CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208780Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208780
Submission Dates	03/29/2016
Brand Name	ESBRIET®
Generic Name	Pirfenidone Film-Coated Tablet
Reviewer	Bhawana Saluja, Ph.D.
Team Leader	Anshu Marathe, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Applicant	Genentech Inc.
Formulation; Strength	Immediate release film-coated tablets; 267 mg, 534 mg and 801 mg pirfenidone
Dosage Regimen	Day 1 through 7 – 267 mg (one 267-mg tablet) three times a day (TID) Day 8 through 14 – 534 mg (two 267-mg tablet) TID Day 15 onward – 801 mg (one 801-mg tablet) TID
Relevant IND/NDA	IND 067284
Indication	Treatment of idiopathic pulmonary fibrosis (IPF)

Table of Contents

List of Tables

List of Figures

1. Executive Summary

This is a 505 (b) (1) NDA for film-coated tablet containing pirfenidone. The proposed proprietary name for this product is ESBRIET® film-coated tablet. Pirfenidone as capsules is approved for the treatment of idiopathic pulmonary fibrosis (IPF).

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 208780 and finds the application acceptable.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The Clinical Pharmacology package submitted for this NDA consisted of a single pivotal bioequivalence (BE) study (GP29830) conducted in 44 healthy adult volunteers. The objective of the clinical study was to determine and compare the rate and extent of absorption of pirfenidone from ESBRIET® film-coated tablet to that from ESBRIET® Capsule under both fasted and fed conditions. This was an open-label, single-dose, randomized, four-period, four-sequence crossover study under fasted and fed conditions. The treatment arms and the statistical summary are presented below. This reviewer has reanalyzed the pharmacokinetic information submitted for this pivotal BE study by employing WinNonlin version 6.4 to obtain the non-compartmental pharmacokinetic (PK) parameters and performed the BE analysis. The results of this reanalysis are in agreement with the results submitted by the Applicant.

Treatment arms –

- Treatment A = pirfenidone 3 × 267-mg ESBRIET® capsules administered as a single oral dose in fed state
- Treatment B = pirfenidone 1 × 801-mg ESBRIET® film-coated tablet administered as a single oral dose in fed state
- Treatment C = pirfenidone 3 × 267-mg ESBRIET® capsules administered as a single oral dose in fasted state
- Treatment D = pirfenidone 1 × 801-mg ESBRIET® film-coated tablet administered as a single oral dose in fasted state

Bioequivalence summary statistics of PK parameters for pirfenidone following single dose (801 mg) administration of ESBRIET® film-coated tablet and ESBRIET® capsule under fasted conditions:

PK Parameter	Test/Ref ratio (%)	90% CI
$AUC_{(0\text{-inf})}$	99.61	96.64, 102.68
$AUC_{(0\text{-t})}$	99.63	96.66, 102.69
C_{max}	101.26	94.41, 108.60

Source: NDA 208780 Module 2.7.1

Overall, the test product, ESBRIET® film-coated tablet (801 mg), is bioequivalent to the corresponding reference product for pirfenidone, ESBRIET® capsule (3 X 267 mg), under fasted conditions.

Food had a small effect on the extent of exposure $AUC_{(0\text{-inf})}$ of the ESBRIET® film-coated tablet (801 mg), but C_{max} was decreased by 39% after administration with a high fat meal. This effect of food on pirfenidone exposure was consistent between the ESBRIET® film-coated tablet and ESBRIET® capsule.

The effect of food on pirfenidone exposure was also consistent with the known effect from ESBRIET® capsule drug product label (NDA 022535).

Overall, Clinical Pharmacology recommends approval of NDA 208780.

2. Question-Based Review

2.1. Background

Pirfenidone is indicated for treatment of idiopathic pulmonary fibrosis (IPF); an orphan disease characterized by chronic, progressive, diffuse parenchymal lung disease with unknown etiology. Pirfenidone was originally approved for the treatment of IPF on October 15, 2014 under NDA 022535 (ESBRIET® Capsule, 267 mg). In the current application, ESBRIET® film-coated tablets (267 mg, 534 mg and 801 mg) are being developed to complement the approved ESBRIET® capsule formulation (NDA 022535). The two strengths of the film-coated tablets will support the approved dose escalation regimen for ESBRIET® in IPF, and will improve subject experience by reducing the pill burden for patients (from nine capsules per day to three tablets per day for daily maintenance dose).

