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Evaluation of the Pharmacokinetics and Safety of a Single Dose of Acalabrutinib in Subjects With Hepatic Impairment

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Abstract

Acalabrutinib received approval for the treatment of adult patients with mantle cell lymphoma who received at least 1 prior therapy and adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma. This study investigated the impact of hepatic impairment (HI) on acalabrutinib pharmacokinetics (PK) and safety at a single 50-mg dose in fasted subjects. This study was divided into 2 parts: study 1, an open-label, parallel-group study in Child-Pugh class A or B subjects and healthy subjects; and study 2, an open-label, parallel-group study in Child-Pugh class C subjects and healthy subjects. Baseline characteristics and safety profiles were similar across groups. Acalabrutinib exposure (area under the plasma concentration–time curve) increased slightly (1.90- and 1.48-fold) in subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment compared with healthy subjects. In severe hepatic impairment (Child-Pugh class C), acalabrutinib exposure (area under the plasma concentration–time curve and maximum plasma concentration) increased ≈5.0- and 3.6-fold, respectively. Results were consistent across total and unbound exposures. Severe hepatic impairment did not impact total/unbound metabolite (ACP-5862) exposures; the metabolite-to-parent ratio decreased to 0.6 to 0.8 (vs 3.1-3.6 in healthy subjects). In summary, single oral dose of 50-mg acalabrutinib was safe and well tolerated in subjects with mild, moderate, and severe hepatic impairment and in healthy control subjects. In subjects with severe hepatic impairment, mean acalabrutinib exposure increased by up to 5-fold and should be avoided. Acalabrutinib does not require dose adjustment in patients with mild or moderate hepatic impairment.

Keywords

acalabrutinib, ACP-5862, hepatic impairment, pharmacokinetics, phase 1 study

B-cell lymphoid malignancies comprise the most common hematologic malignancies.[1] Patients who require treatment are commonly given chemotherapeutic and/or immunotherapeutic agents.[2–5] However, most treated patients will eventually experience disease relapse, and some will experience recurrent disease even with initial induction therapy and subsequent salvage therapy. Bruton tyrosine kinase (BTK) is a nonreceptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells, and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration.[6,7] Functional null mutations of BTK in humans cause the inherited disease X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells.[8] Conversely, BTK activation is implicated in the pathogenesis of several B-cell malignancies.[9]

Acalabrutinib (Calquence; AstraZeneca Pharmaceuticals LP, Wilmington, Delaware) is a selective, irreversible small-molecule inhibitor of BTK, which possesses a reactive butynamide group that binds covalently to Cys481 in BTK.[10,11] Acalabrutinib is approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy, as well as treatment

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of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.

Preclinical acalabrutinib studies indicated that glutathione, glycine-cysteine, cysteine, and oxidized glutathione conjugates were the major biotransformation products observed in rats and dogs. In vitro studies using human liver microsomes and recombinant systems expressing individual cytochrome P450 (CYP) isoforms showed that CYP3A4/5 is mainly responsible for oxidative metabolism of acalabrutinib. Based on available nonclinical and clinical data, acalabrutinib is cleared by multiple CYP and non-CYP metabolic pathways, and CYP3A-mediated oxidation appears to be a major route of metabolism in humans. The major circulating acalabrutinib metabolite, ACP-5862, is formed by CYP3A-mediated oxidation. ACP-5862 is the only human metabolite in plasma that accounted for >10% of total acalabrutinib-related material.[12] In vitro evaluation of acalabrutinib and ACP-5862 demonstrated that ACP-5862 is also a covalent inhibitor of BTK. ACP-5862 has ≈50% potency for BTK inactivation relative to parent acalabrutinib[13] and has a similar kinase selectivity profile.[14] When the kinetics of irreversible binding were compared between wild-type BTK and BTK with the Cys481 replaced by a Ser481, covalent binding to Cys481 was evident for both acalabrutinib and ACP-5862.[14] Moreover, it has been recently reported in an acalabrutinib human absorption, distribution, metabolism, and excretion study[12] that radioactivity after an oral microtracer dose of 14C-labeled acalabrutinib was mainly excreted in feces, and acalabrutinib was shown to undergo significant metabolism-mediated clearance, with CYP3A-mediated clearance in the liver as a major mechanism of biotransformation.

The liver is involved in the clearance of most oncology drugs via hepatic uptake, oxidative and/or conjugative metabolic pathways, and biliary excretion of the unchanged drug or metabolites. Hepatic impairment (HI) can alter hepatic blood flow, as well as the transport and metabolism of compounds with high intrinsic clearance, leading to higher drug exposure and altered efficacy and safety.[15–17] Therefore, hepatic impairment might be expected to lead to increased exposure to acalabrutinib.

