total bilirubin between ≥ 1.5× ULN and ≤ 5× ULN, with direct bilirubin ≤ ULN and no clinical or laboratory evidence of hemolysis.

h) Participants with orthostatic intolerance, orthostatic hypotension (confirmed by retest within 15 minutes) or orthostatic tachycardia (confirmed by retest within 15 minutes) (refer to Section 5.1.2.1 for definitions) at screening or prior to Day 1 study treatment will be excluded from participation in this study.

i) Uncontrolled hypertension, defined as seated SBP > 180 mmHg or seated DBP > 100 mmHg at screening or prior to the first dose of study treatment. BP may be rechecked no more than twice as clinically indicated.

j) Screening total bilirubin > 1.5× ULN unless the participant has Gilbert's syndrome. Participants with Gilbert's syndrome must have total bilirubin between ≥ 1.5× ULN and ≤ 5× ULN, with direct bilirubin ≤ ULN and no clinical or laboratory evidence of hemolysis.

k) Screening WBC < 2.5×10^3, Hemoglobin < 9 g/dL, platelets < 75×10^9/L

4) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated.

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

c) Participants who lack capacity to consent for themselves.

5) Allergies and Adverse Drug Reaction

a) History of allergy to BMS-986278 or related compounds.

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Participants should not consume ≥ 7 units/week of alcohol during the study. One drink "unit" or 1 standard drink is equivalent to 12 ounces of beer, 4 ounces of wine, or 1 ounce of hard liquor.

6.3.1 Meals and Dietary Restrictions

No restrictions are required, except for items specified in APPENDIX 6. However, fed/fasted status and time of morning meal (if fed) must be recorded at every visit, including intensive PK sample days.

6.3.2 Activity

No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials publishing requirements, as applicable,

and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Screening laboratory parameters and/or assessments that are included in Table 1 may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Participants may be rescreened once according to the discretion of the investigator. Additional rescreening may be allowed after consultation with the Medical Monitor. For participants who are rescreened, HRCT does not need to be repeated if obtained within 10 weeks of randomization.

Participants who are included in the intensive PK substudy and/or PET-Tracer substudy will be consented for the substudies in addition to being consented to the main study.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, procedure(s), or medical device intended to be administered to a study participant according to the study protocol.

Study treatment includes investigational [medicinal] product (IP/IMP) as shown in Table 4.

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the SOC for a given diagnosis, may be considered as noninvestigational products.

Table 4: Study Treatments for Study IM027040

Product Description/ Class and Dosage Form	Potency	IP/Non-IP	Blinded or Unblinded	Packaging/ Appearance	Storage Conditions (per label)
BMS-986278/oral tablets	10 mg[a]	IP	Blinded	Film-coated oral tablet	Refer to the label on container Store in a tightly closed container
BMS-986278/oral tablets	30 mg[b]	IP	Blinded	Film-coated oral tablet	Refer to the label on container Store in a tightly closed container
Placebo oral tablets for 10 mg BMS-986278	NA	IP	Blinded	Film-coated oral tablet	Refer to the label on container Store in a tightly closed container
Placebo oral tablets for 30 mg BMS-986278	NA	IP	Blinded	Film-coated oral tablet	Refer to the label on container Store in a tightly closed container

BID = twice daily; IP = investigational product; NA = not applicable; non-IP = noninvestigational product; OTE = optional treatment extension

[a] Participants receiving 10 mg BMS-986278 BID in the OTE will be unblinded

[b] Participants receiving 30 mg or 60 mg BMS-986278 BID in the OTE will remain blinded until database lock for analyses of the 26-week main study

7.1 Treatments Administered

A double-blind design will be employed in the main study. Each participant will take 2 identical oral tablets in a blinded fashion every day in the morning and evening, as following:

- Placebo: 2 × placebo for 30 mg BMS-986278 tablets
- 30 mg dose: 1 × 30 mg BMS-986278 tablet and 1 × placebo for 30 mg tablet
- 60 mg dose: 2 × 30 mg BMS-986278 tablets

If participants receive reduced dose on Day 2 or beyond, they will take 1 tablet (10 mg BMS-986278 BID or matching placebo for 10 mg BMS-986278 BID) in a blinded fashion every day in the morning and evening for the rest of treatment.

Tablets should be taken orally (swallowed whole) with a full glass (240 mL) of water in the morning and in the evening approximately 12 hours after the morning dose every day for 26 weeks. On the days of study visits, participants will not self-administer morning doses; doses will be administered at the site. Doses at any dose reduction visit will also be administered at the site.

Participants will be issued study medication kits/containers on Day 1, and at Weeks 4, 8, 12, 16 and 20 (as shown in Table 1), and at any dose reduction study visit, containing sufficient treatment

to last until the next protocol-scheduled study visit. Participants should bring their study medication kits/containers with them to each study visit. If a participant has leftover treatment at the time of the next protocol-scheduled study visit, they should return it at the visit prior to receiving their next medication kit/container. If a participant has an unscheduled visit (except for dose reduction visits), study medication kits/containers do not need to be brought back to the site until the next protocol-scheduled visit. Starting at the Week 4 visit, any remaining study treatment will be returned to the site with every protocol-scheduled visit.

If a participant meets dose reduction criteria post-Day 1, the site must destroy the treatments previously assigned to the participant once IMP reconciliation has been performed, and contact IRT for new study medication kits/container on the dose reduction visit.

After completing the 26-week main study, participants that elect to continue in the OTE will take 1 or 2 identical oral tablets every day in the morning and evening, as follows:

- 30 mg dose: 1 × 30 mg BMS-986278 tablet and 1 × placebo for 30 mg tablet
- 60 mg dose: 2 × 30 mg BMS-986278 tablets
- 10 mg dose: 1 × 10 mg BMS-986278 tablet

Treatment administration in the OTE will follow the same directions as the main study (described above). Participants will be issued sufficient study medication kits/containers on Day 1, Week 4, Week 16, and at any dose reduction study visit (as shown in Table 2). Refer to the main study above for additional details on study medication kits/container instructions.

7.2 Method of Treatment Assignment

Blinded treatment assignments will be managed using interactive response technology (IRT). Each cohort will be randomized to treatments independently in the IRT.

Before the study is initiated, users at each investigative site will receive log-in information and directions on how to access the IRT system. At the time of the screening visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the IRT system for assignment of a participant number for all participants, including participants not subsequently randomized or treated. The participant number is assigned sequentially by the system and will be unique across all sites. The participant number will not be used for any other participant. If a participant is rescreened, they will be given a new participant number.

Prior to the dosing on Day 1, participants who meet all criteria for enrollment at screening and Day 1 will be centrally randomized in a 1:1:1 ratio to BMS-986278 30 mg BID, BMS-986278 60 mg BID, or placebo, determined by a computer-generated randomization schedule using the IRT. The randomization lists will be generated by the IRT vendor using a permuted block design within each combination of stratum level. For the IPF cohort, randomization will be stratified by country (non-Japan versus Japan). Participants will be further stratified according to concomitant use of approved IPF therapy (pirfenidone vs nintedanib vs none). For the PF-ILD cohort, randomization will be stratified by UIP pattern (present vs absent) of lung injury on either

centrally-read HRCT, surgical lung biopsy, or cryobiopsy. Approximately 75 of 120 participants (62.5%) are expected to have UIP pattern of lung injury. Stratification for the PF-ILD cohort will also be based on category of background therapy (immunosuppression alone [ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus] versus anti-fibrotic [nintedanib, pirfenidone] versus none).

After randomization, a medication kit/container number will be assigned to the participant corresponding to the treatment assignment. At subsequent visits, when new treatment containers need to be provided, the investigative site will access the IRT to obtain the container number assigned to the participant.

All participants in the OTE will receive active treatment with BMS-986278. Participants that receive 30 mg BMS-986278 in the main study will continue on 30 mg BMS-986278 in the OTE and remain blinded to dose. Participants that receive 60 mg BMS-986278 in the main study will continue on 60 mg BMS-986278 in the OTE and remain blinded to dose. Participants that receive 2 placebo tablets for 30 mg BMS-986278 in the main study will be randomized at a ratio of 1:1 to receive either 30 mg BMS-986278 or 60 mg BMS-986278 and will be blinded to dose in the OTE.

Participants that receive 10 mg BMS-986278 or placebo for 10 mg BMS-986278 in the main study will be assigned to receive 10 mg BMS-986278 and will be unblinded in the OTE.

Refer to Figure 3 for the OTE study design.

7.3 Blinding

7.3.1 Maintaining the Blind

BMS-986278 30 mg and placebo for 30 mg are identical in appearance. BMS-986278 10 mg and placebo for 10 mg are also identical in appearance. Investigative site staff, sponsor and designee personnel, participants and their families will remain blinded to treatment assignments until the time of the respective database lock for IPF and PF-ILD cohorts at Week 26 of main study, at which time the OTE phase will be unblinded for that cohort.

During the OTE, participants that complete the main study at reduced dose (10 mg BMS-986278 or placebo for 10 mg BMS-986278) will be unblinded to treatment.

7.3.2 Circumstances for Unblinding

Blinding of study treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency in an individual participant or pregnancy of the partner of a male participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine if the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, or the problem may be properly managed by assuming that the participant is receiving the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the medical

monitor, but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding after the decision to unblind the participant has been documented.

In case of an emergency unblinding, the investigator(s) has unrestricted access to randomization information via the IRT system and is capable of breaking the blind through the IRT system without prior approval from the sponsor. Following the unblinding the investigator shall notify the medical monitor.

In cases of accidental unblinding, contact the medical monitor and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for nonemergency purposes should be discussed with the medical monitor.

A scientist in the NonClinical Disposition and Bioanalysis department of BMS (and/or a designee in the external bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples. Any results shared by the NonClinical Disposition and Bioanalysis group with the Sponsor's study team will be blinded to ensure integrity of the study.

7.4 Dosage Modification

Day 1 study visit:

On Day 1, participants will not self-administer morning the dose; the dose will be administered at the site. Participants will remain at the site for at least 4 hours post dose. Orthostatic BP and HR will be performed predose and 1.5, 2, and 4 hours post dose.

Participants will not receive the Day 1 evening dose if any of the defined low BP criteria are met (refer to Day 1 BP monitoring in Section 5.1.2.1 for details).

If either *asymptomatic* or *symptomatic* low BP criteria are met, participants will not receive the Day 1 evening dose and will remain at the site until:

a) The participant provides 2 consecutive seated BP measurements (at least 30 minutes apart) showing SBP > 85 mmHg and DBP > 55 mmHg

b) The participant does not demonstrate orthostatic hypotension

c) Potential symptoms of decreased BP (as described above) have not been present for at least 30 minutes

Participants will return to the site on Day 2 prior to receipt of the morning dose.

Day 2 study visit:

On Day 2, participants will be issued new kits/containers. Participants will not self-administer the morning dose; the dose will be administered at the site.

At the Day 2 visit, participants will receive a reduced dose. Those randomized to 30 mg or 60 mg BMS-986278 will have their medication kits/containers replaced with 10 mg BMS-986278. Those randomized to placebo will have their medication kits/containers replaced with the placebo for 10 mg BMS-986278. These participants will continue on 10 mg BMS-986278 BID or matching placebo for 10 mg BMS-986278 BID. All instances of dose reduction are communicated by the site or vendor to the central study team.

On Day 2, participants will remain at the site for at least 4 hours post dose. Orthostatic BP and HR will be performed predose and 1.5, 2, and 4 hours post dose. Participants will be carefully monitored for symptoms associated with low BP.

If either *asymptomatic* or *symptomatic* low BP criteria are met (refer to Day 1 BP monitoring in Section 5.1.2.1 for details), participants will be discontinued from study treatment (but continue in the study). All other participants will remain on reduced dose (10 mg BMS-986278 BID or matching placebo for 10 mg BMS-986278 BID).

Post-Day 1 study visits:

At every post-Day 1 study visit, participants will not self-administer morning doses; doses will be administered at the site. Vital signs, including orthostatic assessments, will be performed at every post-Day 1 study visit.

If either *asymptomatic* or *symptomatic* low BP criteria are met (refer to Day 1 BP monitoring in Section 5.1.2.1 for details), participants will remain at the site for at least 4 hours post dose. Orthostatic BP and HR will be performed 1.5, 2, and 4 hours after the low BP criteria at predose are detected. Participants will be carefully monitored for symptoms associated with low BP. If a decision is made to reduce to 10 mg BMS-986278 BID (or placebo for 10 mg BMS-986278 BID), the participant will return to the site the following day prior to receipt of the morning dose. Dose reduction should be appropriately noted in the case report form.

Dose modification criteria described above will apply to the OTE.

Dosage modifications for other reasons are otherwise not permitted.

7.5 Investigational Product Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the IP is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the IP arise, the IP should not be dispensed, and BMS must be contacted immediately.

Study intervention not supplied by BMS will be stored in accordance with the package insert.

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage,

administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 2.

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

At each protocol-scheduled visit from Day 29 (Week 4) to Week 26 (as shown in Table 1 for the main study and Table 2 for the OTE) and at the time of dose reduction or dose discontinuation (if applicable), treatment compliance will be evaluated for each participant by comparing the number of tablets taken by the participant with the number of tablets planned. Percentage compliance will be calculated as follows:

% compliance = (number of tablets taken ÷ number of tablets planned) × 100

If the estimated treatment compliance falls below 90%, the participant must be retrained at the site on study treatment administration.

Participant Study Medication diaries will be used by participants to record study treatment administration. Dosing diaries that have been completed should be reviewed at each study visit.

7.7 Concomitant Therapy

For the PF-ILD cohort, mycophenolate mofetil, mycophenolic acid, azathioprine or and/or tacrolimus are permitted only if the participant is on a stable dose at least 6 months prior to screening. These immunosuppressive medications cannot be initiated during the course of the main study.

Although pirfenidone or nintedanib are allowed during the main study for both cohorts, they are not allowed in combination with one another during the main study.

Stable DMARDs used to manage synovitis in rheumatoid arthritis patients will be permitted, as long as these agents have been in place and stable for at least 6 months prior to screening. DMARDs include, but are not limited to, hydroxychloroquine, sulfasalazine, anti-TNF alpha antagonists, interleukin antagonists, abatacept, tofacitinib, and baricitinib.

During the OTE, modifications and initiation of DMARD use are allowed per clinician discretion or patient preference.

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications during the study are as described in the study exclusion criteria in Section 6.2. Medications taken within 4 weeks prior to study treatment administration must be recorded on the electronic case report form (eCRF).