2.1.1. What are the clinical pharmacology studies submitted in the NDA?

The clinical pharmacology studies/clinical studies are summarized below:

Table 1 Listing of clinical pharmacology/clinical studies

Protocol No.	Location of Synopsis / Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.1 Biopharmaceutic Studies								
GP29830	Module 5.3.1.2	Bioequivalence To assess the bioequivalence of a single oral dose of 801-mg pirfenidone tablet (test) relative to pirfenidone capsules (reference) under both fed and fasted conditions in healthy subjects Food Effect To characterize the impact of food on the pharmacokinetics of pirfenidone following single-dose oral administration of one 801-mg tablet.	Open-label, randomized, four-treatment period, four-sequence, single-dose, crossover, 4 × 4 Williams design	Test: Pirfenidone tablets, two, single oral doses of 801-mg tablet (1 × 801 mg) Reference: Pirfenidone capsules, two, single oral doses of 801-mg capsules (3 × 267 mg)	44 healthy subjects	Healthy subjects	12 days (4 periods of 3 days each)	Full CSR
5.3.3 Human PK Studies								
No new studies have been conducted.								
5.3.4 Human PD Studies								
No new studies have been conducted.								
5.3.5 Efficacy and Safety Studies								
No new studies have been conducted.								

Source: NDA 208780 Module 2.7.6.

2.2. General Attributes

2.2.1. What are pirfenidone's key physicochemical properties?

Pirfenidone has structural formula of $C_{12}H_{11}NO$ with the following chemical name: 5-Methyl-1-phenyl-2-1(H)-pyridone. It has a molecular weight of 185.23 g/mol and its chemical structure is shown in Figure 1 below. Pirfenidone is more soluble in methanol, ethyl alcohol, acetone and chloroform than in water and 1.0 N HCl.

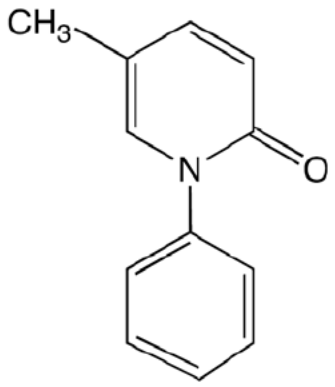


Figure 1 Chemical structure of pirfenidone

2.2.2. What is the formulation for the to-be-marketed film-coated pirfenidone tablet?

Pirfenidone film-coated tablets are available in three strengths: 267 mg, 534 mg and 801 mg. The three strengths of pirfenidone film-coated tablets are dose proportional. (b) (4) (b) (4) The unit composition of pirfenidone film-coated tablets, 267 mg, 534 mg and 801 mg, including the function of each component, is provided in Table 2.

Table 2 Composition of pirfenidone film-coated tablets

Components[a]	Reference to Standards	Function	Quantity per Unit Dose (mg/tablet) 267 mg	534 mg	801 mg
Tablet Core					
Pirfenidone	In-house	Active	267.000	534.000	801.000
Microcrystalline cellulose[b]	NF, Ph. Eur.		(b) (4)		
Silica, colloidal anhydrous (b) (4)	NF, Ph. Eur.				
Povidone (b) (4)	USP, Ph. Eur.				
Croscarmellose sodium	NF, Ph. Eur.				
Magnesium stearate	NF, Ph. Eur.				
Tablet Core Weight	—				
Film-Coating Mixture[c]					
Polyvinyl alcohol	USP, Ph. Eur.				
Titanium dioxide (b) (4)	USP, Ph. Eur.				
Macrogol 3350 (Polyethylene glycol (b) (4))	NF, Ph. Eur.				
Talc	USP, Ph. Eur.				
Iron oxide yellow (E172, C.I. 77492)	NF, EU 231/2012				
Iron oxide red (E172, C.I. 77491)	NF, EU 231/2012				
Iron oxide black (E172, C.I. 77499)	NF, EU 231/2012				
(b) (4)	—				
Total Tablet Weight					

a (b) (4)

b Microcrystalline cellulose (b) (4).

c (b) (4)

Source: NDA 208780 Module 2.3.P.

The study GP28930 used a bio-batch of pirfenidone film-coated tablets that was different from the to-be-marketed drug product with regards to the drug product dimensions (i.e., 20 X 9.7 mm for the bio-batch and 20 X 9.3 mm for the to-be-marketed product), however, according to the Applicant they were

qualitatively and quantitatively the same and used the same manufacturing principle as the to-be-marketed drug product. For more details, please refer to the CMC review for NDA 208780.

2.2.3. What are the findings from OSIS inspection?

OSIS inspection was requested for the clinical and analytical sites for pivotal BE study GP28930. The analytical site was not inspected based on past inspection history. OSIS inspection for the clinical site is not complete and they recommend accepting the clinical portion of the study GP29830 for further Agency review. Refer to OSIS consult report for details.

2.2.4. What are the proposed dosages and routes of administration?

The proposed dosing regimen is 801 mg (one 801 mg tablet) orally three times a day with food. Initial dose titration to the therapeutic dose is recommended. At this time, the Applicant does not plan to market the 534 mg tablet. The negotiations of the final labeling are ongoing at the time of this review. The dose escalation steps are presented in Table 3.