The purpose of this study was to determine the effect of impaired hepatic function on the pharmacokinetics (PK) of acalabrutinib following a single oral dose in subjects with mild and moderate hepatic impairment (study 1) and to determine the effect of severely impaired hepatic function on the single-dose PK of acalabrutinib and its metabolite, ACP-5862 (study 2). The data generated may provide guidance in developing dosage regimens for subjects with chronic hepatic dysfunction.

Methods

Study Design

This investigation was approved by the Human Subjects Protection Committees (institutional review board [IRB]) of the University of Miami Human Subject Research Office (Miami, Florida), IntegReview IRB (Austin, Texas), and Crescent City IRB (New Orleans, Louisiana), and was performed in accordance with the Declaration of Helsinki and good clinical practice. Written informed consent was obtained directly from all participants before entry into the study and before any study procedures. This investigation was a phase 1, open-label, single-dose study conducted at 3 research centers that included 2 studies (NCT04867941 and NCT03968848).

In study 1, 18 enrolled subjects were stratified into 3 groups based on baseline hepatic function as defined by the Child-Pugh classification system: group A: 6 subjects with mild hepatic impairment (Child-Pugh class A); group B: 6 subjects with moderate hepatic impairment (Child-Pugh class B); and group C: 6 healthy control subjects matched to the hepatic impairment groups according to mean age (±10 years) and mean weight (±20%). A similar number of men and women were enrolled in each group.

In study 2, 16 subjects were enrolled (8 control subjects and 8 subjects with severe hepatic impairment). Not more than 25% of the hepatically impaired subjects were allowed to have a transjugular intrahepatic portosystemic shunt. Healthy control subjects were matched in a 1:1 ratio to a subject with severe hepatic impairment for age (within age groups <45 or ≥45 years), weight (±20%), and sex (1:1). Subjects with hepatic impairment were identified by medical records containing Child-Pugh classification at screening.

After a screening period (day −28 to −2), subjects checked in on day −1 and were administered a single dose of acalabrutinib 50 mg on day 1. The confinement period lasted from day −1 to day 3 for subjects with mild and moderate hepatic impairment, from day −1 to day 4 for subjects with severe hepatic impairment, and from day −1 to day 2 for healthy control subjects.

Eligibility

Eligible subjects were men or surgically sterile or postmenopausal (for the past year) women, aged 18–75 years, and with a body mass index between 19 and 40 kg/m^2 at the time of screening. Subjects with normal hepatic function were required to be medically healthy with no clinically significant medical history, and with physical examinations, laboratory profiles, vital signs, or electrocardiograms (ECGs), as deemed by the investigator. Healthy subject liver function tests and serum bilirubin were required to be at or below the upper

limit of normal (ULN) at screening. Subjects with either mild, moderate, or severe hepatic impairment were required to have documented stable liver function for >2 months before screening. Subjects were excluded if they had any of the following conditions: positive results for urine or breathalyzer alcohol test and/or urine drug screen; positive test presence of any clinically significant, ongoing systemic bacterial, fungal, or viral infections (including upper respiratory tract infection, but excluding localized cutaneous fungal infections); history of a bleeding diathesis; any clinically significant condition that could have affected acalabrutinib absorption including gastric restrictions and bariatric surgery; positive results for HIV at screening or using an HIV protease inhibitor; and inability to refrain from or anticipated use of any medication that could not be discontinued ≥14 days before dosing and throughout the study, with the exception of proton pump inhibitors such as omeprazole, which were prohibited for ≥5 days before dosing and until ≥12 hours after dosing. In addition, any drug known to be a strong or moderate inhibitor or inducer of CYP3A or P-glycoprotein, including St John's wort, was restricted for 14 and 28 days, respectively, before dosing and throughout the study. Subjects with hepatic impairment were also excluded if they had history of hepatitis B virus infection or active hepatitis C virus and persistent transaminase elevations >6 times the ULN. However, subjects with hepatic impairment who were taking medications to treat stable diseases or manifestations of hepatic disease with stable regimens for ≈2 weeks before dosing were allowed to participate in the study, as determined by the investigator. Matched control subjects were excluded if they had a positive test for hepatitis B or C, seated blood pressure <90/40 or >150/95 mmHg; seated heart rate <40 or >99 beats per minute; hemoglobin level below the lower limit of normal; or liver function (eg, serum alanine aminotransferase [ALT], aspartate aminotransferase) or serum bilirubin (total) values higher than the ULN at screening.

Safety Evaluation

Safety assessments were performed at screening (baseline), check-in, and days 1 to 4 of patient confinement. Adverse events (AEs) were collected throughout the study period until the follow-up contact (14 days after study drug administrations). Safety variables included AE monitoring, concomitant medication monitoring, serial clinical laboratory testing (hematology, serum chemistry, urinalysis), vital signs, 12-lead ECGs, and physical examinations.