Once a participant completes the 26-week main study, modifications to background treatment of lung fibrosis are allowed per clinician discretion or patient preference for those in either cohort during the OTE. As such, during the OTE, anti-fibrotic therapy (eg, pirfenidone or nintedanib) may be started or used in combination, and no restrictions are placed with regards to concomitant use of immunosuppressive medications or corticosteroids. However, all other concomitant medications specified in Section 6.2 #2) will continue to be restricted in the OTE.

No concomitant prescribed medications are to be administered during study unless they are:

1) Prescribed for treatment of a clinical condition AND

2) Not prohibited in the exclusion criteria or elsewhere in the protocol.

All concomitant therapies (prescription, over the counter, or herbal) must be recorded on the eCRF.

7.8 Treatment After the End of the Study

Upon completion of either the main study or the OTE, treatment for IPF or PF-ILD will be at the discretion of the clinical provider.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986278 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue the IP for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- For participants that were unable to receive the evening dose on Day 1 due to having met either asymptomatic or symptomatic low BP criteria and received a reduced dose of BMS-986278 10 mg BID (or placebo for 10 mg BMS-986278 BID) on Day 2, if either asymptomatic or symptomatic low BP criteria are met on Day 2 (refer to Day 1 BP monitoring in Section 5.1.2.1 for details), they will be discontinued from further treatment (but continue in the study). This also applies to the Day 1 and Day 2 visits in the OTE.
- For participants receiving 10 mg BMS-986278 BID (or placebo for 10 mg BMS-986278 BID) after Day 2, if either asymptomatic or symptomatic low BP criteria are met (refer to Day 1 BP monitoring in Section 5.1.2.1 for details), they will be discontinued from further treatment (but continue in the study). This also applies to the OTE.
- For participants receiving 30 mg or 60 mg BMS-986278 (or placebo) after Day 1, if either asymptomatic or symptomatic low BP criteria are met (refer to Day 1 BP monitoring in Section 5.1.2.1 for details), a decision to reduce to 10 mg BMS-986278 BID (or placebo for

10 mg BMS-986278 BID) or discontinue study treatment (but continue in the study) will be discussed with the Medical Monitor/Study Director. This also applies to the OTE.

- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
  - This may include progression of the participant's lung fibrosis. Decisions about discontinuing the IP due to progression of disease are left to the discretion of the clinical investigator. Similarly, following discontinuation from study treatment during either the main study or the OTE, decisions regarding potential initiation of antifibrotic or immunosuppressive medications not allowed during the 26-week main study are left to the discretion of the investigator.
- Termination of the study and/or program by BMS.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment and agreement of both the investigator and Sponsor.
- The participant becomes pregnant (study treatment must be discontinued immediately). In the case of pregnancy, refer to Section 9.2.6.
- QTcF > 500 msec and/or changes in QTcF > 60 msec compared to baseline (confirmed on repeat ECG). Sites will inform the medical monitor of ECG values meeting discontinuation criteria.
- For participants with normal Day 1 (Randomization) liver enzymes, total bilirubin, and international normalized ratio (INR), if there is new elevation of ALT or AST > 3× ULN, repeat testing should be performed within 48 to 72 hours. If elevation persists, then standard drug induced liver injury (DILI) discontinuation criteria (see Section 9.2.8) will be applied and study treatment will be discontinued if any of the following occur:
  - ALT or AST > 8× ULN
  - ALT or AST > 5× ULN for more than 2 weeks
  - ALT or AST > 3× ULN and (total bilirubin > 2× ULN or INR > 1.5)
  - ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Note: If participant lives remotely to study site, a local laboratory may be used for repeat testing, and results should be promptly communicated to the site. Participants meeting the criteria above may have potential DILI (see Section 9.2.8 for additional details).

For participants with elevated AST, ALT, or total bilirubin at Day 1 (Randomization), if there is a new elevation of ALT or AST > 2× baseline, or total bilirubin > 1.5× Day 1 total bilirubin (and to more than ULN), repeat testing should be performed within 48 to 72 hours. If elevation persists, then study treatment will be discontinued if any of the following occur:

- ALT or AST levels increase to > 5× Day 1 (Randomization) measurement.
- ALT or AST levels increase > 2× Day 1 (Randomization) measurements AND the increase is accompanied by a concomitant increase in total bilirubin to > 2× Day 1 bilirubin or the INR concomitantly increases by > 0.3.

– Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Note: If participant lives in a remote location, a local laboratory may be used for repeat testing, and results should be promptly communicated to the site. Participants meeting the criteria above may have potential DILI (see Section 9.2.8 for additional details).

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Discretion of investigator.

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.6.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in the Schedule of Activities (Section 2). The only exception to this requirement is when a participant withdraws consent for all study procedures including posttreatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the source documents and entered on the appropriate eCRF page.

8.1.1 Posttreatment Follow-up

Posttreatment follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed according to the protocol.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. See the Schedule of Activities (Section 2) for details on the data to be collected at the time of treatment discontinuation and follow-up. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate eCRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Assessments for the end of treatment/end of study visit must be performed, provided that the participant has not withdrawn consent for these activities.
- All required eCRF pages must be completed, including the date of and explanation for the withdrawal.
- As indicated, appropriate follow-up and/or alternate medical care must be arranged for the participant.

If a participant discontinues prematurely from the intensive PK substudy and/or the PET-Tracer substudy, they may still continue in the main study. If, however, a participant withdraws consent from the main study, they should also discontinue from the substudy.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study treatment and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.

- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities in Table 1 for the main study and in Table 2 for the OTE.

Every effort must be made to ensure that the same evaluator(s) completes the assessment for each participant. If the evaluator(s) is unable to complete the evaluation, then a qualified individual with overlapping experience may perform the assessment. It is preferable that assessments be performed at approximately the same time of day throughout the duration of the study. Day 1 (Randomization) assessments must be performed per protocol (SOC assessments may not be used for baseline). Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

9.1 Efficacy Assessments

9.1.1 Forced Vital Capacity

Forced vital capacity (FVC) is the maximum amount of air a person can expel from the lungs after a maximum inhalation. Measurements are used to help diagnose lung disease and determine its severity and progression.

Pulmonary function, which includes FVC assessment, will be assessed through spirometry performed at the study center. Spirometry measures the volume of air that can be exhaled. For this assessment, the participant should be seated in a chair and asked to breath comfortably. A clip will be placed over the participant's nose. The participant should seal their lips tightly over the spirometer tube, inhale as deeply as possible and exhale into the spirometer tube as forcefully as possible. The assessment should be performed according to the manual provided by the central vendor.

The site-based spirometry will be provided to the site by a central vendor and will meet the criteria for acceptability and repeatability as defined in the ATS/ERS guidelines (Miller, et al.).[20]

All spirometry evaluations will be reviewed by a central reader.

Timing of Spirometry:

The spirometry test is to be performed prior to the morning dose, preferably at approximately the same time (± 1 h) at every visit in which spirometry is performed. The spirometry test is permitted to be completed up to 3 days prior to the scheduled study visit.

Timing of Spirometry Versus Bronchodilator Use:

All spirometry evaluations should be performed prebronchodilator. Prebronchodilator spirometry is defined as spirometry testing performed for a participant who has: withheld their short-acting β-agonist (eg, albuterol) or anticholinergic (eg, ipratropium bromide) for > 6 h prior to the spirometry assessment AND withheld their long-acting bronchodilator (eg, salmeterol, formoterol) for > 12 h and other longer-acting agents (eg, indacaterol, tiotropium) for > 24 h prior to the spirometry assessment. If the participant is taking bronchodilators, the participant may use the bronchodilator after the spirometry but prior to HRCT.

Spirometry Parameters and Calculation of Predicted Values:

The following parameters will be measured as part of the spirometry assessment:

- FEV1 (mL) and percent predicted forced expiratory volume in 1 second (ppFEV1)
- FVC (mL) and ppFVC
- FEV1/FVC ratio

The 2012 Global Lung Function Initiative Equations' will be used to estimate ppFVC (Quanjer, et al.).[21]

Additional details on the FVC assessment and ppFVC calculation are in the Study Manual.

9.1.2 Diffusing Capacity of Carbon Monoxide

Diffusing capacity of carbon monoxide (DLCO) is a measurement of the extent to which oxygen passes from the alveoli into the blood. This test involves measuring the partial pressure difference between inspired and expired carbon monoxide. It relies on the strong affinity and large absorption capacity of red blood cells for carbon monoxide and thus demonstrates gas uptake by the capillaries that are less dependent on cardiac output.

The single-breath diffusing capacity test is the most common way to determine DLCO, and is the test employed in the current study. The test is performed by having the participant blow out all of the air that they can, leaving only the residual lung volume of gas. The participant then inhales a test gas mixture rapidly and completely, reaching the total lung capacity as nearly as possible. This test gas mixture contains a small amount of carbon monoxide (usually 0.3%) and a tracer gas (helium or methane) that is freely distributed throughout the alveolar space but which doesn't cross the alveolar-capillary membrane. The test gas is held in the lung for about 10 seconds during which time the carbon monoxide (but not the tracer gas) continuously moves from the alveoli into the blood. The participant then exhales into the analyzer tube. By analyzing the concentrations of carbon monoxide and inert gas in the inspired gas and in the exhaled gas, it is possible to calculate

single-breath diffusing capacity of carbon monoxide (DLCO SB). The DLCO test is permitted to be completed up to 3 days prior to the scheduled study visit.

9.1.3 High-resolution Computed Tomography

High-resolution computed tomography (HRCT) has become the most common and sensitive imaging method for diagnosing ILD, as it offers the most detailed images of the lungs.[22] IPF is a specific form of chronic, progressive fibrotic interstitial pneumonia of unknown cause, limited to the lungs and associated with the histopathologic and/or radiologic pattern of UIP.[23] The hallmark pathologic feature of UIP is a heterogeneous, variegated appearance with alternating areas of healthy lung, interstitial inflammation, fibrosis, and honeycomb change, while fibrosis predominates over inflammation. The characteristic HRCT manifestations of IPF consist of symmetric bilateral reticulation, architectural distortion, and honeycombing involving mainly the subpleural lung regions and lower lobes. As IPF progresses, honeycombing becomes more prominent.[24]

Although identification of UIP on surgical lung biopsy has been considered the gold standard for diagnosis,[25] typical clinical and HRCT features may suffice for a confident diagnosis and eliminate the need for surgical lung biopsy.[23, 26] Considering that some centers perform cryobiopsy and data suggest this technique compares favorably with histologic accuracy of surgical lung biopsy, UIP pattern identification via cryobiopsy will be considered on a case-by-case basis in this protocol.[27] Accordingly, HRCT assessment has been adopted as an important diagnostic criterion in the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guidelines.[28] Extent of reticulation and honeycombing on HRCT findings is considered an important independent predictor of mortality in patients with IPF.[29] HRCT has been applied in multiple clinical studies of lung fibrosis for drug development, serving as an inclusion criterion,[30, 31] a predictive marker of positive treatment response,[32, 33, 34] and efficacy readout.[35, 36]

For the PF-ILD cohort, > 10% extent of fibrosis on screening thoracic HRCT is required. Participants will be stratified by UIP pattern (present vs absent) vs other fibrotic pattern. The target enrollment for UIP pattern (present vs absent) is expected at 75 out of 120 participants (62.5%). For the PF-ILD cohort, stratification will also be by category of background therapy (immunosuppression alone [ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus] versus anti-fibrotic [nintedanib, pirfenidone] versus none).

A computer-assisted diagnosis (CAD) score to quantify lung fibrosis as the percentage involvement of reticulation patterns based on texture measures from HRCT has been developed and validated[37, 38] as a measure of quantitative lung fibrosis (QLF) and a potential surrogate imaging marker. Computer-assisted diagnosis scores of QLF have been successfully applied as outcome measurements to test treatment efficacy in an ILD trial.[35] Compared with visual assessments, CAD scores have been shown to improve objectivity, sensitivity, and repeatability when measuring quantitative changes in lung features.[39, 40, 41]

In this study, full-chest HRCT will be performed at qualified imaging centers per guidelines outlined in the Study Imaging Manual. HRCT will be performed on all study participants during the screening period and at Week 26. To ensure comparability, the same scan, equipment, method,

and technique used during the baseline HRCT scan should be used for the follow-up HRCT scan (Week 26). For all participants, screening HRCT scans will be performed at total lung capacity and residual volume, with no contrast agent administration, reconstructed every 1 to 1.5 mm, using a low-dose protocol. At Week 26, HRCT will be performed at total lung capacity. Residual volume HRCT is optional at Week 26. For efficacy assessments, HRCT images of both during the screening period and follow-up scans (Week 26) will be analyzed by a centralized blinded reader. The HRCT analysis will focus on visual and CAD scores for regional lung fibrosis evaluation. Changes in the lung fibrosis scores from the screening period HRCT will be used to evaluate the treatment responses. The correlation of HRCT data to other efficacy readouts and biomarker data will be performed if applicable. Sites should be trained prior to scanning the first study participant. Detailed imaging procedures of HRCT will be defined in the Study Imaging Manual, and detailed image analysis procedures of HRCT will be defined in the Study Imaging Review Charter.

In addition to the screening and Week 26 scans in the main study, participants that enter the OTE will have HRCT performed at Week 26 of the OTE.

9.1.4 Clinical Outcome Assessments

The evaluation of clinical outcome assessments (COAs) is an increasingly important aspect of clinical efficacy in studies of treatments for IPF and other fibrotic ILDs that may present a progressing phenotype. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting.

Participants will be asked to complete COA measures, including the Living with Pulmonary Fibrosis Questionnaire (L-PF), St. George's Respiratory Questionnaire (SGRQ), University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ), a visual analog scale (VAS) measuring cough severity, patient global impression of lung fibrosis symptom severity (PGI-S), and perform the 6-Minute Walk Test (6MWT) at the Day 1, Week 12, and Week 26 visits. Additionally, all participants will be asked to perform an oxygen titration walk at screening and complete the patient global impression of lung fibrosis symptom severity change (PGI-C) at the Week 12 and Week 26 visits. COA measures other than the 6MWT (including oxygen titration walk) will be administered electronically, and the responses entered by trial participants into source records cannot be overridden by site staff or investigators. If possible, eCOAs should be administered using the electronic device prior to other study related procedures (except for the Day 1 visit where COAs should be administered after vital signs and ECG). Table 1 provides information regarding the timing of COAs during the study.