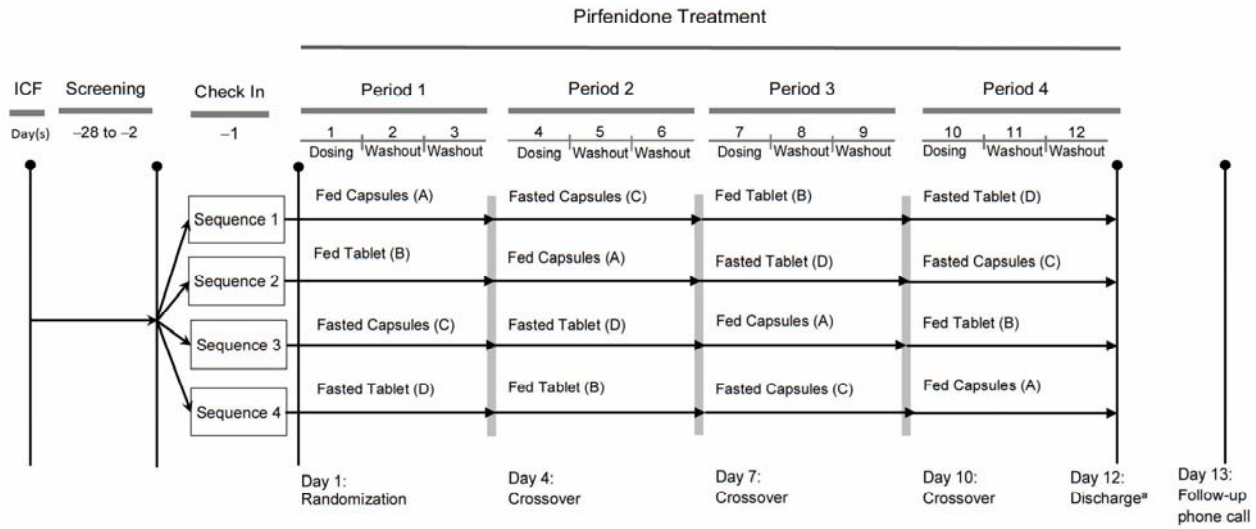
Table 3 Dose escalation steps for pirfenidone

Treatment days	Dosage
Days 1 through 7	a dose of 267 mg (one 267 mg tablet) administered three times a day with meals (801 mg/day)
Days 8 through 14	a dose of 534 mg (two 267 mg tablets) administered three times a day with meals (1602 mg/day)
Days 15 onward	a dose of 801 mg (one 801 mg tablet) administered three times a day with meals (2403 mg/day)

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

The Clinical Pharmacology package submitted for this NDA consisted of a single relative bioavailability study (GP29830) conducted in 44 healthy adult volunteers. The objectives of the clinical study were to determine and compare the rate and extent of absorption of pirfenidone from pirfenidone film-coated tablet to that from ESBRIET® capsule under fasted and fed conditions. This was an open-label, single-dose, randomized, four-period cross-over study under both fasted and fed conditions. Figure 2 shows the design for the Study GP28930.



ICF = informed consent form signed.
[a] Discharge after completion of PK blood draws and assessments.

Figure 2 Study design

Source: Study GP28930 study report Page 16

No clinical study to determine safety and efficacy of the product was carried out in this NDA. The Applicant is relying on the Agency's review findings for safety and efficacy of ESBRIET ® Capsule, NDA 022535.

2.3.2. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameter and exposure response relationships?

Pirfenidone in the plasma samples was measured. No metabolites were quantified because the metabolite (5-carboxy-pirfenidone) is not active.

2.4. What are the PK characteristics of the drug?

2.4.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single oral doses of pirfenidone were administered to healthy volunteers under fasting and fed conditions in Study GP28930.

The mean PK profiles of ESBRIET® film-coated tablet and capsule after single dosing under fasted and fed state is shown in Figure 3. A single dose administration of ESBRIET® 801 mg tablet under fasted conditions resulted in comparable rate and extent of plasma exposure (C_{max} and $AUC_{(0\text{-}inf)}$), relative to ESBRIET® capsule 3 X 267 mg (Table 4 and Figure 3). The time to reach peak plasma concentrations (T_{max}) of pirfenidone under fasted state were generally observed around one hour for tablet and capsule dosage forms.

The presence of food reduced both the rate (C_{max}) and extent (AUC) of pirfenidone absorption. In comparison to the fasted state, the tablet T_{max} was approximately 1 hour later (i.e., around 2 hours), and the C_{max} and AUC were decreased by approximately 39% and 17%, respectively. A similar trend was

observed and previously reported[1] for the ESBRIET® capsule dosage form (see Section 2.4.3 of this review).

The terminal half-life was not affected by formulation type. The half-life of pirfenidone under both fasted and fed conditions was around 3 hours. The pre-dose concentrations for the ESBRIET® film-coated tablet and capsule formulations between the study periods were not quantifiable suggesting that the washout period of 2 days was adequate and pre-dose concentrations did not contribute to the PK results.