Sample Collection

In study 1, each subject received a single 50-mg dose of acalabrutinib (2 × 25-mg capsule) administered orally with ≈240 mL of water on the morning of day 1 at hour 0 following an overnight fast. Blood samples (4 mL) were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 36, and 48 hours after dosing for subjects with mild or moderate hepatic impairment; samples were collected according to the same schedule up to 24 hours after dosing for control subjects. On day 1, blood samples collected at 0.75, 6, and 24 hours after dosing were used to determine acalabrutinib plasma protein binding. In study 2, each subject received a single 50-mg dose of acalabrutinib (1 × 50-mg capsule) administered orally with ≈240 mL of water on the morning of day 1 at hour 0 following an overnight fast. Care was taken to avoid lactulose administration in the morning until 6 hours after acalabrutinib dosing. Blood samples (4 mL) were collected before dosing and at 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 36, 48, 60, and 72 hours after dosing for subjects with severe hepatic impairment. On day 1, 4-mL blood samples collected at 0.863, 1.75, and 6.5 hours after dosing were used to determine plasma protein binding of acalabrutinib and its active metabolite, ACP-5862. Urine samples from each subject were collected before dosing, 0–4 hours after dosing, and 4 to 24 hours after dosing (samples collected within each time frame were pooled for each subject).

Analytical Methods and PK Analyses

All collected plasma and urine samples were analyzed using a validated liquid chromatography with tandem mass spectrometry method (Inotiv, West Lafayette, Indiana) and Covance Laboratories (Indianapolis, Indiana). The internal standards were deuterated acalabrutinib and deuterated ACP-5862. Briefly, protein precipitation was used to extract the analytes and internal standards from human plasma using dipotassium ethylenediaminetetraacetic acid as an anticoagulant, and a linear 1/concentration^2-weighted least-squares regression algorithm was used to quantitate unknown samples. The nominal plasma concentration range was 1 to 1000 ng/mL for acalabrutinib and 5 to 5000 ng/mL for ACP-5862. The nominal urine concentration range was 5 to 5000 ng/mL. Acceptable calibration standards were within ±15% of nominal (±20% at the lower limit of quantitation). The quality control concentrations for plasma acalabrutinib were 3, 50, 400, and 800 ng/mL; for plasma ACP-5862 were 15, 250, 2000, and 4000 ng/mL; and for urine acalabrutinib and ACP-5862 were 15, 2500, and 3750 ng/mL. During validation, all quality controls passed with inter- and intra-assay accuracy within ±15% of nominal and with precision ≤15%. Acceptable stability within ±15% of nominal was demonstrated in freeze/thaw, room temperature, and extract stability tests. Frozen storage stability at −20°C and −70°C was demonstrated up to 102 days. Unbound acalabrutinib concentrations could

not be determined in study 1 because of inconsistent data; in study 1, quantification of acalabrutinib in dialysate following equilibrium dialysis could not be validated due to problems attaining equilibrium and poor recovery from the apparatus. In study 2, in vitro protein binding (%) (to estimate fraction unbound) for acalabrutinib and ACP-5862 in human plasma was assessed using ultracentrifugation methodology by Sekisui Medical Co., Ltd (Ibaraki, Japan).

Plasma PK parameters were determined on the basis of individual plasma concentration–time profiles. The following PK parameters were calculated from plasma concentrations of acalabrutinib and ACP-5862 (total and unbound) using noncompartmental analysis: area under the plasma concentration–time curve (AUC) by the trapezoidal rule from time 0 to 24 hours ($AUC_{0\text{-}24}$), time 0 to the last quantifiable concentration ($AUC_{0\text{-}last}$), and time 0 to infinity ($AUC_{0\text{-}inf}$); maximum observed plasma concentration (C_{max}) and time to reach C_{max} (t_{max}); apparent terminal elimination rate constant and terminal half-life ($t_{1/2}$); apparent oral clearance (CL/F) calculated as dose/$AUC_{0\text{-}inf}$; apparent volume of distribution based on the terminal phase after oral administration; and metabolite/parent C_{max} and AUC ratios (study 2 only).

Statistical Analyses

The safety analysis included all subjects who received study drug, and the PK analysis included all subjects who received the study drug and had an evaluable PK profile.

A sample size of 34 subjects (6 each with mild or moderate hepatic impairment and 6 with normal hepatic function from study 1 and 8 with severe hepatic impairment and 8 with normal hepatic function from study 2) was considered sufficient for determining the PK and safety profiles of a single, oral 50-mg dose of acalabrutinib. In accordance with US Food and Drug Administration guidelines on PK evaluation in patients with impaired hepatic function, eligible subjects were grouped according to Child-Pugh classification: no impairment, mild impairment (Child-Pugh class A, score 5-6), moderate impairment (Child-Pugh class B, score 7-9), and severe impairment (Child-Pugh class C, score 10-15). To the extent possible, healthy subjects were to be similar in age, weight, and sex to subjects with hepatic impairment.[16]

All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina). Phoenix WinNonlin version 6.3 or higher (Certara, Princeton, New Jersey) was used for PK analysis with the AUC parameters estimated using the linear trapezoidal with linear interpolation method. The total plasma concentration of acalabrutinib from study 1 and the total and unbound plasma and urine concentrations of acalabrutinib and ACP-5862 from study 2 were summarized by sample size, arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum. In addition, geometric mean and geometric coefficient of variation were calculated for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} by severity of liver disease (mild, moderate, severe, or absent [ie, healthy control]).