The same COA measures will be administered in both study cohorts. Patients with IPF and those with PF-ILD experience worsened respiratory symptoms and fatigue, though the impact of symptoms on functioning and well-being may be more pronounced for the latter individuals.[42, 43, 44, 45] There have been few specific studies of the quality of life of patients with PF-ILD, and additional research is needed to assess the performance characteristics of existing COA measures in this population.[42]

Participants in the OTE will be asked to complete the L-PF, PGI-S, and PGI-C at the Day 1 and Week 26 visits, and also perform the 6MWT at the Week 26 visit. Refer to Table 2.

9.1.4.1 Living with Pulmonary Fibrosis Questionnaire

The Living with Pulmonary Fibrosis Questionnaire (L-PF) is a multidimensional measure of the health-related quality of life (HRQoL) of patients living with pulmonary fibrosis (PF). The L-PF was adapted from the Living with Idiopathic Pulmonary Fibrosis Questionnaire (L-IPF),[46] which was in turn adapted from A Tool to Assess Quality of Life in IPF (ATAQ-IPF)[47] based on input received though the Food and Drug Administration (FDA) Drug Development Tool (DDT) Qualification Process (DDT COA #000027). There are no material differences in the item content of the L-PF and L-IPF. The 2 measures differ only in regard to PF as being "idiopathic".

The conceptual framework for the L-PF includes 4 domains: shortness of breath, cough, energy, and global. Items are divided between modules targeting symptoms (eg, coughing and dyspnea), measured using as 24-hour recall, and their impacts (eg, frustration, embarrassment, perceived inconvenience, diminished quality of life), measured using a 1-week recall. Additional items included in the symptoms module assess supplemental oxygen use. Validation of the psychometric properties of the L-PF is ongoing, though the instrument has been used in trials of treatments for patients with PF-ILD.[5, 48]

9.1.4.2 St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire developed to measure symptoms and health impairments in patients with airway obstruction.[49, 50] The questionnaire includes 8 items assessing the frequency and severity of symptoms, while the remaining items assess activity limitations due to breathlessness, including reduced social functioning and psychological disturbances resulting from airway disease. The SGRQ is scored from 0 to 100 with higher scores indicating greater health impairment. In patients with IPF, clinically meaningful score changes have been estimated to range from 5 to 8 points.[51] The questionnaire is widely used in studies of respiratory disease to assess disease symptoms, activities, and impacts and has been validated in IPF.[51]

9.1.4.3 University of California San Diego Shortness of Breath Questionnaire

The University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) includes 21 items assessing the severity of shortness of breath experienced during activities of daily living.[52, 53, 54, 55, 56] Three additional items assess limitations due to shortness of breath, fear of harm from overexertion, and fear of shortness of breath. Respondents who do not routinely perform an activity are requested to estimate the degree of shortness of breath anticipated. The SOBQ is scored by summing responses across all 24 items to generate a total score ranging from 0 to 120 with higher scores indicating greater symptom severity. In patients with IPF, clinically meaningful score changes have been estimated to range from 5 to 11 points.[55] The SOBQ has been widely used in IPF trials, and evidence exists for its content validity in IPF.[56]

9.1.4.4 Cough Severity Visual Analog Scale

A 100 mm visual analog scale (VAS) similar to that utilized in the INPULSIS-1 trial will be used to assess cough severity in the planned study. Participants will be asked to assess their cough by making a mark on a 100 mm line with 0 mm representing “no cough” and 100 mm representing “the worst imaginable cough.”

9.1.4.5 Patient Global Impression of Lung Fibrosis Symptom Severity and Patient Global Impression of Lung Fibrosis Symptom Severity Change

Single items measuring patient global impression of lung fibrosis symptom severity (PGI-S) and patient global impression of lung fibrosis symptom severity change (PGI-C) will be administered in the study. The PGI-S will assess perceptions of the overall severity of lung fibrosis symptoms during the preceding 7 days with response options ranging from "none" to "very severe." The PGI-C will assess perceptions of the overall change in symptom severity since before treatment with response options ranging from "much worse" to "much improved." Data collected via the PGI-S and PGI-C will be used as anchors in assessing the psychometric properties of other COA measures and deriving and interpreting thresholds for meaningful change.

9.1.4.6 6-Minute Walk Test

The 6-Minute Walk Test (6MWT) is a submaximal exercise test used to assess aerobic capacity and endurance. Before starting the test, the participant should be informed that the objective is to walk as far as possible during 6 minutes. The test should be conducted on a hard, flat surface, such as located in a hallway. If the participant becomes breathless or exhausted, then he or she may slow down, stop, or rest as necessary. The participant may lean against a wall while resting but should resume walking as soon as able to do so. He or she should be informed of the time remaining after each minute elapses and 15 seconds prior to the test's conclusion. At the end of 6 minutes, the participant should be told to stop, and the distance traveled should be measured and recorded in the eCRF. In patients with IPF, the threshold for clinically meaningful change in 6MWT outcomes has been estimated to range from 24 to 45 meters.[57, 58]

If possible, the 6MWT should be administered after eCOAs. Additional details on the 6MWT assessment and related oxygen titration walk are provided in the Guidance Manual for Conducting a 6MWT.

9.2 Adverse Events

The definitions of an AE or SAE can be found in APPENDIX 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Refer to APPENDIX 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until discharge, at the timepoints specified in the Schedule of Activities (Section 2). The Reference Safety Information in Appendix 1 of the Investigator's Brochure should be used to determine the expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 30 days of discontinuation of the study treatment or participant's participation in the study if the last scheduled visit occurs at a later time.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to sponsor or designee within 24 hours, as indicated in APPENDIX 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in APPENDIX 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious (see APPENDIX 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the eCRF. Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in APPENDIX 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 AEs of Special Interest

AEs of special interest (AESIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AESIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the BMS-986278 clinical development program, certain *asymptomatic* and *symptomatic* BP-related AEs are defined as AESIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with BMS-986278. Additional information about *asymptomatic* and *symptomatic* BP-related AEs will be collected on the case report form in order to better characterize and understand them.

Symptomatic Decreased Blood Pressure AESI

Includes events associated with the following symptoms: confusion, lightheadedness, dizziness, palpitations, falls, tremulousness, generalized weakness, blurred vision, exercise intolerance (if different from baseline), fatigue upon standing (if different from baseline), angina, transient ischemic attack, pre-syncope, or syncope.

Clinical Evaluation of Hypotension AESI

Includes any of the events meeting any of the *asymptomatic* or *symptomatic* low BP criteria.

Asymptomatic low BP criteria:

- Seated SBP < 85 mmHg (confirmed by retest within 15 minutes)
- Seated DBP < 55 mmHg (confirmed by retest within 15 minutes)
- Orthostatic hypotension (defined as a drop in SBP of ≥ 20 mmHg or DBP of ≥ 10 mmHg with assumption of an upright posture from either supine or seated to upright position[16]) (confirmed by retest within 15 minutes)

Symptomatic low BP criteria:

a) The participant is experiencing symptoms that, in the opinion of the investigator, could be associated with low BP (eg, confusion, lightheadedness, dizziness, palpitations, falls, tremulousness, generalized weakness, blurred vision, exercise intolerance [if different from baseline], fatigue upon standing [if different from baseline], angina, transient ischemic attack, pre-syncope, or syncope) AND at least one of the following BP thresholds:

   i. Seated SBP < 100 mmHg (confirmed by retest within 15 minutes) or seated DPB < 60 mmHg (confirmed by retest within 15 minutes)

   ii. Decrease of seated SBP of ≥ 20 mmHg (confirmed by retest within 15 minutes) from previous visit or decrease of seated DBP of ≥ 10 mmHg (confirmed by retest within 15 minutes) from previous visit

   iii. Orthostatic hypotension (defined as a drop in SBP of ≥ 20 mmHg or DBP of ≥ 10 mmHg with assumption of an upright posture from either supine or seated to upright position[16]) (confirmed by retest within 15 minutes)

   iv. Orthostatic tachycardia (defined as a sustained increase in HR of ≥ 30 bpm within approximately 10 minutes of moving from a recumbent to a quiet [nonexertional] standing position; defined as the difference in HR from either supine or seated to upright position[16]) (confirmed by retest within 15 minutes)

9.2.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page or SAE eCRF, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an AE or SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.8 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and APPENDIX 3 for reporting details).

Potential DILI is defined as:

1) Treatment-emergent ALT or AST > 3× ULN (> 2× baseline AND > 3× ULN for participants with baseline elevation),

   AND

2) Total bilirubin > 2× ULN (> 2× baseline AND > 2× ULN for participants with baseline elevation) or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase),

   AND

3) No other immediately apparent possible causes of elevated liver enzymes and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.9 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious AE or an SAE, as appropriate, and reported accordingly.

To collect information around the impact of COVID-19 on this study, COVID-19–related AEs/SAEs, changes in study visit schedules, missing study visits, study drug modification/ discontinuation, study discontinuation, etc, will be captured in the CRF.

9.3 Overdose

For this study, any dose of BMS-986278 greater than 180 mg within a 24-hour time period (± 4 hours) will be considered an overdose. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see APPENDIX 3).

In the event of an overdose the investigator should:

1) Contact the medical monitor immediately.
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until [study treatment] can no longer be detected systemically (at least 3 days).
3) Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned timepoints for all safety assessments are listed in the Schedule of Activities (Section 2). All urgent safety concerns must be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

The safety of BMS-986278 will be assessed by evaluation of the incidence of all AEs and SAEs, physical examinations, vital signs, laboratory data, ECG monitoring, and biomarkers.

9.4.1 Physical Examinations and Physical Measurements

Schedules for physical examinations are provided in Schedule of Activities (Section 2). Physical examinations may be performed by a Doctor of Medicine (MD) or equivalent, or someone who is authorized to perform the examinations by training and has been delegated this task by the principal investigator.

Physical examinations will be performed at the timepoints indicated in the Schedule of Activities for the main study (Table 1) and for the OTE (Table 2).

Every effort should be made to ensure the same evaluator will complete the examination for each participant at all visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

Schedules for physical measurements are provided in Schedule of Activities (Section 2).

9.4.2 Vital Signs

Predose vital signs will be collected at the timepoints provided in Schedule of Activities for the main study (Table 1) and for the OTE (Table 2), and will include body temperature, respiration rate, and orthostatic BP and HR.

During visits when orthostatic BP and HR are required (refer to Section 5.1.2.1), body temperature and respiration rate will only be required predose.

During orthostatic assessments, participants will be monitored for orthostatic intolerance, orthostatic hypotension, and orthostatic tachycardia, as defined in Section 5.1.2.1.

Additional serial BP and HR measurements will be collected as part of the intensive PK substudy in the main study, as shown in Table 7.

BP monitoring on Days 1 and 2 and for all subsequent study visits is described in Section 5.1.2.1.

Details for BP measurements and orthostatic assessments will be provided.

Participants who are discontinued from study treatment do not require BP monitoring and orthostatic assessments, as described in Section 5.1.2.1. Vital signs will be collected per the Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

ECGs will be performed before study treatment administration (except at Week 26) at the timepoints specified in Table 1 for the main study and in Table 2 for the OTE. All ECGs must be performed prior to bronchodilator administration OR at least 20 hours after bronchodilator administration. Additional ECG collections post dose will be conducted as part of the intensive PK substudy in the main study (see Table 7). Additional ECG assessments must be conducted any time during the main study and the OTE if clinically indicated.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. A central laboratory will perform the analyses and will provide reference ranges for these tests. Local laboratory testing may be permitted for repeats or as per Medical Monitor approval when central laboratory testing cannot be performed.

Hematology, serum chemistry and urinalysis assessments are listed in Table 5.

Table 5: Laboratory Assessments

Hematology	
Complete blood count (including differential) Prothrombin time Partial thromboplastin time International normalized ratio White blood cell (absolute) Hemoglobin	Hematocrit Mean corpuscular volume Mean corpuscular hemoglobin concentration Red cell distribution width Platelet count
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Glucose Estimated glomerular filtration rate (screening only)	Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase
Urinalysis	
pH Specific gravity Protein Glucose Ketones	Leukocyte esterase Nitrite Creatinine Microscopic examination (only to follow-up abnormal findings)
Serology (screening only)	
Hepatitis C antibody or RNA Hepatitis B surface antigen and core antibody. Hepatitis B virus (HBV) DNA test can be performed directly in participants with suspected positive Hepatitis B surface antigen and core antibody in participating countries with high HBV prevalence. Human immunodeficiency virus (HIV)-1 antibody HIV-2 antibody Hepatitis C RNA will be performed in hepatitis C antibody-positive participants. Hepatitis B surface antigen (HBsAg)-positive participants or hepatitis B core antibody (HBcAb)-positive participants will be tested for hepatitis B virus (HBV) DNA.	

Table 5: Laboratory Assessments

Other Analyses
Test for drugs of abuse (screening): Amphetamines, Barbiturates, Benzodiazepines, Phencyclidine, Cocaine, Opiates, Ethanol (per local regulations). Follicle-stimulating hormone (FSH) (screening only for postmenopausal women < 55 years of age). Urine pregnancy test prior to Day 1 dosing and if pregnancy is suspected at any time throughout the study (women < 55 years of age); performed locally.

9.5 Pharmacokinetics

The PK of BMS-986278 and inactive major metabolite BMT-323719 will be derived from plasma concentration vs time data.

The plasma samples will be analyzed for BMS-986278 by a validated assay and BMT-323719 by a qualified assay. PK samples collected from participants who received placebo will not be analyzed.

In addition, plasma samples will be archived for potential analysis of other metabolite(s) if the need arises and to the extent possible.

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual. Participants will receive a document to record the date and exact clock time of the morning and evening doses of study treatment taken on the day prior to the Week 4, Week 12, and Week 26 study visits for the main study, and on the day prior to the Week 4 and Week 26 study visits for the OTE. In the main study, if the participant is taking nintedanib or pirfenidone, he/she will also be asked to record the last dosing date and exact clock time of nintedanib or pirfenidone taken prior to sample collection.

9.5.1 Sparse PK Sampling (All Participants not Participating in PK Substudy)

All participants will have PK samples collected before the first administration of study treatment on Day 1. PK samples will also be collected at approximately 1.5 and 4 hours after the first administration of study treatment on Day 1, before the morning administration of study treatment at Week 4 and Week 12, and up to 5 days after the last study treatment administration at the Week 26 visit (see Table 6). Fed/fasted status and time of morning meal (if fed) must be recorded at each visit.

In addition to assessing concentrations of BMS-986278 and the BMT-323719 metabolite, additional PK samples will be collected predose on Day 1 and at Week 12 and will be used to analyze for concentrations of pirfenidone or nintedanib by validated assays in participants that receive these medications.