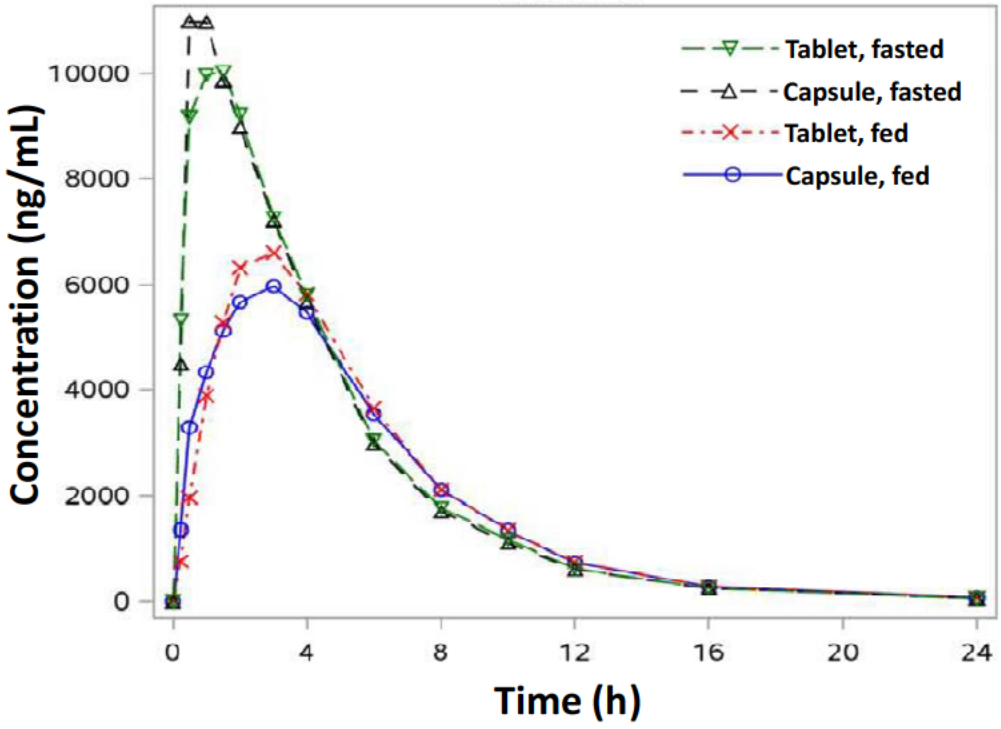


Figure 3 Mean plasma concentrations of pirfenidone vs. time at single dose following ESBRIET® tablet 801 mg or ESBRIET® capsule 3 X 267 mg under fasted (n=42) and fed (n=43) conditions
Source: NDA 208780 Clinical Study Report GP29320

The PK parameters are presented below in Tables 4 and 5. No multiple dose PK studies were conducted.

[1] See Clinical Pharmacology Review for NDA 022535 dated 09/02/2014

Table 4 Pharmacokinetic parameters for pirfenidone after single-dose administration in study GP29830 under fasted conditions

Geometric Mean Parameters (±CV%)	Study GP29830 N - 42 Age Range – 20 to 54 years	
	ESBRIET® Tablet 801 mg Dose (one 801 mg tablet)	ESBRIET® Capsule 801 mg Dose (three 267 mg capsules)
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	49400 (35.5)	49700 (34.9)
$AUC_{(0\text{-}t)}$ (ng.h/mL)	49200 (35.1)	49500 (34.5)
C_{max} (ng/mL)	12600 (32.8)	12500 (27.9)
T_{max} (h)[a]	1.00 (0.25, 3.00)	0.75 (0.25, 2.00)
$t_{1/2}$ (h)[b]	2.77 (0.571)	2.77 (0.589)

$AUC_{(0\text{–}inf)}$ = area under the plasma concentration-versus-time curve from time zero to infinity; $AUC_{(0\text{-}t)}$ = area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration; C_{max} = peak plasma concentration; CV = coefficient of variation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration.
[a] Median (minimum, maximum)
[b] Mean (SD)
Source: Study GP29830 Module 2.7.2

Table 5 Pharmacokinetic parameters for pirfenidone after single-dose administration in study GP29830 under fed conditions

Geometric Mean Parameters (±CV)	Study GP29830 N - 43 Age Range - 20 to 54 years	
	ESBRIET® Tablet 801 mg Dose (one 801 mg tablet)	ESBRIET® Capsule 801 mg Dose (three 267 mg capsules)
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	40900 (35.5)	39800 (37.0)
$AUC_{(0\text{-}t)}$ (ng.h/mL)	40600 (35.0)	39500 (36.6)
C_{max} (ng/mL)	7640 (27.9)	6560 (25.5)
T_{max} (h)[a]	2.05 (1.00, 6.00)	3.00 (0.50, 6.00)
$t_{1/2}$ (h)[b]	2.74 (0.579)	2.75 (0.585)

$AUC_{(0\text{–}inf)}$ = area under the plasma concentration-versus-time curve from time zero to infinity; $AUC_{(0\text{-}t)}$ = area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration; C_{max} = peak plasma concentration; CV = coefficient of variation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration.
[a] Median (minimum, maximum)
[b] Mean (SD)
Source: Study GP29830 Module 2.7.2

Excluded subjects

Although all 44 healthy subjects enrolled in study GP29830 completed all scheduled treatments and had a full complement of pirfenidone concentration-time profiles, one and two subjects had incidence of vomiting reported within the first 6 hours post-dosing under the fed and fasted state, respectively. Therefore, these subjects were excluded from the PK analysis. This is in agreement with the Agency's recommendations on data deletion because of vomiting stated in draft Guidance for Industry titled

"Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (2014).