Analysis of variance (linear mixed-effect model) was used to assess the effect of hepatic impairment (mild, moderate, or severe) versus absence of hepatic impairment (healthy controls), and was performed on the natural log-transformed values of $AUC_{0\text{-}inf}$ and C_{max} with the hepatic impairment group as a fixed effect and group (mild, moderate, or severe hepatic impairment, healthy [mean] matched control subjects) as a categorical factor, sex as a categorical covariate, and age and weight as continuous covariates. Comparisons were performed between each hepatic impairment group and the corresponding healthy matching group, and between the hepatic impairment groups and the pooled healthy subject groups. The inferential results (least-squares means [LSM], difference between LSMs, and 90%CI of the difference) were exponentiated to the original scale. Geometric LSMs, geometric mean ratios, and 90%CIs were calculated. Safety findings were summarized descriptively.

Results

Subject Disposition and Baseline Characteristics

In study 1, 18 subjects were enrolled into and completed the study (6 mild hepatic impairment, 6 moderate hepatic impairment, and 6 healthy control subjects matched to the hepatic insufficiency groups according to age and weight). In study 2, 16 subjects were enrolled into and completed the study (8 severe hepatic impairment and 8 healthy control subjects matched in a 1:1 ratio to hepatic impairment subjects for age, weight, and sex). Baseline and demographic characteristics of the 34 subjects are shown in Table 1.

Overall, demographic characteristics were comparable across all groups. In study 1, mean weight was slightly lower for control subjects (77.67 kg compared with 84.13 kg for subjects with mild hepatic impairment and 85.50 kg for subjects with moderate hepatic impairment); body mass index values, however, were comparable between groups. No control subjects had any concurrent medical condition. The use of concomitant medications was evaluated in all subjects with hepatic impairment. Although subjects with hepatic impairment reported use of prior and concomitant medications for the treatment of ongoing medical conditions, all medications were allowed per the protocol. All strong or moderate inhibitors or inducers of CYP3A or P-glycoprotein transporters (prescription or nonprescription, including St John's wort) were not

Table 1. Demographics and Baseline Characteristics

Characteristic	Category/Statistic	Mild (n = 6)	Moderate (n = 6)	Severe (n = 8)	Normal (n = 14)	Overall (N = 34)
Sex, n (%)	Female	4 (67)	3 (50)	1 (13)	4 (29)	12 (35)
	Male	2 (33)	3 (50)	7 (88)	10 (71)	22 (65)
Race, n (%)	Black or African American	0	1 (17)	0	1 (7)	2 (6)
	White	6 (100)	5 (83)	8 (100)	13 (93)	32 (94)
Ethnicity, n (%)	Hispanic or Latino	1 (17)	2 (33)	4 (50)	5 (36)	12 (35)
	Not Hispanic or Latino	5 (83)	4 (67)	4 (50)	9 (64)	22 (65)
Age, y[a]	Mean ± SD	50.5 ± 15.9	58.8 ± 5.9	57.6 ± 8.0	58.0 ± 4.5	56.7 ± 8.6
Weight, kg	Mean ± D	84.1 ± 22.7	85.5 ± 16.0	87.6 ± 9.8	83.1 ± 8.9	84.8 ± 13.1
Height, cm	Mean ± SD	170.1 ± 12.8	165.9 ± 11.0	173.9 ± 10.0	171.9 ± 6.4	171.0 ± 9.4
BMI, kg/m^2	Mean ± SD	28.6 ± 4.4	31.2 ± 6.3	29.3 ± 5.3	28.1 ± 3.0	29.0 ± 4.4

BMI, body mass index; SD, standard deviation.

Mild: Child-Pugh class A; moderate: Child-Pugh class B; severe: Child-Pugh class C; control: normal hepatic function.

[a] Age is calculated at the time of signed informed consent.

allowed for 14 and 28 days before dosing and throughout the study, respectively.

Pharmacokinetics

Acalabrutinib PK. Figure 1 illustrates mean acalabrutinib plasma concentrations over time for subjects with mild, moderate, or severe hepatic impairment and control subjects. A single, 50-mg dose of acalabrutinib resulted in mean total plasma acalabrutinib exposure that differed with hepatic impairment, with the lowest mean concentrations observed in control subjects and the highest mean concentrations observed in subjects with severe hepatic impairment.