Table 6: Sparse PK Sampling Schedule for IPF and PF-ILD Cohorts

Study Day of Sample Collection	Event	Time Relative to BMS-986278 Dose (hr:min)[a]	BMS-986278 and BMT-323719 Metabolite PK Plasma Sample[b]	Concomitant Medication PK Plasma Samples[c]
Day 1	Predose[a]	0:00	X	X
		1:30	X	
		4:00	X	
Day 29 Week 4 (± 3 days)	Predose[a]	0:00	X	
Day 85 Week 12 (± 5 days)	Predose[a]	0:00	X	X
Day 183 Week 26 (+ 5 days)	Day after last dose		X	
Early treatment discontinuation (if applicable)[d]	Day of treatment discontinuation		X	

IPF = idiopathic pulmonary fibrosis; PF-ILD = progressive fibrotic interstitial lung disease; PK = pharmacokinetic

[a] Actual PK sampling times will be recorded. Samples should be collected as close as possible to the scheduled time.

[b] One PK sample will be collected at each timepoint and analyzed for BMS-986278 and BMT-323719. The date and time of the morning and evening doses of study medication taken prior to the study visit must be recorded at the Week 4, Week 12, and Week 26 study visits.

[c] Participants who are on pirfenidone or nintedanib therapy will have an additional plasma sample collected for that specific concomitant medication. The last dosing date and time of the concomitant medication taken prior to the concomitant PK sample collection must be recorded.

[d] No further samples should be taken at subsequent visits.

9.5.2 Intensive PK Substudy

An intensive PK substudy will be conducted in approximately 10 participants per treatment arm in both the IPF and PF-ILD cohorts, for which serial PK samples, ECGs, and BP and HR measurements will be collected (see details in Table 7 and further below).

Table 7: PK Sampling, ECG, BP, and HR Schedule for Intensive PK Substudy (IPF and PF-ILD Cohorts)

Study Day of Sample Collection	Event	Time Relative to BMS-986278 Dose (hr:min)[a]	BMS-986278 and BMT-323719 Metabolite PK Plasma Sample[b]	Concomitant Medication PK Plasma Sample[c]	ECG	Blood Pressure and Heart Rate[d]
Day 1	Predose[a]	0:00	X	X	X	X
		1:30	X		X	X
		2:00	X			X
		4:00	X			X
		6:00	X		X	X

Table 7: PK Sampling, ECG, BP, and HR Schedule for Intensive PK Substudy (IPF and PF-ILD Cohorts)

Study Day of Sample Collection	Event	Time Relative to BMS-986278 Dose (hr:min)[a]	BMS-986278 and BMT-323719 Metabolite PK Plasma Sample[b]	Concomitant Medication PK Plasma Sample[c]	ECG	Blood Pressure and Heart Rate[d]
		8:00	X			X
Day 29 Week 4 (± 3 days)	Predose[a]	0:00	X	X	X	X
		1:30	X		X	X
		2:00	X			X
		4:00	X			X
		6:00	X		X	X
		8:00	X			X
Day 85 Week 12 (± 5 days)	Predose[a]	0:00	X	X	X	X
		1:30	X		X	X
Day 183 Week 26 (+ 5 days)	Day after last dose		X		X	X
Early treatment discontinuation (if applicable)[e]	Day of treatment discontinuation		X		X	X

BP = blood pressure; ECG = electrocardiogram; HR = heart rate; IPF = idiopathic pulmonary fibrosis; PK = pharmacokinetic

[a] Actual PK sampling times will be recorded. Samples should be collected as close as possible to the scheduled time.

[b] One PK sample will be collected at each timepoint and analyzed for BMS-986278 and BMT-323719. The date and time of the morning and evening doses of study medication taken prior to the study visit must be recorded at the Week 4, Week 12, and Week 26 study visits.

[c] Participants who are on pirfenidone or nintedanib therapy will have an additional plasma sample collected for that specific concomitant medication. The last dosing date and time of the concomitant medication taken prior to the concomitant PK sample collection must be recorded.

[d] Refer to vendor manual.

[e] No further samples should be taken at subsequent visits.

Fed/fasted status and time of morning meal (if fed) must be recorded at each visit.

In addition to assessing concentrations of BMS-986278 and the BMT-323719 metabolite, additional PK samples will be collected predose on Day 1, Week 4, and Week 12 and will be used to analyze for concentrations of pirfenidone or nintedanib by validated assays in participants that receive these medications.

Key PK parameters to be assessed in the intensive PK sampling study include:

Cmax	Maximum observed plasma concentration (Day 1 and Week 4)
Tmax	Time of maximum observed plasma concentration (Day 1 and Week 4)
AUC(0-8)	Area under the plasma concentration-time curve from time zero to 8 hours post dose (Day 1 and Week 4)
Ctrough	Trough observed plasma concentration (Week 4 and Week 12)

Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

Concentration data from this study may be combined with data from the Phase 1 studies in healthy subjects to further characterize the PK of BMS-986278 using population PK analysis. The relationship between measures of exposure and endpoints for efficacy and safety may also be explored using model-based exposure-response analysis. Results of these analyses will be reported separately.

9.5.3 Sparse PK Sampling for Optional Treatment Extension

All participants in the OTE will have PK samples collected before the first administration of study treatment on Day 1. PK samples will also be collected at approximately 1.5 and 4 hours after the first administration of study treatment on Day 1, before the morning administration of study treatment at Week 4, and up to 5 days after the last study treatment administration at the Week 26 visit (see Table 8). Fed/fasted status and time of morning meal (if fed) must be recorded at each visit.

Table 8: PK Sampling Schedule for the OTE

Study Day of Sample Collection	Event	Time Relative to BMS-986278 Dose (hr:min)[a]	BMS-986278 and BMT-323719 Metabolite PK Plasma Sample[b]
OTE Day 1	Predose[a]	0:00	X
		1:30	X
		4:00	X
OTE Day 29 Week 4 (± 3 days)	Predose[a]	0:00	X
OTE Day 183 Week 26 (+ 5 days)	Day after last dose		X
OTE Early treatment discontinuation (if applicable)[c]	Day of treatment discontinuation		X

OTE = optional treatment extension; PK = pharmacokinetic

[a] Actual PK sampling times will be recorded. Samples should be collected as close as possible to the scheduled time.

[b] One PK sample will be collected at each timepoint and analyzed for BMS-986278 and BMT-323719. The date and time of the morning and evening doses of study medication taken prior to the study visit must be recorded at the OTE Week 4 and OTE Week 26 study visits

[c] No further samples should be taken at subsequent visits.

PK concentrations of BMS-986278 and BMT-323719 will be listed and summarized by treatment.

9.6 Biomarkers

Blood-based biomarkers of disease activity will be evaluated to support pharmacodynamic effects, dose selection, mechanism of action, demonstration of impact on disease, and treatment response prediction. Blood, plasma, and serum will be collected at the times indicated in Table 9 for the measurement of soluble factors and blood cell phenotypes, characterization of gene expression profiles, and analysis of DNA single nucleotide polymorphisms (SNPs).

Soluble factors related to IPF may include but will not be limited to the lung injury biomarkers MMP-7 and SP-D; fibrosis biomarkers TIMP-1, OPN, periostin, decorin, and tenascin-C; and inflammation biomarkers CXCL13, CCL18, YKL-40, EN-RAGE, eotaxin, and adiponectin. Biomarkers of tissue collagen turnover that have been associated with IPF disease progression may include but will not be limited to the collagen neoepitopes C3M, C6M, PRO-C3, and PRO-C6. In addition, plasma LPA concentrations will be measured.

Additionally, since some leukocytes play a significant role in fibrotic processes, and have been associated with IPF disease progression, flow cytometric analyses for changes in leukocytes subsets (eg, monocytes, T cells, and B cells) will be evaluated. Blood cell gene expression (mRNA) analyses may also be explored. In all participants, predose samples for biomarkers will include blood and serum, collected at baseline, Week 4, Week 12, and Week 26 of the main study, and also at Week 26 of the OTE.

Additionally, blood samples for DNA SNP analysis will be collected for exploratory analysis of genes previously associated with IPF and/or familial pulmonary fibrosis, possibly including but not limited to variants in surfactant proteins (*SFTPA2, SFTPC*), telomerase (*TERT, TERC*), toll interacting protein (*TOLLIP*), and mucin 5B (*MUC5B*). Since BMS-986278 is a weak inhibitor of OATP1B, DNA SNP analysis in absorption, distribution, metabolism, and excretion genes will also be analyzed. Blood samples for DNA will be drawn on Day 1, as indicated in Table 1, from all participants.

As indicated in Table 9, serum will be collected for possible assessments of SARS-CoV-2 serologic status (anti-SARS-CoV-2 IgG or total antibody) at baseline, at the end of the main study, and at the end of the OTE. SARS-CoV-2 serology will also be performed approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

Table 9: Biomarker Sampling Schedule for All Participants

Study Day of Sample Collection[a]	Whole Blood for Genotyping	Whole Blood for Gene Expression Analysis	Whole Blood for Flow Cytometry	Serum Exploratory Biomarkers	Plasma Exploratory Biomarkers[b]	Plasma LPA Quantification[b]	SARS-CoV-2 Serology (IgG or Total)[c]
Day 1 (Predose)	X	X	X	X	X	X	X
Day 29 Wk 4 (± 3 days)		X	X	X	X	X	
Day 85 Wk 12 (± 5 days)				X	X	X	
Day 183 Wk 26 (+ 5 days)		X	X	X	X	X	X
OTE Day 183 Wk 26 (+ 5 days)		X		X	X		X
Day of early treatment discontinuation (if applicable)[d]				X	X	X	

LPA = lysophosphatidic acid; Wk = Week

[a] All samples are to be collected prior to the first dose of study treatment on Day 1 and before the morning dose of study treatment on the day of the other indicated visits.

[b] Samples are aliquots of a single blood collection at each visit.

[c] Also to be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection, for potential future assessment of anti-SARS-CoV-2 total or IgG, per national and local requirements.

[d] No further samples should be taken at subsequent visits.

9.6.1 Additional Research Collection

This protocol will include residual sample storage for additional research (AR).

For All US sites:

AR is required for all study participants, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the AR should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory AR retention and/or collection, then the study participant must agree to the mandatory AR as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the AR retention and/or collection.

For Non-US Sites

AR is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

AR is intended to expand the translational R&D capability at BMS and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment, etc.

Sample Collection and Storage

All requests for access to samples or data for AR will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Residual samples from PK collections (see Table 6, Table 7, and Table 8) and biomarkers (see Section 9.6) will also be retained for AR purposes.

Samples kept for future research will be stored at the BMS Biorepository in [redacted] or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

9.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

In determining the sample size for the IPF cohort, both statistical considerations and clinical feasibility criteria were utilized. Among the considerations were:

- Sizing of published early phase trials in IPF.
- Precision to estimate the difference of the 30 mg BID and 60 mg BID doses to placebo on the primary efficacy measure of ppFVC.
- The assumption that a 2.5% difference in ppFVC (favoring 30 mg BID or 60 mg BID vs placebo) would be meaningful and that the standard deviation of this difference would 6.5%.
- The assumption that 80% of participants randomized will complete the 26-week treatment period.
- PK and tolerability data will be key factors in the selection of a dose for further evaluation. Given the limitations on participant recruitment and resulting sample size, it is not anticipated that the 30 mg BID and 60 mg BID cohorts will be differentiated relative to FVC.

95% two-sided confidence intervals were computed for a range of sample sizes. The confidence level was based on an overall Type 1 error of 0.10, with 0.05 allocated to each dose comparison (30 mg BID and 60 mg BID) relative to placebo. The resulting confidence intervals are described in Table 10.

Table 10: 95% CI of the Absolute Difference in ppFVC (%) Between BMS-986278 (30 mg BID or 60 mg BID) Compared to Placebo Based on an Observed Difference of 2.5%

Sample Size per Arm	Lower Bound 95% CI	Upper Bound 95% CI
60	0.17	4.83
80	0.49	4.51
100	0.70	4.30

CI = confidence interval

Based on these considerations, a sample size of 80 participants per arm was selected. Note that for all sample sizes, the lower bound of the 95% confidence interval excludes zero, consistent with a nominal p-value < 0.05. For the purposes of this study, if either dose comparison achieves a p-value of 0.05 or less, it will be described as "statistically significant."

With regards to the PF-ILD cohort, statistical considerations were not utilized. A total of 120 participants will be enrolled. A target of enrolling 75 out of 120 (62.5%) with UIP pattern is expected and randomization will be stratified by UIP pattern (present versus absent) and by category of background therapy (ILD-targeted immunosuppression [ie, azathioprine, mycophenolate mofetil, mycophenolic acid, and/or tacrolimus] alone versus anti-fibrotics [nintedanib, pirfenidone] with or without ILD-targeted immunosuppression versus no ILD-targeted immunosuppression or anti-fibrotics). These participants will be analyzed separately and considered as supportive to the findings within the IPF cohort.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent.
Full Analysis Set (FAS)	All participants who are randomized and receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment group assigned at randomization. The FAS will be the primary efficacy analysis population.
Pharmacokinetic	All randomized participants who receive at least 1 administration of BMS-986278 and have any quantifiable concentration data.
Safety	All participants who are randomized and receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment group assigned; participants who receive incorrect study treatment will be analyzed according to the actual treatment received.

10.3 Endpoints

10.3.1 Primary Endpoints

The primary endpoint is the rate of change in ppFVC (%) in IPF participants, estimated from measurements taken over 26 weeks of treatment. The decrease in ppFVC is assumed to be linear within each participant over the 26 weeks.

10.3.2 Secondary Endpoints

Secondary endpoints are as follows:

Safety Assessments:

- AEs
- SAEs
- AEs leading to early discontinuation of study treatment
- Treatment-emergent deaths
- Clinical laboratory findings and ECGs
- Vital signs
- Physical exam findings

Efficacy Endpoints:

- PF-ILD cohort only:
  - Rate of change in ppFVC (%) in PF-ILD participants will be estimated from measurements taken over 26 weeks of treatment. The decrease in ppFVC is assumed to be linear within each participant over the 26 weeks.