Bioequivalence
The GMR and 90% CI of the ratio with single dose treatments of ESBRIET® film-coated tablet and ESBRIET® capsule under fasted state, based on log-transformed parameters, are represented in Table 6. The 90% CI of the GMR of $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} were contained within the BE limits of 80.00-125.00 % following single dose treatment.

Table 6 90% CI on the GMR of pirfenidone PK parameters following a single dose oral administration of ESBRIET® film-coated tablet and ESBRIET® capsule under fasted state

PK Parameter	N[a]	Tablet vs Capsules % GLSM Ratio (90% CI[b])
$AUC_{(0-inf)}$ (ng.h/mL)	42	99.61 (96.64, 102.68)
$AUC_{(0-t)}$ (ng.h/mL)	42	99.63 (96.66, 102.69)
C_{max} (ng/mL)	42	101.26 (94.41, 108.60)

[a]N=42; excludes two subjects due to incidence of vomiting
[b]90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio
Source: NDA 208780 Module 2.7.1

2.4.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The pharmacokinetics of pirfenidone in patients was not characterized in this NDA submission. See Clinical Pharmacology Review of NDA 022535 dated 09/02/2014.

2.4.3. How does food affect the bioavailability of pirfenidone film-coated tablet?

Study GP29830 was a four-treatment period, four-treatment. single-dose, randomized, crossover study to determine, among other things, the relative bioavailability of single doses of ESBRIET® film-coated tablet in the fed and fasted state in 44 healthy male and female subjects. The meal selected was the standard, high-fat meal used to assess food effect as described by the FDA guidance document. Following the oral administration of a single dose of ESBRIET® film-coated tablet, the geometric mean (GM) C_{max} values of pirfenidone under fed and fasted conditions were 7640 and 12600 ng/mL, respectively, (Table 4 and 5), a 39% reduction with food. The exposure [$AUC_{(0-t)}$ and $AUC_{(0-inf)}$] of pirfenidone under fed state was 17% lower as compared to the fasted state. In the same study, food led to approximately 48% and 20% reduction in C_{max} and $AUC_{(0-inf)}$ for ESBRIET® capsule, respectively . Thus, the effect of food on pirfenidone exposure for tablet was consistent with ESBRIET® capsule. This effect of food on rate and extent of absorption for ESBRIET® capsule has been previously reported under NDA 022535; food led to a 49% reduction in C_{max} and 16% reduction in AUC of pirfenidone.

Although the C_{max} was 17% higher for the ESBRIET® tablet as compared to the ESBRIET® capsules in the fed state, the difference in C_{max} between the two dosage forms is not expected to have any clinically meaningful impact on the safety and efficacy of pirfenidone. In addition, there was no corresponding increase in exposure [$AUC_{(0-t)}$ and $AUC_{(0-inf)}$] of pirfenidone between ESBRIET® tablet and ESBRIET® capsules in the fed state.

2.5. Bioanalytical

2.5.1. Are the bioanalytical methods properly validated to measure pirfenidone in plasma samples?

Bioanalytical method using high performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) for the quantitation of pirfenidone in human plasma was validated (Table 7). Pirfenidone, along with the internal standard, deuterium-labelled pirfenidone-d5, were extracted from human plasma treated with K_2EDTA using a supported-liquid extraction.

Table 7 Validation summary for bioanalytical method

Validation report	(b) (4)
Matrix (anticoagulant)	Human plasma (K_2EDTA)
Sample volume	0.025 mL
Analytical method/detection	Supported-liquid extraction/LC-MS/MS
Internal standard	Pirfenidone-d5
Validated range	5 ng/mL to 3000 ng/mL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Quantitation method	Peak area ratio
Sensitivity	5 ng/mL (lower limit of quantitation)
Inter-assay accuracy (%Bias)	-4.8% to 0.5%
Inter-assay precision (%RSD)	1.3% to 7.6%
Extraction efficiency	94.9%
Freeze-thaw matric stability	5 cycles at -10°C to -30°C 5 cycles at -60°C to -80°C
Frozen matrix stability	347 days at -10°C to -30°C 347 days at -60°C to -80°C
Ambient matrix stability	24 hr
Studies	GP29830

Source: NDA 208780 Module 5.3.1.4

All validations for the LC-MS/MS bioanalytical assay of pirfenidone appear acceptable with reasonable precision and accuracy.

3. Label Recommendations

Red strikethrough text means deletion of the Applicant's proposed text.