Statistical analyses of the effect of mild, moderate, and severe hepatic impairment on plasma PK parameters of acalabrutinib are presented in Table 2. Compared with control subjects, administration of acalabrutinib to subjects with moderate hepatic impairment did not result in any appreciable difference in C_{max}, while 1.9- and 4.8-fold increases in C_{max} were estimated for subjects with mild and severe hepatic impairment, respectively, compared with control subjects; the greatest variability in PK parameters was observed in subjects with moderate hepatic impairment (Figure 2 and Table 2). The t_{max} of acalabrutinib was similar between subjects with hepatic impairment and control subjects (Table 2). After single-dose administration, the AUC of acalabrutinib increased 1.46-, 1.30-, and 4.8-fold in subjects with mild, moderate, and severe hepatic impairment compared with control subjects (Figure 2 and Table 2). Exposure to unbound acalabrutinib, as measured by C_{max} and $AUC_{0\text{-last}}$, was also higher (by 3.8- and 3.6-fold, respectively) in subjects with severe hepatic impairment compared with control subjects. Consistent with the observed effect on AUC, the apparent CL/F of acalabrutinib was reduced in subjects with mild and severe hepatic impairment compared with control subjects, and mean total plasma acalabrutinib $t_{1/2}$ values were similar across both subject populations. Individual CL/F and $t_{1/2}$ values were variable in subjects with hepatic impairment, and mean values were greater in subjects with moderate hepatic impairment than in control subjects. Analysis of urine samples produced similar results to a mass-balance study of acalabrutinib.[12] In matched normal hepatic function subjects for the mild and moderate hepatic impairment groups, ≈0.6% of the 50-mg oral dose of acalabrutinib was excreted in urine over the 24-hour urine collection interval and the mean renal clearance (1271 mL/h) represented ≈0.5% of the systemic clearance (246.8 L/h). In subjects with severe hepatic impairment, mean renal clearance was 772.7 mL/h (representing ≈1.7% of the apparent systemic clearance of 48.7 L/h), and approximately 1.8% of the 50-mg oral dose of acalabrutinib was excreted in urine. In matched control subjects with normal hepatic function, ≈0.415 mg of the metabolite was excreted in urine with a mean renal clearance of 605.3 mL/h. The excretion parameters were similar in subjects with severe hepatic impairment, for which ≈0.415 mg of the metabolite was excreted in urine for a mean renal clearance of 692.6 mL/h.

ACP-5862 PK. ACP-5862 was measured only in subjects with severe hepatic impairment and control subjects in study 2. The mean plasma concentrations of ACP-5862 were comparable for subjects with severe hepatic impairment and control subjects (Figure 1). Descriptive statistics for the noncompartmental plasma PK parameter estimates of ACP-5862 following the administration of a single, 50-mg dose of acalabrutinib in study 2 are summarized in Table 3. Mean $AUC_{0\text{-inf}}$ values of ACP-5862 were generally similar in subjects with severe hepatic impairment and control subjects. Mean plasma exposure to ACP-5862 was also comparable in