- IPF and PF-ILD cohorts:
  - Proportion of participants with a at least 10% absolute decline from baseline in ppFVC (%) at Weeks 4, 8, 12, 16, 20, and 26
  - Proportion of participants with > 0% change in ppFVC at Weeks 4, 8, 12, 16, 20, and 26
  - Time to first acute exacerbation
  - Time to first occurrence ≥ 10% absolute decline in ppFVC (%)
  - Absolute change in ppFVC (%) from baseline to Week 26
  - Absolute change in FVC (mL) from baseline to Week 26
  - Absolute change in DLCO SB (mL/min/mmHg) (corrected for hemoglobin) from baseline to Week 26
  - Absolute change in ppDLCO SB (%) (corrected for hemoglobin) from baseline to Week 26
  - Change in walking endurance/distance from baseline at Week 26 as measured using the 6MWT
  - Proportion of participants with acute exacerbations (evidence of which will be captured in the eCRF) of lung fibrosis defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality, as follows:[15]
    1. Acute worsening or development of dyspnea (< 1 month duration)
    2. Imaging with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrotic lung disease.
    3. Respiratory deterioration not fully explained by cardiac failure of fluid overload

BMS-986278 PK Parameters:

- Cmax
- Tmax
- AUC(0-8)
- Ctrough

10.3.3 Exploratory Endpoints

Exploratory endpoints in the main study and/or OTE include but are not limited to the following:

HRCT:

- Change in QLF using the Quantitative HRCT Fibrosis Score from baseline to Week 26

COAs:

- Change in HRQoL from baseline at each assessment timepoint during treatment as measured by the L-PF
- Change in HRQoL from baseline at each assessment timepoint during treatment as measured by the SGRQ

- Change in dyspnea from baseline at each assessment timepoint during treatment as measured by the UCSD SOBQ
- Change in cough severity from baseline at each assessment timepoint during treatment as measured using a VAS
- Change in walking endurance/distance from baseline at each assessment timepoint during treatment as measured using the 6MWT

PK:

- Cmax, Tmax, and AUC(0-8) on Day 1 and Week 4 and Ctrough on Week 4 and Week 12 of intensive PK substudy
- Plasma concentrations of nintedanib and pirfenidone in participants who receive nintedanib or pirfenidone alone and co-administered with BMS-986278
- Plasma concentrations of the BMT-323719 metabolite (including but not limited to AUC(0-8), Ctrough, Cmax, and Tmax of intensive PK study)

Disease Outcomes:

- Composite endpoint of time to first all-cause hospitalization or overall survival
- Pulmonary fibrosis progression-free survival (pulmonary fibrosis progression is defined as any of the following: ≥ 10% decline in ppFVC relative to baseline, ≥ 50 m decline in 6MWT relative to baseline, lung transplantation, or death)

Clinical Assessments of Disease:

- Proportion of participants with > 5% decline in FVC (mL) relative to baseline
- Proportion of participants with > 10% decline in FVC (mL) relative to baseline
- Proportion of participants with > 5% absolute decline in ppFVC (%)
- Proportion of participants with > 5% decline in ppFVC (%) relative to baseline
- Proportion of participants with > 10% decline in ppFVC (%) relative to baseline
- Time to first > 5% absolute decline in ppFVC (%)
- Time to first > 5% decline in ppFVC (%) relative to baseline
- Time to first > 10% decline in ppFVC (%) relative to baseline
- Time to first > 5% decline in FVC (mL) relative to baseline
- Time to first > 10% decline in FVC (mL) relative to baseline

Biomarkers:

- Change from baseline of blood-based biomarkers (including gene expression profiles) of lung fibrosis and inflammation
- Presence or absence of single nucleotide variants in genes associated with lung fibrosis

- Presence or absence of SNP variants in genes encoding organic anion transporting polypeptides, CYP 2C8, and breast cancer resistance protein
- Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) from serum samples collected at baseline, main study completion, and end of the OTE

10.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before first unblinding event of the study (see Section 10.4.5), and will provide detailed specifications of the analysis of all efficacy endpoints and safety data. This section provides a summary of planned statistical analyses.

Categorical data will be summarized using counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

10.4.1 Efficacy Analyses

10.4.1.1 Primary Efficacy Endpoint

The primary endpoint is the rate of change in ppFVC in IPF participants (estimated from measurements taken over 26 weeks of treatment). The decrease in ppFVC is assumed to be linear within each participant over the 26 weeks.

The primary analysis will compare the rate of change in ppFVC from baseline to Week 26 using a random coefficient linear mixed model using the Full Analysis Set (FAS). The model will include ppFVC at each visit as dependent variable, random coefficients for intercept and slope and fixed effect terms for treatment, time since randomization, treatment × time interaction, and baseline stratification factors. No imputation of missing values will be performed for the primary analysis. Sensitivity analysis may be performed to assess the impact of missing values as well as impact of dose reduction on the primary analysis. There will be no adjustment for multiple comparisons.

Subgroup analyses will be performed for concomitant use of pirfenidone or nintedanib therapy (vs neither pirfenidone nor nintedanib) for IPF and for other demographic and baseline characteristics.

10.4.1.2 Secondary Efficacy Endpoints

All secondary analyses will be based on the FAS population. As appropriate, continuous secondary endpoints will be analyzed using mixed model repeated measures (MMRM) with a random effect for participant and fixed effects for treatment, visit, treatment-by-visit interaction, and baseline stratification factors. The baseline value of the endpoint being tested will be added into the model as a covariate. In addition, as appropriate analysis of covariance models will be used to analyze continuous secondary endpoints with treatment and factors used for randomization as fixed effects. The baseline value will be added into the model as a covariate.

Cochran-Mantel-Haenszel tests will be used to compare dichotomous endpoints between either BMS-986278 dose group vs placebo.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-event endpoints. Treatment comparisons between each BMS-986278 dose group and placebo will be performed using the log-rank test stratified by baseline stratification factors.

The PF-ILD cohort will be analyzed separately from the primary study cohort of IPF. The PF-ILD statistical analysis methods will be similar to IPF cohort. The details will be described in the SAP.

10.4.2 Pharmacokinetic Analyses

The PK population will be defined as all randomized participants who receive at least 1 administration of BMS-986278 and have any quantifiable concentration data. PK analyses will be based on the PK population. BMS-986278 and BMT-323719 concentration data as well as nintedanib and pirfenidone concentration data from participants also receiving nintedanib or pirfenidone will be summarized by visit and timepoint, as applicable, using descriptive statistics for the PK population. Descriptive statistics will also be provided for the plasma BMS-986278 PK parameters for each BMS-986278 dose. In addition, trough concentrations of nintedanib and pirfenidone will be summarized by visit. For the participants that undergo intensive PK assessments, geometric means and percent coefficients of variation (%CV) will be presented for PK parameters such as AUC(0-8), Cmax, and Ctrough. Participants in the PET-tracer substudy will only have their PK concentration data listed and not summarized.

Medians and ranges will be presented for Tmax. Scatter plots for Ctrough over time will be presented for each active treatment to assess the attainment of steady state. Additionally, Ctrough will be summarized (geometric mean and %CV) by visit and active treatment. Results of these analyses will be reported separately.

Concentration data from both sparse and intensive PK samples will be used to further characterize the PK of BMS-986278 using population PK analysis, and to estimate model-based PK parameters such as apparent oral clearance at steady state (CLss/F) and apparent volume of distribution at steady state (Vss/F). Results of these analyses will be reported separately.

10.4.3 Safety Analyses

Analyses of safety data will be based on the safety set, which is defined as all participants who take at least 1 dose of study treatment.

Treatment-emergent AEs and study drug-related AEs and SAEs will be summarized using counts and percentages of participants experiencing the event as well as the number of events by system organ class, preferred term, and treatment group. Physical examination findings, vital signs, clinical laboratory test results, and ECG test results will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions (counts and percentages) for categorical variables.

The proportions of participants in each treatment group who discontinue study treatment due to changes in BP will be summarized using descriptive statistics.

The PF-ILD cohort will be analyzed separately from the primary study cohort of IPF.

10.4.4 Other Analyses

PK and biomarker exploratory analyses will be described in the SAP and finalized before database lock. The population pharmacokinetics analysis and pharmacodynamic analyses will be presented separately from the main clinical study report. Exploratory analyses of COAs will be described in the SAP finalized before database lock.

Exploratory PK will be summarized by dose and timepoint for the PK population. If warranted, analysis of PK and exposure-response relationships will be reported separately from the clinical study report (CSR).

Selected biomarkers will be summarized by treatment and timepoint using the FAS population. Summaries will be provided for raw, change from baseline, and percent change from baseline.

At the time of database lock for the IPF cohort (Week 26 of the main study), the OTE for the IPF cohort will continue unblinded until completion. To better assess longer-term efficacy and safety with BMS-986278, select efficacy (eg, FVC) and safety data from the OTE portion of the IPF cohort will be reviewed by the sponsor based on the locked database. The blind will be maintained for the PF-ILD cohort until the database lock for the PF-ILD cohort (Week 26 of the main study).

An analysis is planned for the PF-ILD cohort when 100% of participants (N = 40/arm) complete Week 26. This analysis will be performed and results reviewed by the independent DMC. Results will be descriptive and based on estimation of effect size and associated confidence intervals. Further details on statistical considerations, review of data, and unblinding will be included in the DMC Charter and SAP. At the time of the PF-ILD cohort main study database lock (Week 26 of the main study), the OTE for the PF-ILD cohort will continue unblinded until completion.

All safety, tolerability, and efficacy data from the OTE will be analyzed separately from the main study. The presentation of participants treated with BMS-986278 during the OTE will be done by the following groups: participants randomized to 30 mg at the start of the main study, participants randomized to 60 mg at the start of the main study, participants randomized to 30 mg in the OTE (placebo participants in the main study), participants randomized to 60 mg in the OTE (placebo participants in the main study), participants who received an unblinded reduced dose of 10 mg at the start of the OTE.

10.4.5 Interim Analyses

An interim analysis is planned for the IPF cohort when approximately 50% of participants (N = 40/arm) complete Week 26. This analysis will be performed and results reviewed by the independent DMC. No formal test of statistical significance is planned given the limited sample size at Week 26. Results will be descriptive and based on estimation of effect size and associated confidence intervals. Thus, no adjustments to overall type I error will be made. Further details on statistical considerations, review of data, and unblinding will be included in the DMC Charter and SAP.

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APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
6MWT	6-Minute Walk Test
ACC/AHA/HRS	American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society
AE	adverse event
ALT	alanine aminotransferase
AR	additional research
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-24h)	area under the plasma concentration-time curve form time 0 to 24 hours post dose
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
BAL	bronchoalveolar lavage
BID	twice daily
BLEO	bleomycin
BMS	Bristol-Myers Squibb
BP	blood pressure
CAD	computer-assisted diagnosis
CFR	Code of Federal Regulations
CLss/F	apparent oral clearance at steady state
Cmax	maximum observed concentration
COA	clinical outcome assessment
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	clinical study report
Ctrough	trough observed plasma concentration
CTAg	clinical trial agreement
%CV	percent coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure

Term	Definition
DDT	Drug Development Tool
DILI	drug induced liver injury
DLCO	diffusing capacity of carbon monoxide
DLCO SB	single-breath diffusing capacity of carbon monoxide
ppDLCO SB	percent predicted single-breath diffusing capacity of carbon monoxide
DMARD	disease modifying anti-rheumatic drug
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
PF	pulmonary fibrosis
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
FIH	first-in-human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
ppFVC	percent predicted forced vital capacity
GCP	Good Clinical Practice
GD	gestation day
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life

Term	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILD	interstitial lung disease
I(M)P	investigational (medicinal) product
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
L-IPF	Living with Idiopathic Pulmonary Fibrosis Questionnaire
L-PF	Living with Pulmonary Fibrosis Questionnaire
LPA	lysophosphatidic acid
LPA_1	lysophosphatidic acid receptor 1
MMRM	mixed model repeated measures
MRHD	maximum recommended human dose
mRNA	messenger ribonucleic acid
NA	not applicable
NOAEL	no-observed adverse effect level
O_2	oxygen
OATP	organic anion transport protein
OTE	optional treatment extension
PAH	pulmonary arterial hypertension
PET	positron emission tomography
PF-ILD	non-IPF, progressive fibrotic interstitial lung disease
PGI-C	patient global impression of lung fibrosis symptom severity change
PGI-S	patient global impression of lung fibrosis symptom severity
PK	pharmacokinetics
PT	prothrombin time
QD	once daily

Term	Definition
QLF	quantitative lung fibrosis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SGRQ	St. George's Respiratory Questionnaire
SNP	single nucleotide polymorphism
SOC	Standard of Care
TEAE	treatment-emergent adverse event
T-HALF	elimination half-life
Tmax	time of maximum observed concentration
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
UIP	usual interstitial pneumonia
ULN	upper limit of normal
VAS	visual analog scale
Vss/F	apparent volume of distribution at steady state
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, sponsor or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC for
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by ICH GCP and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study, and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or the participant's legally acceptable representative and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or participant's legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF and, in the US, the participants' signed HIPAA Authorization.

The ICF must also include a statement that BMS and foreign regulatory authorities have direct access to participant records.

In situations where consent cannot be given by participants, their legally acceptable representatives (as per country regulation) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, AE tracking/reporting, protocol-required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through

destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/ bioequivalence/biocomparability, if applicable • dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procures/standards of the sourcing pharmacy. •

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the eCRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance

understanding of product safety. eCRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and paper Pregnancy Surveillance Form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on case report forms (CRFs).

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature are completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor, or sourced by the investigator) such as partially used study treatment containers, vials, and syringes may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory investigator must be selected to sign the clinical study report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- National coordinating investigator
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event) • Elective surgery, planned prior to signing consent • Admissions as per protocol for a planned medical/surgical procedure • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.8 for the definition of potential DILI.)

Pregnancy and potential DILI must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.6 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information for marketed products in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.

  The required method for SAE data reporting is through the eCRF.

  The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).

  In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission.

  When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: [redacted]

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

APPENDIX 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:

  Documented hysterectomy

  Documented bilateral salpingectomy

  Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgment in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the timepoint where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] Oral (birth control pills) Intravaginal (rings) Transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] Oral Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD)

• Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c] • Bilateral tubal occlusion
• Vasectomized partner Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants choose to forego complete abstinence. • Periodic abstinence (including but not limited to calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.6 and APPENDIX 3.

APPENDIX 5 POTENT INHIBITORS OF ORGANIC ANION TRANSPORT PROTEINS

Potent inhibitors of organic anion transport proteins (OATPs), defined as inhibitors expected to increase exposures of OATP substrates by more than 2× are prohibited within 4 weeks of Day 1 and during the study.