12.3 Pharmacokinetics

Absorption:

After single oral-dose administration of 801 mg ESBRIET (three 267 mg capsules), the maximum observed plasma concentration (C_{max}) was achieved between 30 minutes and 4 hours (median time of 0.5 hours). Food decreased the rate and extent of absorption. Median T_{max} increased from 0.5 hours to 3 hours with food. Maximum plasma concentrations (C_{max}) and $AUC_{0\text{-}inf}$ decreased by approximately 49% and 16% with food, respectively.

Bioequivalence was demonstrated in the fasted state when comparing the 801 mg tablet to three 267 mg capsules. (b) (4) The effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations.

4. Appendix

4.1. Analysis

Geometric mean of pirfenidone PK parameters under fed and fasted state conditions, and bioequivalence determination between ESBRIET® film-coated tablet and ESBRIET® capsule under fasted state conditions in study GP29830 were confirmed by independent analysis and were found to be similar to that reported by the Applicant.

Table 8 90% CI on the GMR of pirfenidone PK parameters following a single dose oral administration of ESBRIET® film-coated tablet and ESBRIET® capsule under fasted state

PK Parameter	Tablet vs Capsules % GLSM Ratio (90% CI)
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	100.61 (97.13, 104.21)
$AUC_{(0\text{-}t)}$ (ng.h/mL)	100.63 (97.17, 104.22)
C_{max} (ng/mL)	103.36 (95.39, 112.00)

Source: Reviewer's analysis

4.2. Individual Study Synopsis

4.2.1. GP29830

Study Title:

A Phase I, Open-Label, Randomized, Four-Treatment Period, Four – Sequence, Single-Dose, Crossover, Pharmacokinetic Bioequivalence Study Comparing Pirfenidone Tablet and Capsule Dosage Forms in Healthy Adult Volunteers

Pharmacokinetic Objectives:

- To assess the bioequivalence of pirfenidone after a single-dose oral administration of one 801 mg pirfenidone tablet (test) relative to a single dose (comprising three 267 mg capsules) of pirfenidone capsules (reference)
- To characterize the impact of food on the pharmacokinetics of pirfenidone following single-dose oral administration of one 801 mg tablet

Safety Objectives:

- To evaluate the safety and tolerability of a single dose of 801mg pirfenidone tablet (test) and a single dose (comprising three 267-mg capsules) of pirfenidone capsules (reference) under both fed and fasted conditions in healthy subjects

Study Design:

This was a single-center, open-label, randomized, four-treatment period, four-sequence, balanced crossover PK study of single doses of ESBRIET® film-coated tablet and ESBRIET® capsule administered orally in the fasted and fed state conditions to 44 healthy male and female subjects

between the ages of 18 and 55 years. Each subject was to receive the following treatments in four treatment periods with 11 subjects per sequence.

Treatment A = pirfenidone 3 × 267-mg capsules administered as a single oral dose in fed state
Treatment B = pirfenidone 1 × 801-mg tablet administered as a single oral dose in fed state
Treatment C = pirfenidone 3 × 267-mg capsules administered as a single oral dose in fasted state
Treatment D = pirfenidone 1 × 801-mg tablet administered as a single oral dose in fasted state

A 4 × 4 Williams design was used in this study. The treatment sequences were ACBD, BADC, CDAB, and DBCA. With this design, subjects served as their own control. Treatments were given on Days 1, 4, 7, and 10. There was a washout period of 2 days between treatments.

Number of Subjects (Planned and Analyzed):
Forty-four (44) subjects were planned and enrolled; 44 subjects were analyzed for safety; 42 and 43 subjects were included in the analyses of pharmacokinetic variables for fasted and fed state, respectively.

Diagnosis and Main Criteria for Inclusion:
Healthy male or female volunteer adult subjects between ages of 18-55 years with a body mass index of 18.5−30.0 kg/m^2.

Duration of Treatment: The total duration of the study for each subject was approximately 41 days divided as follows:

Screening: up to 28 days
Treatment: 4 treatment periods of 3 days, each treatment period includes 1 day of dosing followed by 2 days of washout
Follow-up: 1 day after last PK sample of fourth treatment period

Test Product, Dose and Mode of Administration, Lot Number:
Pirfenidone was supplied as an 801 mg tablet (Lot#1149831, corresponding to the bulk batch number M0006), and as 3 x 267 mg capsules (Lot#1149354, corresponding to the bulk batch number 1402340) and was administered under both fed and fasted conditions.

Pharmacokinetic Assessments:
Blood samples (approximately 4 mL) were collected for determination of plasma concentrations of pirfenidone on Days 1 − 2, 4 − 5, 7 − 8, and 10 − 11 at the following time points in relation to pirfenidone dosing

Days 1, 4, 7, and 10:

Predose: 0 hours (up to 3 hours before dosing)
Postdose: 0.25, 0.5, 1, 1.5, 2, 3, and 4 hours (± 2 minutes)
Postdose: 6, 8, 10, 12, and 16 hours (± 10 minutes)

Days 2, 5, 8, and 11:

Postdose: 24 hours (± 15 minutes)

The total blood volume drawn for PK sampling was 56 mL on Days 1 − 2, Days 4 − 5, Days 7 − 8, and Days 10 − 11 and 224 mL during the study period.