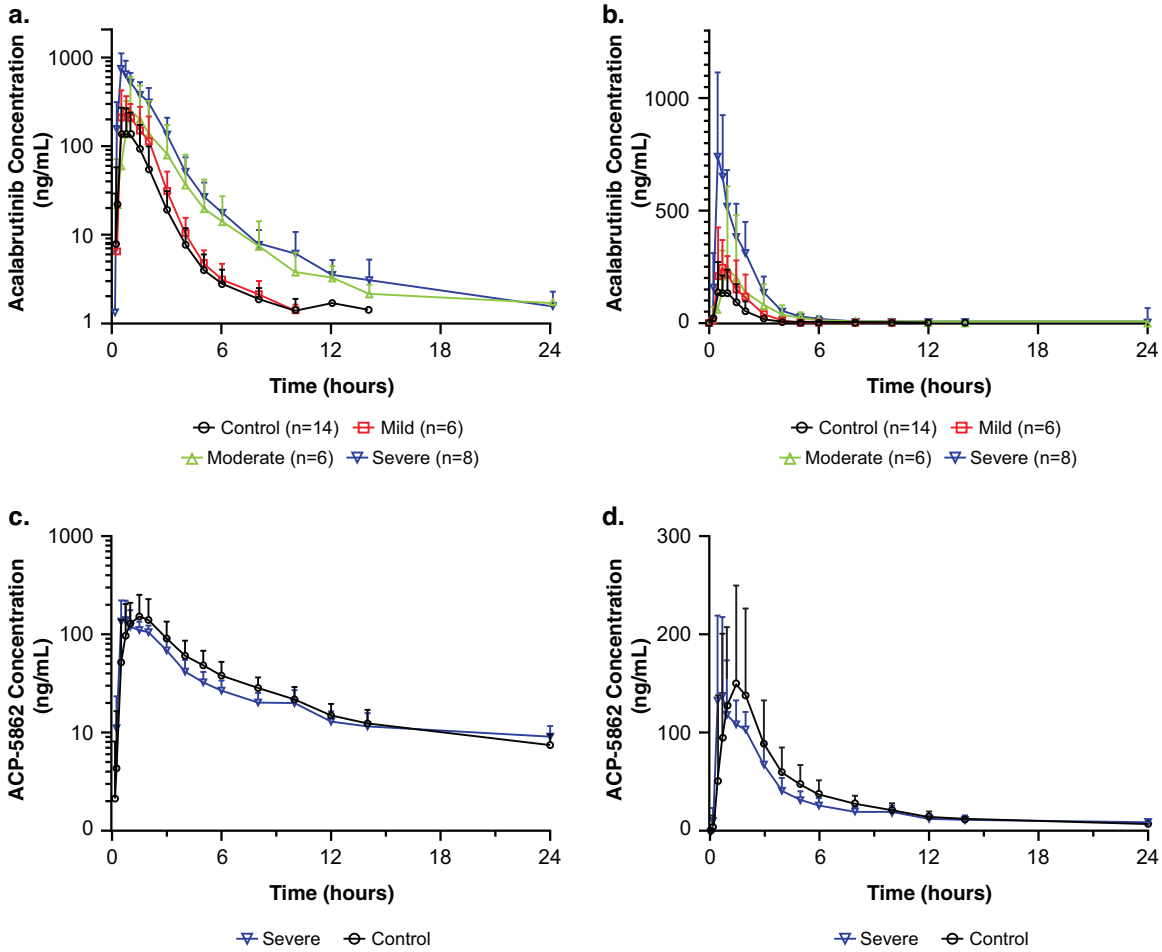

Figure 1. Mean (± standard deviation) plasma concentration–time profile of acalabrutinib in subjects with mild, moderate, or severe hepatic impairment and matched control subjects (a and b) and of ACP-5862 (active metabolite of acalabrutinib) in subjects with severe hepatic impairment and matched control subjects (c and d). Mild: Child-Pugh class A; moderate: Child-Pugh class B; severe: Child-Pugh class C; control: normal hepatic function.

subjects with severe hepatic impairment and control subjects, with geometric mean ratio for C_{max} of 1.01 and AUC of 0.9 (Table 4). ACP-5862 t_{max} occurred earlier in subjects with severe hepatic impairment than in control subjects (median 0.8 vs 1.5 hours, respectively). Mean total ACP-5862 $t_{1/2}$ was comparable in subjects with severe hepatic impairment and control subjects. The metabolite-to-parent ratio was ≈4.5 to 5.5 times lower in subjects with severe hepatic impairment compared with control subjects (Table 3). Exposure to unbound ACP-5862, as measured by C_{max} and $AUC_{0\text{-last}}$, was also similar in subjects with severe hepatic impairment and control subjects.

In Vitro Protein Binding and Impact on PK. In study 2, the mean protein binding values for both acalabrutinib and ACP-5862 were ≈98% in healthy matched controls and ≈94% in subjects with severe hepatic impairment, resulting in higher unbound fractions in subjects with severe hepatic impairment. This resulted in higher exposure ($AUC_{0\text{-last}}$ and C_{max}) to unbound acalabrutinib in patients with severe hepatic impairment compared with matched control subjects (Table S1).

Safety Assessment

Acalabrutinib administered as a single oral dose of 50 mg was well tolerated in healthy subjects and subjects with mild, moderate, or severe hepatic impairment (Table 5). There were no deaths, serious AEs, or subject discontinuations due to AEs in either study. In study 1, 2 subjects reported 2 grade 1 AEs during the study (headache, considered possibly related to acalabrutinib, and dyspepsia, considered not related to acalabrutinib). In study 2, 2 grade 1 AEs were reported by 1 subject (hypomagnesemia and hypokalemia, considered