Examples of potent inhibitors of OATPs are:

atazanavir	**boceprevir**	**clarithromycin**	**clopidogrel**
cobicistat	**cyclosporine**	**darolutamide**	**dasabuvir**
darunavir	**elbasvir**	**elvitegravir**	**emtricitabine**
erythromycin	**faldaprevir**	**gemfibrozil**	**glecaprevir**
grazoprevir	**itraconazole**	**ledipasvir**	**letermovir**
lopinavir	**ombitasvir**	**paritaprevir**	**pibrentasvir**
rifampin	**ritonavir**	**simeprevir**	**sofosbuvir**
telaprevir	**tenofovir**	**tipranavir**	**velpatasvir**
voxilaprevir			

These lists are not meant to be all inclusive. Please consult individual drug labels for further information.

Please consult the Study Director/Medical Monitor for any commonly used concomitant medications you use for your patients, or in case of questions on other inhibitors of OATP.

APPENDIX 6 STRONG INHIBITORS OR INDUCERS OF CYP3A4

Strong inhibitors of CYP3A4 are prohibited within 4 weeks of Day 1 and during the study. Strong inhibitors are drugs that increase the exposure of substrates of a given metabolic pathway ≥ 5-fold.

Some examples of strong inhibitors of CYP3A4 are:

boceprevir	**ceritinib**	**clarithromycin**	**cobicistat**
conivaptan	**danoprevir**	**elvitegravir**	**idelalisib**
indinavir	**lopinavir**	**itraconazole**	**ketoconazole**
LCL161	**nelfinavir**	**mibefradil**	**mifepristone**
nefazodone	**saquinavir**	**posaconazole**	**ribociclib**
ritonavir	**tipranavir**	**saquinavir**	**telaprevir**
telithromycin		**troleandomycin**	**voriconazole**
VIEKIRA PAK2			

In addition, excessive consumption of the following foods should be avoided:

- **Grapefruit and grapefruit juice**
- **Seville oranges and Seville orange juice**

Strong inducers of CYP3A4 are prohibited within 4 weeks of Day 1 and during the study. A strong inducer is one that causes a ≥ 50% decrease in the plasma AUC values of a substrate of a given metabolic pathway. Some examples of strong inducers of CYP3A4 are:

apalutamide	**avasimibe**	**carbamazepine**	**enzalutamide**
ivosidenib	**lumacaftor**	**mitotane**	**phenobarbital**
phenytoin	**rifampin**	**rifapentine**	**St John's Wort extract**

These lists are not meant to be all inclusive. Please consult individual drug labels for further information.

Please consult the Study Director/Medical Monitor for any commonly used concomitant medications you use for your patients, or in case of questions on other inhibitors/inducers of CYP3A4.

APPENDIX 7 STRONG INHIBITORS OR INDUCERS OF CYP2C8

Strong inhibitors of CYP2C8 are prohibited within 4 weeks of Day 1 and during the study. Strong inhibitors are drugs that increase the exposure of substrates of a given metabolic pathway ≥ 5-fold.

Some examples of strong inhibitors of CYP2C8 are:

clopidogrel	**gemfibrozil**

Strong inducers of CYP2C8:

There are no known strong inducers of CYP2C8.

These lists are not meant to be all inclusive. Please consult individual drug labels for further information.

Please consult the Study Director/Medical Monitor for any commonly used concomitant medications you use for your patients, or in case of questions on other inhibitors/inducers of CYP2C8.

APPENDIX 8 SITE-SPECIFIC PROTOCOL FOR QUALIFIED PET-TRACER SITES in US

The following site-specific protocol was previously published as a separate document (Site-specific Amendment Number 01, dated 12 March 2020) and has been combined into the main protocol due to changes in BMS protocol standards.

Note: The substudy now includes PF-ILD participants as well as IPF participants. The text has been updated accordingly.

Positron Emission Tomography (PET) Tracer Substudy in Pulmonary Fibrosis (IPF or PF-ILD) Participants
Site-specific Amendment Number 01
Site Numbers: Qualified PET-Tracer sites

This protocol amendment is filed to IND 139,558, and also to the PET tracer (BMS-986327) IND 142,580

1 PROTOCOL SUMMARY

1.3 Schedule of Activities

The assessments in APPENDIX 8 Table 1 will be conducted in addition to the assessments in the main protocol for all participants enrolled at sites participating in the amendment.

Table 1: Positron Emission Tomography Imaging Procedural Outline (IM027040)

	Screening Period (Day 42 to Day-1)	Treatment (Day 1 to Week 26)		Notes
		Day 8	Day 29	
		Week 1 (+ 7 days)	Week 4 (± 7 days)	
Informed consent for substudy	X			The participant must complete informed consent and be enrolled in the main study prior to providing consent for the substudy in a separate ICF that must be signed prior to the PET-CT scan administered during the screening period.
[^{18}F]-BMS-986327 administration	X	X	X	IV bolus injection prior to PET-CT scan.
PET-CT scan	X	X	X	The first PET-CT scan will be administered during screening. A second PET-CT at Week 1 must occur after at least 7 days of continuous dosing with main study treatment and approximately 3.5 hours (after a meal) or approximately 1.5 hours (without a meal) after the morning dose of main study treatment on the day of the visit. The third PET-CT scan will be performed at Week 4 (± 7 days) prior to the morning dose of main study treatment on the day of the visit. The PET scan visit may occur on a different day from the main protocol visit.
BMS-986278 PK sample		See Notes		See Section 8.5.3 of APPENDIX 8 for further details.
Vital signs	X	X	X	Vital signs (BP, pulse oxygen, HR) will be monitored per local site standard of care. Vital signs taken before and after tracer injection will be reported to the sponsor.
Adverse events for PET scan visits	X	X	X	Participants will be advised to report any symptoms that occur within 24 hours following PET scan visit. Sponsor will collect events that are reported to occur within 24 hours following PET scan visit. See Section 8.2 of APPENDIX 8.

BP = blood pressure; CT = computed tomography; HR = heart rate; ICF = informed consent form; IV =intravenous; PET = positron emission tomography; PK = pharmacokinetics

2 INTRODUCTION

The purpose of this site-specific amendment is to include evaluation of a positron emission tomography (PET) imaging tracer, [^{18}F]BMS-986327, as part of the ongoing "Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of the Efficacy and the Safety and Tolerability of BMS-986278 in Participants with Pulmonary Fibrosis" (Clinical Protocol IM027040).

Approximately 12 to 15 pulmonary fibrosis (IPF or PF-ILD) participants (approximately equal distribution between main study treatment arms: 30 mg BMS-986278, 60 mg BMS-986278, and placebo) will have [^{18}F]BMS-986327 PET-computed tomography (CT) imaging under this site-specific amendment across qualified centers.

2.2 RATIONALE FOR [^{18}F]BMS-986327 PET

For many therapies, the level of specific target engagement by therapeutic drugs appears to be related to response, though direct measurement requires specialized assays. Currently, there are no existing biomarkers to assess target engagement of lysophosphatidic acid receptor (LPA_1) antagonist therapies, especially at the site of disease in IPF (ie, the lung). Consequently, a comprehensive and quantitative approach to assess LPA_1 target engagement is needed to help establish a relationship between the level of target engagement, dose selection, and potential patient benefit as a result. Human imaging studies with target-specific PET tracers have been utilized in IPF and other diseases to directly visualize specific organ uptake and quantify the level of drug target engagement.[1,2]

An ongoing Phase 1 trial (IM033-002) involving [^{18}F]BMS-986327 – an ^{18}F-labeled PET imaging agent engineered to specifically bind to LPA_1, – is being conducted in normal healthy volunteers as well as participants with IPF at baseline. As [^{18}F]BMS-986327 directly competes with BMS-986278 and other LPA_1 antagonists for binding to LPA_1, we anticipate that PET imaging with [^{18}F]BMS-986327 will reflect the level of target engagement of these therapeutic molecules. Preclinical studies have shown the ability of [^{18}F]BMS-986327 to demonstrate dose-dependent target engagement of BMS-986278 in the lungs of animal models. We hypothesize that PET imaging with [^{18}F]BMS-986327 will allow for in vivo quantification of LPA_1 drug target engagement in the lungs of study participants receiving BMS-986278 therapy. Furthermore, evaluation of target engagement at 2 key time points – maximum observed plasma concentration (Cmax) and minimum observed plasma concentration (Ctrough) – will help to elucidate the level of drug target interaction across the entire dosing period. We also hypothesize that target engagement data, together with additional pharmacokinetics (PK)/pharmacodynamics biomarkers, will help determine the appropriate dose(s) of LPA_1 antagonist therapy to study in future clinical trials with this asset.

2.3 BENEFIT/RISK ASSESSMENT

Each participant may receive up to three [^{18}F]BMS-986327 PET-CT scans if deemed appropriate. Based on previous practice in similar PET studies, tracers are administered as a microdose

(< 100 µg). An initial dose of 222 MBq of [^{18}F]BMS-986327 was selected based on the preliminary data from nonclinical radiation dosimetry studies, with the gallbladder wall as the dose-limiting organ.[3] The estimated radiation dose of administering 222 MBq of [^{18}F]BMS-986327 is approximately 7.11 mSv (male) to 9.04 mSv (female). The estimated dose from a low-dose CT is about 1.5 to 3 mSv. Thus, the total radiation exposure from each [^{18}F]BMS-986327 PET-CT scan will be approximately 8.61 to 12.04 mSv, which is less than or equal to the radiation of a conventional diagnostic CT scan (~ 15 mSv). At such low radiation exposures, scientists disagree about the amount of health risk, and there may be no additional risk at all. Upon availability of human dosimetry data from the ongoing Phase 1 clinical trial, IM033-002, the administered dose of [^{18}F]BMS-986327 may be adjusted, if necessary, but not to exceed microdose guidelines per ICH M3(R2).

Imaging objectives and endpoints are listed in APPENDIX 8 Table 2 below.

3 IMAGING OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Not applicable	• Not applicable
Secondary	
• Not applicable	• Not applicable
Exploratory	
• Assess organ and tissue distribution of [^{18}F]BMS-986327 before and after administration of LPA_1 antagonist BMS-986278 • Assess lung target engagement of BMS-986278	• Calculated SUV and/or V_T in lung and other key organs and tissues • Additional endpoints may be evaluated as data become available

LPA_1 = lysophosphatidic acid receptor; PET = positron emission tomography; SUV = standardized uptake values; V_T = tracer lung volume of distribution

4 STUDY DESIGN

4.1 OVERALL DESIGN

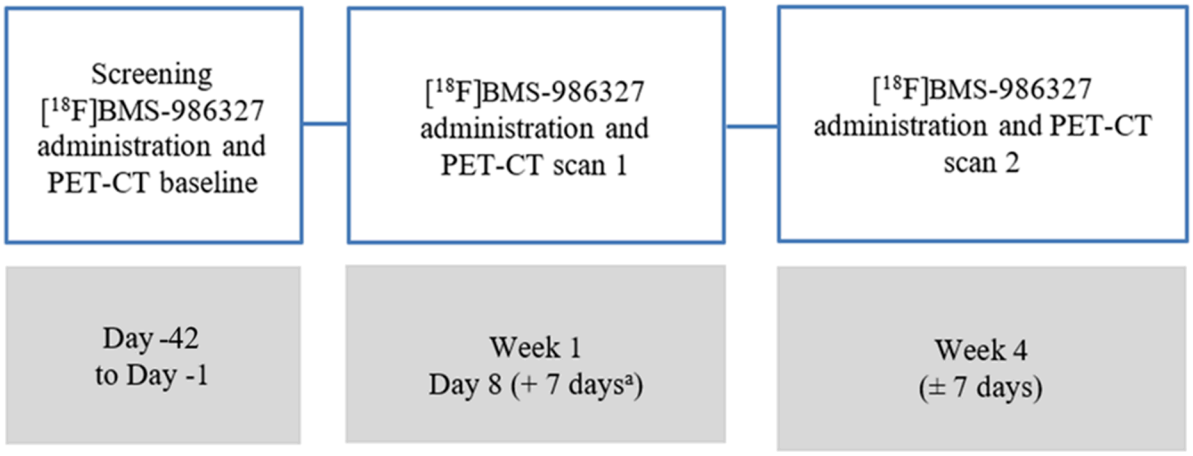
The [^{18}F]BMS-986327 PET-CT will be performed at selected qualified sites, for participants currently participating in the main IM027040 study, and will be implemented after Health Authority review and Institutional Review Board/Ethics Committee approval, in compliance with all applicable laws, rules, and regulations.

The first PET-CT scan will be performed during the screening period after the substudy-specific informed consent form has been signed. The second PET-CT scan will be performed at the Week 1 visit (after at least 7 days of continuous dosing with main study treatment) approximately 3.5 hours (after a meal) or approximately 1.5 hours (without a meal) after the morning dose of main study treatment on the day of the visit. The third PET-CT scan will be performed at the Week 4 visit

(± 7 days) prior to the morning dose of main study treatment on the day of the visit. See Section 8.1 of APPENDIX 8 for further details.

The study design schematic is presented in APPENDIX 8 Figure 1 below.

Figure 1: PET-Tracer Study Design Schematic



CT = computed tomography; PET = positron emission tomography

[a] Week 1 PET-CT scan should occur after at least 7 days of continuous dosing with main study treatment.

4.2 NUMBER OF PARTICIPANTS

Approximately 12 to 15 participants distributed approximately evenly across main study treatment arms (30 mg BMS-986278, 60 mg BMS-986278, and placebo) who are enrolled in the IPF or PF-ILD cohorts of the IM027040 study across multiple qualified imaging centers will participate in [^{18}F]BMS-986327 PET-CT imaging assessments.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants enrolled in IM027040 (IPF or PF-ILD cohort), who can be imaged at qualified sites, and do not meet any PET imaging exclusion criteria will be eligible to participate in this PET imaging study. Participants will sign a separate PET imaging informed consent form.

5.2 EXCLUSION CRITERIA

Participants with the following condition(s) may be considered for participation in the main study, but will not undergo the [^{18}F]BMS-986327 PET-CT imaging:

1) Participants with issues that prevent them from lying still for PET-CT imaging procedure;
2) Participants who have received therapeutic radiopharmaceutical within 7 days prior to participation in this study;
3) Participants who do not have adequate venous access for tracer injection;

4) Participation in other research studies involving clinical PET scans (eg, fluorodeoxyglucose-PET) within 24 hours prior to and after injection of [^{18}F]BMS-986327.

6 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study participant according to the study.

An investigational product (IP), also known as investigational medicinal product (IMP) in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products (non-IP)/noninvestigational medicinal product (non-IMP).

Study drug includes IP/IMP as shown in the APPENDIX 8 Table 3 below.