Pharmacokinetic Methods:
The pirfenidone plasma concentration-time profiles were analyzed by non-compartmental approach using Phoenix® WinNonlin® 6.3 (Certara USA Inc., St. Louis, Missouri) to obtain estimates of the pharmacokinetic parameters.

Safety Assessments:
Safety was evaluated by monitoring and recording adverse events, including serious adverse events (AEs) and non-serious AEs of special interest, performing safety laboratory assessments (hematology, serum chemistry profile, calculated creatinine clearance rate, urinalysis, urine drug screen, urine alcohol test, serum pregnancy test for women of childbearing capacity, and serology for HBsAg, HCV antibody, and HIV antibody) measuring vital signs, complete physical examinations, and ECG, and conducting other tests that are deemed critical to the safety evaluation of the study.

Statistical Methods:
In agreement with the Food and Drug Administration (FDA) (IND 67284 Type-C meeting minutes [WRO] dated May 27, 2015) bioequivalence (BE) was established under fasting conditions. In addition, exposure parameters after single dose administration of pirfenidone film-coated tablet were also examined under the fed state.

ANOVA was performed on log-transformed pirfenidone PK parameters for a single dose ($AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max}) under fasting conditions. The ratios of geometric means (i.e. ESBRIET® Film-coated Tablet/ESBRIET® capsule) and 90% confidence intervals were determined.

Safety:
Safety was assessed through summaries of AEs, changes from baseline in laboratory test results, and changes from baseline in vital signs.

CONCLUSIONS
Pharmacokinetic Conclusions:
The following conclusions are based on the results of the pharmacokinetic analyses:

- The ESBRIET® film-coated tablet (1 X 801mg) is bioequivalent to the commercially available ESBRIET® capsule (3 X 267 mg) based on AUC and C_{max} comparisons under single dose conditions in healthy volunteers under fasting conditions.
- Food intake reduced the rate and extent of pirfenidone absorption with the 801 mg tablet, as shown by the decreases in C_{max} and AUC, relative to the fasted state.

Safety Conclusions:
ESBRIET® film-coated tablet and ESBRIET® capsule were generally well tolerated by healthy male and female subjects in the fasted and fed state. For more details, please refer to the clinical review for NDA 208780.

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Application Information

NDA Number	208780 (related IND 067284)	**SDN**	1
Applicant	Genentech	**Submission Date**	03/29/2016
Generic Name	Pirfenidone	**Brand Name**	ESBRIET®
Drug Class	Anti-inflammatory and anti-fibrotic agent		
Indication	Treatment of idiopathic pulmonary fibrosis (IPF)		
Dosage Regimen	801 mg (one 801-mg tablet) three times a day (TID)		
Dosage Form	Immediate release film-coated tablet: 267, 534 and 801 mg	**Route of Administration**	Oral
OCP Division	DCP II	**OND Division**	DPARP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Bhawana Saluja, Ph. D.	Anshu Marathe, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	05/28/2016	**74-Day Letter Date**	6/10/2016
Review Due Date	12/25/16	**PDUFA Goal Date**	01/27/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain

This is 505(b)(1) submission for pirfenidone tablet dosage form under NDA 208780 referencing Esbriet® capsules (NDA 022535), and the clinical pharmacology/clinical program includes a single pivotal pharmacokinetic (PK) bioequivalence study to support the application. The pivotal PK study was conducted at a single clinical site and the bioanalysis of the PK samples was done at a single bioanalytical site. Therefore, we request that both the clinical site and analytical site be inspected for this study.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence			Study GP29830 (Module 5.3.1.2, Clinical Study Report, pages 1-918)
☑ Food Effect			Conducted under Study GP29830
☑ Bioanalytical methods			Determination of Pirfenidone in Human Plasma Samples from GP29830 by HPLC with MS/MS Detection (Module 5.3.1.2, Clinical Study Report, pages 921-2039) Validation of a Method for the Determination of Pirfenidone in Human Plasma by HPLC with MS/MS Detection (Module 5.3.1.4, GP29830 Bioanalytical Method Validation Report)
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		Conducted under Study GP29830
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			

☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies/Reports	**In Vitro**	2	**In Vivo**	1
Total Number of Studies/Reports to be Reviewed		2		1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☑No ☐N/A	Sponsor submitted comparative dissolution data for their bio-batch and to-be-marketed (TBM) product. They state that the drug product composition is the same between the bio-batch and TBM product, with minor differences in tablet dimensions (20 X 9.7 mm and 20 X 9.3 mm, respectively)
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Cross-referenced NDA 022535
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	The sponsor submitted a pharmacokinetic bioequivalence study for 801 mg strength product. They submitted bio-waiver request for the TBM product, and two lower strengths (i.e., 267 & 534 mg tablet)
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	This is a 505(b)(1) application that cross-references the FDA's finding of safety and efficacy of the listed drug (Esbriet® Capsule, NDA 022535). The clinical pharmacology program includes a single pivotal pharmacokinetic bioequivalence study to support the application.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	Cross-referenced NDA 022535
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	The submission contains PK datasets in .xpt format.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	

Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Pirfenidone was granted orphan drug designation for the treatment of idiopathic pulmonary fibrosis on March 5, 2004 (Orphan Drug Designation 03-1779). Therefore, this drug product is exempt from PREA requirements.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this	☐Yes ☐No ☑N/A	

submission?		