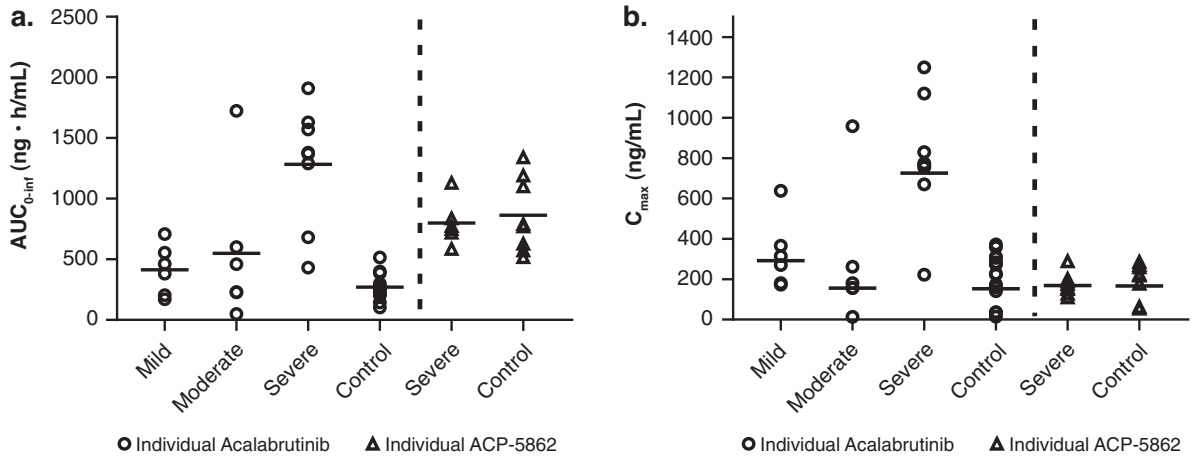

Figure 2. Acalabrutinib and ACP-5862 individual and mean $AUC_{0\text{-}inf}$ (a) and C_{max} (b) by hepatic function. Mild: Child-Pugh class A; moderate: Child-Pugh class B; severe: Child-Pugh class C; control: normal hepatic function. $AUC_{0\text{-}inf}$, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration.

Table 2. Acalabrutinib Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	Control (n = 14)	Mild (n = 6)	Moderate (n = 6)	Severe (n = 8)
C_{max}, ng/mL	152.5 (133.3)	291.6 (51.2)	155.7 (246.9)	726.0 (56.2)
t_{max}, h	0.6 (0.3, 3.0)	0.8 (0.5, 1.5)	1.0 (0.5, 3.0)	0.5 (0.5, 1.0)
$t_{1/2}$, h	2.2 ± 0.8[a]	2.3 ± 0.9	7.9 ± 12.7	2.7 ± 1.1
$AUC_{0\text{-}inf}$, ng • h/mL	250.2 (44.5)[a]	365.8 (61.2)	326.4 (177.9)	1169.0 (53.8)
CL/F, L/h	218.1 ± 103.1[a]	156.6 ± 91.1	280.8 ± 372.7	48.7 ± 30.7
Vz/F, L	722.5 ± 519.6[a]	471.2 ± 221.5	2135.0 ± 2715.3	167.4 ± 70.3

$AUC_{0\text{-}inf}$, area under the plasma concentration–time curve from time 0 to infinity; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}; Vz/F, apparent volume of distribution.
Mild: Child-Pugh class A; moderate: Child-Pugh class B; severe: Child-Pugh class C; control: normal hepatic function. Data for AUC and C_{max} presented as geometric mean (geometric CV%); data for t_{max} presented as median (minimum, maximum); data for other PK parameters presented as arithmetic mean (SD).
[a] n = 13.

Table 3. ACP-5862 Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	Severe (n = 8)	Control (n = 8)
C_{max}, ng/mL	168.7 (30.1)	166.5 (74.7)
t_{max}, h	0.8 (0.5, 2.0)	1.5 (0.8, 3.0)
$AUC_{0\text{-}last}$, ng • h/mL	638.4 (19.3)	699.7 (42.8)
$AUC_{0\text{-}inf}$, ng • h/mL	782.2 (21.9)[a]	817.0 (36.8)
$t_{1/2}$, h	11.9 ± 4.1[a]	10.7 ± 3.9
MR:C_{max}	0.2 ± 0.1	1.1 ± 0.4
MR:$AUC_{0\text{-}last}$	0.6 ± 0.4	3.1 ± 0.7
MR:$AUC_{0\text{-}inf}$	0.8 ± 0.5[a]	3.6 ± 0.9

AUC_{last}, area under the plasma concentration–time curve from time 0 to time of the last quantifiable concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration; MR, metabolite-to-parent ratio; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}.
Severe: Child-Pugh class C; control: normal hepatic function. Data for AUC and C_{max} presented as geometric mean (geometric CV%); data for t_{max} presented as median (minimum, maximum); data for other PK parameters presented as arithmetic mean (SD).
[a] n = 6.

not related to acalabrutinib). No notable findings in ECG, vital signs, clinical laboratory values, or physical examination results were seen.