Table 3: BMS-986278 PET Imaging Precursor Materials for IM027040 (Qualified Sites or Vendors Only)

Product Description	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMT-382761	3 mg/mL (1.87 gm /1 vial)	IP	Open Label	Glass vials closed with stoppers and sealed/ Liquid	-20°C, protected from light

Note: [^{18}F]BMS-986327 will be prepared on site or at a local vendor prior to administration.
IMP = investigational medicinal product; IP = investigational product; PET = positron emission tomography

Tracer production and radiolabeling with F-18 will be performed according to Standard Operating Procedures and performed according to state-of-the-art Good Manufacturing Practice standards.

For details on prepared drug storage, preparation, and administration, refer to the most recent version of the BMS-986327 Investigator Brochure.[3]

7 DISCONTINUATION CRITERIA

Refer to main protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Each participant will receive three [^{18}F]BMS-986327 PET-CT scans.

Approximately 12 to 15 IPF or PF-ILD participants will undergo a baseline [^{18}F]BMS-986327 PET-CT scan within the screening window.

Two additional [^{18}F]BMS-986327 PET-CT scans will be performed during main study treatment dosing to assess drug target engagement at nominal Cmax [Week 1 (Day 8; + 7 days)] and Ctrough [Week 4 (Day 29; ± 7 days)] time points.

Images will be acquired per specifications provided in a separate IM027040 Image Acquisition Guideline document. All PET-CT images will be collected and submitted to an imaging core lab for central analysis.

8.1 [^{18}F]BMS-986327 IMAGING

Images will be acquired per specifications provided in a separate IM027-040 Image Acquisition Guideline document.

8.2 ADVERSE EVENTS

Participants will be advised to report any symptoms that occur within 24 hours following PET scan visit. Sponsor will collect events that are reported to occur within 24 hours following PET scan visit in the study case report form.

8.5 PHARMACOKINETICS

8.5.3 PET TRACER SUBSTUDY

Plasma PK samples of BMS-986278 will be collected for analysis of target engagement at the times described in APPENDIX 8 Table 4 below. PK samples will be collected at 3.5 hours (after a meal) or 1.5 hours (without a meal) after the morning dose of main study treatment on Day 8 (+ 7 days) and prior to the morning dose of main study treatment on Day 29 (± 7 days). Methodology for analysis of PK samples is described in the main protocol.

Table 4: Pharmacokinetic Sampling Schedule for PET Tracer Substudy

Study Day of Sample Collection	Event	Time Relative to Main Study Treatment Morning Dose (hr:min)	BMS-986278 Plasma PK Sample
Day 8 (+ 7 days)		1:30 (fasted) or 3:30 (fed)	X
Day 29 (± 7 days)	Predose	0:00	X

9 STATISTICAL CONSIDERATIONS

The small sample size is not based on statistical power considerations, but is intended to provide sufficient data to enable comparison of lung target engagement across treatment arms.

Methodology for exploratory biomarker analyses including [^{18}F]BMS-986327 PET-CT will be described in the statistical analysis plan and imaging corelab charter. Concentration summaries will not be reported for PK samples collected for the PET tracer substudy.

10 REFERENCES

1. Maher T, Simpson J, Porter J, et al. Late Breaking Abstract - A PET imaging study to confirm target engagement in the lungs of patients with IPF following a single dose of a novel inhaled avβ6 integrin inhibitor. European Respiratory Journal. 2019;54(suppl 63):OA246.

2. Lukey PT, Coello C, Gunn R, et al. Clinical quantification of the integrin alphavbeta6 by [(18)F]FB-A20FMDV2 positron emission tomography in healthy and fibrotic human lung (PETAL Study). Eur J Nucl Med Mon Imaging 2019.

3. BMS-986327 LPA1 PET Tracer Investigator's Brochure, Version 01. Bristol-Myers Squibb Company, 2019. Document Control No. 930137711.

APPENDIX 9 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 04, 21-Dec-2021

The primary purpose of this protocol amendment is to implement the following changes:

- Revise the positron emission tomography (PET) tracer substudy to allow incorporation of participants with non–idiopathic pulmonary fibrosis, progressive fibrotic interstitial lung disease (PF-ILD)
- Clarify phrasing in select inclusion and exclusion criteria
- Add 2 secondary endpoints evaluating the effect of BMS-986278 treatment

In addition, clarifications were made throughout the protocol amendment to align with updated BMS protocol regulations, requirements, and best practices.

All changes applied to the body were applied to the synopsis, as necessary, although not all synopsis changes are included in the table below.

Generally, only major additions and deletions are provided in this summary of changes, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes are not included.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
2 Schedule of Activities -Table 1 -Table 2	Added footnote "a" to both Schedule of Activities tables	To accommodate participant vacation and scheduling needs
2 Schedule of Activities -Table 2 5.1.2.1 Blood Pressure Monitoring 7.4 Dosage Modification 9.4.2 Vital Signs	Clarified procedures for participants with asymptomatic or symptomatic low BP criteria at post-Day 1 study visits	To rectify an error in the previous protocol version
4 Objectives and Endpoints 10.3.2 Secondary Endpoints 10.3.3 Exploratory Endpoints	Clarified that characterizing the PK of BMS-986278 in PF-ILD participants is an exploratory objective, not a secondary objective	To provide for a potential lower sample size in the intensive PK substudy of the PF-ILD cohort
	Added time point (Week 20) to secondary endpoint evaluating the effect of BMS-986278 treatment	To ensure consistency between endpoint analyses
	Added 2 secondary efficacy endpoints evaluating the effect of BMS-986278 treatment	To align secondary endpoints with those listed in the product labels of existing anti-fibrotic medications
5.1.2.1 Blood Pressure Monitoring 7.4 Dosage Modification	Clarified that dose reductions should be reported on the case report form, not reported to the Medical Monitor/Study Director	To clarify best procedures for reporting a dose reduction

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.1 Inclusion Criteria	Inclusion criterion 2)a)i was updated to create new criterion 2)a)v. Criterion 2)a)i was no longer applicable to this protocol.	To clarify that screening period is not included in the 7-year diagnosis time frame
6.2 Exclusion Criteria	Exclusion criterion 1)p was updated to create new criterion 1)y. Criterion 1)p is no longer applicable to this protocol.	To clarify that potential participants should only be excluded if on an active transplant list
	Exclusion Criterion 2)f was updated to create new criterion 2)i. Criterion 2)f is no longer applicable to this protocol.	To clarify exclusion criterion regarding long-acting and short-acting phosphodiesterase 5 inhibitors
	Exclusion Criterion 3)c was updated to create new criterion 3)i. Criterion 3)c is no longer applicable to this protocol.	To correct study definition of uncontrolled hypertension
	Exclusion Criterion 3)g was updated to create new criterion 3)j. Criterion 3)g is no longer applicable to this protocol.	To correct “baseline” total bilirubin to “screening” total bilirubin
	Exclusion Criterion 3)k was added.	To add WBC, hemoglobin, and platelet minimums for participation
6.4.1 Retesting During Screening	Changed rescreening procedure so potential participants do not need to repeat HRCT scan if rescreen takes place within 10 weeks of randomization	To reduce burden on participants who are admitted after rescreening
7.7.1 Prohibited and/or Restricted Treatment	Clarified text from administrative letter 03 (13-Apr-2021)	To clarify that prescribed medications listed in the exclusion criteria and Section 7.7 are still prohibited, even if the participant has a clinical condition
9.5.1 Sparse PK Sampling (All Participants no Participating in PK Substudy), Table 6 9.5.2 Intensive PK Substudy, Table 7 9.5.3 Sparse PK Sampling for Optional Treatment Extension, Table 8 9.6 Biomarkers, Table 9	Added footnote to each table regarding participants who discontinue early	To clarify that no further PK samples should be taken at subsequent visits for participants who discontinue treatment early
10.2 Populations for Analysis	Corrected definition of Safety population	To correct wording that was previously unclear

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
10.4.3 Safety Analyses	Clarified planned analysis of safety information	To clarify that PF-ILD cohort will be analyzed separately from the primary study cohort of IPF
APPENDIX 8 Site-specific Protocol for Qualified PET-Tracer Sites in US (new appendix; previously was separate protocol)	Combined site-specific protocol for qualified PET-Tracer sites into a new appendix, as opposed to a separate amendment	To allow PF-ILD participants to participate in the PET Tracer substudy
Title Page 2 Schedule of Activities 7 Treatment 7.3.2 Circumstances for Unblinding 7.5 Investigational Product Handling/Storage Accountability 8.1 Discontinuation from Study Treatment 8.2 Discontinuation from the Study 8.2.1 Individual Discontinuation Criteria (new section) 9.2 Adverse Events 9.2.2 Method of Detecting AEs/SAEs 9.2.4 Regulatory Reporting Requirements for SAEs 9.2.7 Laboratory Test Result Abnormalities 9.2.8 Potential Drug Induced Liver Injury (DILI) 9.2.9 Other Safety Considerations 9.3 Overdose 9.4.4 Clinical Safety Laboratory Assessments APPENDIX 2 Study Governance Considerations APPENDIX 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting APPENDIX 4 Women of Childbearing Potential Definitions and Methods of Contraception	Updated with most recent BMS Protocol Model Document language and organizational requirements	To align with up-to-date BMS protocol regulations, requirements, and best practices.

OVERALL RATIONALE FOR REVISED PROTOCOL 03

The primary rationale for this revised protocol is in response to the evolving landscape of treatment of non-IPF ILD, as the intention is to enroll a representative population of patients with progressive, non-IPF ILD. Most fibrotic ILD patients with a progressive phenotype, ie, the PF-ILD cohort in this study, are treated with immunosuppressive therapies and an increasing number of these patients are being treated with anti-fibrotic therapies as well. In response to these changes, the protocol is being updated to allow for a number of certain stable background ILD-targeting therapies in the PF-ILD cohort.

In addition, clarifications were made throughout the revised protocol to maintain consistency.

All changes applied to the body were applied to the synopsis, as necessary, although not all synopsis changes are included in the table below.

Generally, only major additions and deletions are provided in this summary of changes, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes are not included.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated Clinical Trial Physician/Medical Monitor name and contact information. Added Clinical Scientist name and contact information.	To integrate the Administrative Letter 01 clarification. To adhere to the BMS template structure.
Section 1.3 Schedule of Activities	Added an "X" to the OTE Day 1 column for clinical laboratory samples (Table 2).	[redacted] clinical laboratory samples will be collected on Day 1 of the OTE.
Section 2.4.3.4 Nonclinical Combination Toxicology	Updated the paragraph discussing nintedanib.	To further clarify the language.
Section 2.5.1 COVID-19-related Benefit/Risk Assessment	Added a new section to describe a COVID-19-related risk assessment.	To provide guidance for site investigators on conducting this study in IPF and PF-ILD patients during the pandemic.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3 Objectives and Endpoints	Added an additional exploratory objective and endpoint related to SARS-CoV-2 serologic status to the main study and OTE.	To collect baseline and end of study serum samples from participants to allow for an optional analysis of SARS-CoV-2 serologic status on participants with IPF or PF-ILD receiving BMS-986278.
Section 4.1 Overall Design	Updated language to allow participants with PF-ILD to remain on stable background therapies.	The landscape of non-IPF ILD is evolving and the intention is to enroll a representative population of real-world of non-IPF ILD. Most patients with a progressive phenotype (ie, PF-ILD) are treated with immunosuppressive therapies. Leading therapies include mycophenolate mofetil (or mycophenolic acid), azathioprine and/or tacrolimus. Furthermore, many patients are now being treated with nintedanib or pirfenidone.
	Updated screening period from 28 to 42 days. This update also applies to other applicable sections throughout the protocol.	To offer additional flexibility to participants and study sites in order to meet enrollment requirements.
Section 4.1.2 Treatment Period	Added language to the PF-ILD cohort to include stratification by background therapy category. This language has been implemented throughout the protocol where applicable.	Now that PF-ILD participants are permitted to remain on stable background therapy, there is a desire for balance within the treatment cohorts. This can be achieved by stratifying by the broad treatment categories indicated.
Section 4.1.2.1 Blood Pressure Monitoring	Clarified orthostatic hypotension and orthostatic tachycardia definitions. These clarifications were also made to Section 8.2.5, as applicable.	To align with the definitions in the vendor manual.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Clarified that findings of orthostatic hypotension and orthostatic tachycardia must be confirmed by retest.	To ensure uniform BP data collection.
Section 4.4.1 Rationale for Optional Treatment Extension (OTE)	Added a new section to provide context for the OTE.	To incorporate changes from the UK-specific revised protocol.
Section 5 Study Population	Added an additional paragraph to the inclusion and exclusion criteria introduction to further clarify protocol entry criteria.	To incorporate changes from the UK-specific revised protocol.
Section 5.1 Inclusion Criteria	Inclusion criterion (IC) 1)a) was updated to 1)c) to remove the reference to legally authorized representative.	To incorporate changes from the UK-specific revised protocol and the [redacted] site-specific amendment.
	IC 2)b)i) was removed.	Any PF-ILD participants will have had to demonstrate progression within 24 months, which negates the need for the 7-year disease duration cutoff.
	IC 2)b)iv), v), and vi) were added.	To permit stable immunosuppressive and anti-fibrotic background therapies for PF-ILD participants.
Section 5.2 Exclusion Criteria	Exclusion criterion (EC) 1)d)ii) was updated to 1)d)iv).	To further clarify existing terminology.
	EC 1)d)iii) was removed.	Stable anti-fibrotic background therapies are to be permitted for PF-ILD participants.
	EC 1)i) was updated to 1)w).	To further clarify existing terminology in light of the COVID-19 pandemic.
	EC 1)u) was updated to 1)x).	To further clarify existing terminology in light of the COVID-19 pandemic.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	EC 2)b) was updated to 2)h).	To permit stable immunosuppressive background therapies for PF-ILD participants.
	EC 3)b) was updated to 3)h).	To ensure uniform BP data collection.
	EC 3)f)i)&ii) were removed.	To enable the enrollment of older adults with lung fibrosis. Slight widening of the QRS interval is very common with common cardiac comorbid conditions. Similarly, it is not uncommon to have some prolongation of the PR interval in elderly patients. Removing these restrictions is appropriate for this patient population and allows for better success in recruiting a representative study population of individuals suffering with lung fibrosis.
	EC 4)c) was added to further clarify protocol entry criteria.	To incorporate changes from the UK-specific revised protocol and the [redacted] site-specific amendment.
Section 6.2 Method of Treatment Assignment	Added language to include stratification by background therapy category for the PF-ILD cohort.	Refer to rationale for Section 5.1.2.
Section 6.6 Treatment Compliance.	Added language about dosing diaries as part of treatment compliance.	To integrate the Administrative Letter 01 clarification.
Section 6.7 Concomitant Therapy	Added new language to allow for stable immunosuppressive background therapies.	Refer to rationale for Section 5.1.
	Added language regarding concomitant anti-fibrotic therapies.	To clarify that pirfenidone and nintedanib are not allowed in combination with one another during the main study.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.7.1 Prohibited and/or Restricted Treatments	Removed sentence about prohibiting anti-fibrotics.	Stable anti-fibrotic background therapies are to be permitted for PF-ILD participants.
Section 7.1 Discontinuation from Study Treatment	Added a subbullet to bullet #5 to clarify that a participant can be discontinued from the study in case of disease progression or if it is in the participant's best interest to start any standard of care treatment that is prohibited in the study.	To incorporate changes from the UK-specific revised protocol.
Section 8.1.1 Forced Vital Capacity	Added language to clarify how and when spirometry testing can be performed.	To integrate the Administrative Letter 01 clarification and to provide more flexibility for study sites.
Section 8.1.2 Diffusing Capacity of Carbon Monoxide	Added language to clarify when the DLCO test can be performed. Removed requirement for DLCO calculations to be recorded on eCRF.	To provide more flexibility for study sites. The CRF will be updated to capture the raw data, therefore study sites will no longer be required to enter calculated DLCO values.
Section 8.1.3 High-resolution Computed Tomography	Added language to include stratification by background therapy category for the PF-ILD cohort.	Refer to rationale for Section 5.1.2.
Section 8.1.4 Clinical Outcome Assessments	Revised language regarding timing of COAs. Language was also updated in the COA notes in the Schedule of Activities in Section 1.3.	To integrate the Administrative Letter 01 clarification, as a means to give study sites flexibility in the order of study procedures being performed.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.4.6 6-Minute Walk Test	Added language regarding timing of 6-MWT administration. Language was also updated in the 6-MWT notes in the Schedule of Activities in Section 1.3.	To provide clarification for study sites.
Section 8.2.9 Other Safety Considerations	Added language for collecting AEs and SAEs related to COVID-19.	To ensure COVID-19 events are captured appropriately in the CRF.
Section 8.4.4 Laboratory Assessments	Provided guidance on Hepatitis B virus DNA serology testing.	To integrate the Administrative Letter 01 clarification.
Section 8.5 Pharmacokinetics	Added language for recording date and time of study treatment administration the day prior to study visits.	Collection of the morning and evening study dose details from the day prior to PK sampling is required to accurately assess PK.
Section 8.5.1 Sparse PK Sampling (All Participants not Participating in PK Substudy)	Added language to footnote b in Table 6.	Refer to rationale for Section 9.5.
Section 8.5.2 Intensive PK Substudy	Added language to footnote b in Table 7. Modified language describing the number of participants per treatment arm.	Refer to rationale for Section 9.5. To allow flexibility in the number of participants per treatment arm.
Section 8.6 Biomarkers	Added a paragraph for the collection of serum for possible assessments of SARS-CoV-2 serologic status. A column for the serum collection was also added to Table 9.	To allow for possible measurements of SARS-CoV-2 serology.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2 Populations for Analyses	Updated Full Analysis Set (FAS) population definition. Updated Safety population definition.	To clarify the intent-to-treat principle consistent with the ICH E9 guidance. The updated FAS definition is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects. To clarify participants will be analyzed according to the actual treatment received in case of mis-treatment.
Section 9.3.3 Exploratory Endpoints	An additional exploratory endpoint was added to the Biomarkers category.	Refer to rationale for Section 3.
APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING	Added definitions of mild, moderate, and severe AEs.	To provide definitions of AE intensity within the protocol.