CLINICAL PHARMACOLOGY
FILING MEMO FOR NDA 208780

Regulatory History
Genentech submitted a 505(b)(1) NDA 208780 for ESBRIET® film-coated tablet [pirfenidone immediate release (IR) film-coated tablet: 267, 534 and 801 mg]. The drug product is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

The proposed drug product is described as "film-coated tablets: oval, biconvex, debossed with "PFD", containing 267 mg (yellow), 534 mg (b) (4), and 801 mg (brown) Pirfenidone". The proposed drug product contains pirfenidone and the following inactive ingredients: microcrystalline cellulose, colloidal anhydrous silica, povidone, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol (polyethylene glycol), talc, and iron oxide.

This NDA relies on the Agency's previous findings of safety and effectiveness for ESBRIET® capsule [listed drug, pirfenidone immediate release capsule: 267 mg, NDA 022535]. The clinical pharmacology/clinical program includes one pharmacokinetic (PK) study (Table 1) - an open-label single-dose four-way crossover pivotal PK study (Study GP29830), comparing the proposed pirfenidone IR tablet (801 mg strength) and ESBRIET® capsule (reference, 267 mg capsule X 3), under both fed and fasted conditions in healthy subjects:

(a) To establish bioequivalence of their proposed drug product to the listed drug, and
(b) To characterize the impact of food on pharmacokinetics (PK) of pirfenidone following single-dose oral administration of one 801 mg tablet.

Table 1. List of clinical studies

Protocol No.	Location of Synopsis Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.1 Biopharmaceutic Studies								
GP29830	Module 5.3.1.2	Bioequivalence To assess the bioequivalence of a single oral dose of 801-mg pirfenidone tablet (test) relative to pirfenidone capsules (reference) under both fed and fasted conditions in healthy subjects Food Effect To characterize the impact of food on the pharmacokinetics of pirfenidone following single-dose oral administration of one 801-mg tablet.	Open-label, randomized, four-treatment period, four-sequence, single-dose, crossover, 4 × 4 Williams design	Test: Pirfenidone tablets, two, single oral doses of 801-mg tablet (1 × 801 mg) Reference: Pirfenidone capsules, two, single oral doses of 801-mg capsules (3 × 267 mg)	44 healthy subjects	Healthy subjects	12 days (4 periods of 3 days each)	Full CSR
5.3.3 Human PK Studies								
No new studies have been conducted.								
5.3.4 Human PD Studies								
No new studies have been conducted.								
5.3.5 Efficacy and Safety Studies								
No new studies have been conducted.								

Bioanalytical methods and datasets for the Study GP29830 could be located in the submission.

Pending review, dosing in the fasted state met the BE criteria [i.e., 90% confidence interval (CI) of 80.00-125.00%] for both C_{max} and AUC for pirfenidone IR tablet and listed drug. Similarly, dosing under the fed state met the BE criteria for AUC, however, the 90% CI for C_{max} were slightly outside the BE limit (i.e., 108.26-125.60%).

In addition, according to the sponsor, the effect of food on pirfenidone exposure was consistent between the proposed tablet dosage form and the listed drug – C_{max} in fed state was considerably reduced (39%), and a small effect was observed for $AUC_{(0\text{-infinity})}$ (17% reduction). According to the listed drug product label, "Food decreased the rate and extent of absorption. Median T_{max} increased from 0.5 hours to 3 hours with food. Maximum plasma concentrations and $AUC_{0\text{-inf}}$ decreased by approximately 49% and 16% with food, respectively."

The study GP28930 used a bio-batch of the proposed drug product that is different from the to-be-marketed drug product with regards to the drug product dimensions (i.e., 20 X 9.7 mm for the bio-batch and 20 X 9.3 mm for the to-be-marketed product)[1]. The sponsor has submitted comparative dissolution profiles for the bio-batch and the to-be-marketed product as a basis for the biowaiver request.

The sponsor is requesting a biowaiver for the two lower tablet strengths of 276 and 534 mg based on (1) comparative dissolution profiles across all strengths, (2) proportional similarity of the formulations across different strengths, (3) similar manufacturing process across all strengths, and (4) acceptable bioequivalence study of the 801 mg strength.

Acceptance of these findings will be a review issue.

The NDA is considered fillable from a clinical pharmacology perspective.

[1] According to the sponsor, the to-be marketed formulation and the formulation used in the pivotal bioequivalence Study GP29830 (i.e., the bio-batch) are qualitatively and quantitatively the same (exact match) and use the same manufacturing principle.

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/s/

BHAWANA SALUJA
05/18/2016

ANSHU MARATHE
05/18/2016