OVERALL RATIONALE FOR REVISED PROTOCOL 02

The primary rationale for this revised protocol is to include an "optional treatment extension" (OTE) for participants with either idiopathic pulmonary fibrosis (IPF) or non-IPF, progressive fibrotic interstitial lung disease (PF-ILD) that complete the 26-week main study. The objectives of the OTE are to enhance understanding of the safety, tolerability, and efficacy of BMS-986278 in lung fibrosis patients.

In addition, clarifications were made throughout the revised protocol to maintain consistency.

All changes applied to the body were applied to the synopsis, as necessary, although not all synopsis changes are included in the table below.

Generally, only major additions and deletions are provided in this summary of changes, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes are not included.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Changed Medical Monitor.	Study Director will resume Medical Monitor responsibilities for this study.
Section 1.1 Synopsis	Added the OTE. Clarified main study vs OTE. Clarified that dose reduction is permitted for both the main study and OTE (also in Section 1.2).	To enhance understanding of the safety, tolerability, and efficacy of BMS-986278 in lung fibrosis patients, an OTE was added for IPF and PF-ILD participants that complete the 26-week main study.
Section 1.2 Schema and Section 4 Study Design	Added the OTE schema (Figure 3) and modified the main study schemas (Figure 1 and Figure 2).	To illustrate the OTE study design.
Section 1.3 Schedule of Activities	Clarified the note in Table 1 regarding posttreatment HRCT requirement.	All participants are to have HRCT performed at Week 26 in the main study.
	Added spirometry measurements to the Week 20 visit in Table 1.	To provide an additional FVC assessment to more accurately estimate the slope of ppFVC.
	Permitted enrollment of PF-ILD participants in intensive PK substudy in Table 1.	To collect additional PK data from participants in the PF-ILD cohort.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added Table 2 OTE Schedule of Activities.	To list all OTE study procedures.
Section 2.3 Study Rationale	Added language for the OTE.	To describe the OTE rationale.
Section 3 Objectives and Endpoints	Added exploratory objectives and endpoints for the OTE.	To continue assessing the safety, tolerability, and select efficacy measures of BMS-986278 in the OTE. In addition, select COAs, PK, and biomarkers will be collected.
	Adjusted the secondary and exploratory endpoints in Table 3 and in the Synopsis (Section 1.1).	All secondary and exploratory endpoints using the expression ">xx% absolute decline in FVC (mL)" were deleted, as there are no known clinically relevant cutoffs for the decline of FVC in mL in the literature. Furthermore, the definition for pulmonary fibrosis progression-free survival was modified.
Section 4 Study Design	Clarified that participants in the OTE need to adhere to BP monitoring requirements in Section 4.1.2.1 Blood Pressure Monitoring.	All participants in the OTE must continue to follow BP monitoring to maintain blinding, as participants receiving placebo in the main study will be exposed to BMS-986278 for the first time in the OTE.
	Added the OTE study design schema (Figure 3) and Section 4.1.4 Optional Treatment Extension. Revisions made throughout Section 4 to include the OTE.	To enhance understanding of the safety, tolerability, and efficacy of BMS-986278 in lung fibrosis patients, an OTE was added for IPF and PF-ILD participants that complete the 26-week main study.
	Added "end of study" definition to Section 4.3.	[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5 Study Population	Added a note referring to OTE guidance on all applicable inclusion criteria (Section 5.1) and exclusion criteria (Section 5.2).	To clarify which concomitant therapies and prohibited/restricted treatments will/will not be permitted in the OTE.
	Added "Known" to the beginning of Exclusion Criterion 1) k).	To clarify that only those participants that have a pre-existing history of left-ventricular dysfunction are excluded from the study (ie, screening echocardiography to assess ejection fraction not required).
	Added Exclusion Criterion 3) g).	[redacted]
	Added Exclusion Criteria 5) a) and b).	[redacted]
Section 6 Treatment	Revisions made throughout Section 6 to include the OTE.	To include details on study treatment, treatment assignment, blinding, dose modification, and concomitant therapies in the OTE.
	Revised treatment compliance formula in Section 6.6.	The number of tablets taken is collected in the eCRF.
Section 7.1 Discontinuation from Study Treatment	Clarified discontinuation criteria in the OTE.	Discontinuation criteria apply to the main study and the OTE.
Section 8 Study Assessments and Procedures	Clarified timing of spirometry assessment. Removed FEF25-75 from the list of spirometry parameters in Section 8.1.1 Forced Vital Capacity.	Spirometry will be performed prior to morning dosing. The standard FEF25-75 spirometry test was originally provided by the vendor, but it is not needed for this study.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Permitted use of cryobiopsy results instead of HRCT at screening on a case-by-case basis and also clarified when HRCT will be performed during the OTE in Section 8.1.3 High-resolution Computed Tomography. This was also clarified in Section 5.1 Inclusion Criteria, item 2)a)ii) (2) and in Section 5.2 Exclusion Criteria, item 1)d)i)	To account for the possibility that some centers perform cryobiopsy and to clarify when HRCT will be performed during the OTE.
	Clarified the required safety and COA assessments for the OTE in Section 8.4 Safety and Section 8.1.4 Clinical Outcome Assessments.	To clarify which assessments will be performed during the OTE and when.
	Clarified additional ECG assessments to be performed as clinically indicated in Section 8.4.3 Electrocardiograms.	[redacted]
	Added a PK sample collection at Week 4 (Table 6) of the main study in Section 8.5.1 Sparse PK Sampling.	To obtain an additional PK trough sample from participants undergoing the sparse PK sampling schedule.
	Modified Section 8.5.2 Intensive PK Substudy to include at least 10 participants per arm in both IPF and PF-ILD cohorts in the intensive PK substudy.	To obtain intensive PK data from the PF-ILD cohort.
	Added Section 8.5.3 Sparse PK Sampling for OTE.	To collect sparse PK data from participants in the OTE.
	Added biomarker sample collections during the OTE in Table 9 in Section 8.6 Biomarkers.	To explore potential changes in biomarkers associated with 52 weeks of treatment with BMS-986278.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9 Statistical Considerations	Added a caption title to create Table 10.	[redacted]
	Modified Section 9.4.1.1 Primary Efficacy Endpoint.	The model was revised to include all factors necessary to estimate the rate of change.
	Modified Section 9.3.2 Secondary Endpoints and Section 9.3.3 Exploratory Endpoints.	All secondary and exploratory endpoints using the expression ">xx% absolute decline in FVC (mL)" were deleted, as there are no known clinically relevant cutoffs for the decline of FVC in mL in the literature. To include the exploratory endpoints for the OTE.
	Modified Section 9.4.4 Other Analyses.	To perform a statistical analysis on the PF-ILD cohort once the cohort completes the main study. To clarify the data presentation for the OTE results.
	Modified Section 9.4.5 Interim Analyses.	To specify that details will be described in the DMC Charter and SAP. Language pertaining to DMC was removed and revised wording was added to Section 4.1.5.

OVERALL RATIONALE FOR REVISED PROTOCOL 01

The primary rationale for this revised protocol was to permit stable disease modifying anti-rheumatic drug (DMARD) use and the lower age allowed for the PF-ILD cohort to enhance recruitment potential of participants with PF-ILD, including rheumatoid arthritis-associated ILD. Pregnancy testing for women < 55 years of age was added, [redacted].

In addition, clarifications were made throughout the revised protocol to maintain consistency.

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SUMMARY OF KEY CHANGES OF REVISED PROTOCOL		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added Medical Monitor.	The Medical Monitor was confirmed for this study.
Section 1.3 Schedule of Activities, Table 1	Added eligibility check.	Eligibility check was added to clarify that inclusion and exclusion criteria must be met at screening and Day 1 predose.
	Added pregnancy test.	Pregnancy test was added [redacted]
	Adjusted language to "Dispense Study Treatment" row.	To clarify the drug dispensing frequency and treatment compliance check.
	Modified the language in footnote "b"	To clarify that Day 1 orthostatic BP and HR measurements apply to all participants.
Study Acknowledgement/ Disclosure	Removed from Protocol.	To be included as a separate stand-alone document with the Study Director/Medical Monitor signature.
Section 4.1.2 Treatment Period	Removed approximate blood volumes to be collected from participants.	The estimated blood volume is indicated in the ICF.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.1.2.1 Blood Pressure Monitoring	Minor adjustments made throughout section.	To clarify that orthostatic BP and HR are required at every scheduled visit. To specify that participants will not receive study treatment during scheduled visits if their predose orthostatic BP and/or HR meet low BP criteria.
Section 5.1 Inclusion Criteria	Revised inclusion criterion 2)b) for the PF-ILD cohort. Revised inclusion criteria 4)a) and 4)b) to lower the age limit for PF-ILD cohort from 40 to 21 years of age. This revision was also incorporated into sections 1.1 and 2.5 for consistency.	To clarify the "progression" definition for PF-ILD. IPF is not seen in individuals under 40, but as PF-ILD represents heterogeneous forms of ILD, they can be seen in younger adults. This adjustment was made to align recruitment potential of a broader pool of PF-ILD participants.
Section 5.2 Exclusion Criteria	Revised exclusion criteria 1)e) and 1)i) to broaden language about excluding significant lung disease from both cohorts. Added exclusion criterion 1)v) to exclude participants with a positive pregnancy test. Revised exclusion criterion 2)b) to permit stable DMARD use for PF-ILD participants.	To exclude non-ILD respiratory abnormalities to avoid potential impact on efficacy or safety assessments. To clarify that female participants with a positive pregnancy test prior to Day 1 dosing will be excluded from the study. To enhance the recruitment potential of rheumatoid arthritis-ILD participants as part of the PF-ILD cohort.
Section 6.1 Treatments Administered	Added minor clarification to the section.	To ensure participants who are dose reduced/discontinued have their medication kits either replaced or returned to the site.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.6 Treatment Compliance	Minor adjustments made to language in the first paragraph.	To clarify when the treatment compliance checks will take place.
Section 6.7 Concomitant Therapy	Added language to allow for the use of stable DMARDs that have been in place for at least 6 months prior to screening.	DMARDs are commonly used for rheumatoid arthritis. Allowing these agents enhances the recruitment of rheumatoid arthritis-ILD participants as part of the PF-ILD cohort.
Section 8.4.2 Vital Signs	Minor adjustments made to language.	To clarify that vital signs will be collected predose at every visit and to clarify when orthostatic BP and HR are measured, so that orthostatic BP and HR are not measured twice at predose.
Section 8.4.4 Laboratory Assessments, Table 4	Added HBcAb to the list of Serology tests made minor adjustments to the Other Analyses section. Added urine pregnancy test to the Other Analyses list of tests. Removed cannabinoids from the test for drugs of abuse in Other Analyses section.	To ensure participants are screened for HBcAb and to clarify the requirement for hepatitis C RNA and/or hepatitis B DNA testing. To ensure no females have a positive pregnancy test prior to Day 1 dosing (or at any time throughout the study if a pregnancy is suspected). Participants who use marijuana are allowed to participate in this study per local regulation.