Discussion

In vitro metabolism studies and clinical mass-balance results indicate that the elimination of acalabrutinib is mainly through metabolism in the liver by CYP3A to its major active metabolite, ACP-5862.[12] Further, in vitro studies also indicate acalabrutinib is highly bound to plasma protein. To this end, the effect of mild, moderate, or severe hepatic impairment on the PK of acalabrutinib was assessed in subjects with mild and moderate hepatic impairment compared with matched healthy subjects (study 1) and in subjects with severe hepatic impairment compared with matched healthy subjects (study 2).[16,17] A single-dose study design was selected, as acalabrutinib has a short mean elimination $t_{1/2}$ of ≈1 hour[13]; thus, with minimal accumulation, a single dose of acalabrutinib was considered sufficient

Table 4. Statistical Comparison of Plasma Acalabrutinib and ACP-5862 Pharmacokinetic Parameters

Analyte	Parameter (Unit)[a]	Group	n	LS Mean[b]	GMR: Test/ Reference (%)[c]	90%CI[d]
Acalabrutinib	$AUC_{0\text{-inf}}$ (ng • h/mL)	Mild	6	365.8	146.2	84.0-254.5
		Moderate	6	326.4	130.5	74.9-227.1
		Severe	8	1169.0	467.3	282.1-774.1
		Control	13	250.2		
	C_{max} (ng/mL)	Mild	6	291.6	191.3	88.3-414.5
		Moderate	6	155.8	102.2	47.1-221.4
		Severe	8	726.0	476.2	235.9-961.2
		Control	14	152.5		
ACP-5862	$AUC_{0\text{-inf}}$ (ng • h/mL)	Severe	6	782.2	95.7	72.7-126.0
		Control	8	817.0		
	C_{max} (ng/mL)	Severe	8	168.7	101.4	63.5-161.9
		Control	8	166.5		

ANOVA, analysis of variance; $AUC_{0\text{-inf}}$, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio; LS, least squares; LSM, least squares mean.

[a] Data natural log-transformed prior to analysis.

[b] Calculated by exponentiating LSMs from the ANOVA model.

[c] Transformed back to the linear scale. Normal hepatic function group was used as the reference (control) and test groups are subjects with hepatic impairment.

[d] 90%CI for the ratio of parameter means (expressed as percentage).

to assess the impact of liver function on exposure. A 50-mg single oral dose of acalabrutinib was selected for both studies because this dose was well tolerated with no safety concerns in previous studies in healthy subjects and subjects with disease.[18] To date, single doses of up to 400 mg in healthy subjects (data on file) and repeat doses of 100 to 400 mg daily for ≥28 days in subjects with relapsed/refractory chronic lymphocytic leukemia were tested and were well tolerated, with no dose-limiting toxicity observed.[19] In healthy subjects, the mean C_{max} and $AUC_{0\text{-last}}$ values were 1672 ng/mL and 3966 ng • h/mL, respectively, after a single 400-mg dose,[20] providing a clinical margin of safety for the 50-mg dose of ≈7.5- and 16-fold for C_{max} and $AUC_{0\text{-last}}$, respectively (data on file). Two potential mechanistic pathways may be affected in subjects with hepatic impairment: (1) CYP3A4/5-mediated metabolism of acalabrutinib and (2) direct conjugation of acalabrutinib with glutathione through glutathione S-transferase. Acalabrutinib is extensively and almost completely metabolized. In a CYP3A interaction study in healthy subjects (n = 17), mean plasma acalabrutinib C_{max} and $AUC_{0\text{-last}}$ values increased 3.9- and 5.1-fold, respectively, in the presence of itraconazole, a strong inhibitor of CYP3A4/5, relative to no pretreatment.[21] No treatment-related AEs were reported in the acalabrutinib drug interaction study. Based on Food and Drug Administration guidance, if the drug shows a substantial first-pass effect due to extensive hepatic metabolism, a dose reduction should be considered in the hepatically impaired group(s) for safety reasons. Therefore, an oral dose of 50 mg was selected for the hepatic impairment studies.

Following administration of a single 50-mg acalabrutinib dose to healthy subjects in these analyses, acalabrutinib geometric mean PK parameters were as expected and were approximately half that of the geometric mean values achieved in previous studies in which healthy subjects received 100-mg acalabrutinib doses.[18,22] In the present study, mean AUC with acalabrutinib was 1.5-, 1.3-, and 4.7-fold higher in mild, moderate, and severe hepatic impairment, respectively, relative to matched healthy controls. Our results compare favorably with a previous report of PK data by degree of hepatic impairment for ibrutinib, where mean AUC was 2.7-, 8.0-, and 9.5-fold higher in mild, moderate, and severe hepatic impairment, respectively, compared with healthy controls.[23] Following administration to subjects with hepatic impairment, similar elimination profiles were seen regardless of hepatic impairment severity for acalabrutinib, with a similar $t_{1/2}$ ranging from 2 to 3 hours observed in the mild hepatic impairment, severe hepatic impairment, and healthy control groups, indicating a low risk of accumulation with repeated dosing. This is in line with the fact that acalabrutinib clearance is mostly first-pass, and hence, no large effect on $t_{1/2}$ is expected. Subjects with moderate hepatic impairment had the lowest mean C_{max} (156 ng/mL) and $AUC_{0\text{-inf}}$ (326 ng • h/mL) and the longest mean $t_{1/2}$ (7.9 hours), resulting in the highest intersubject variability in geometric mean $AUC_{0\text{-last}}$ and C_{max} (191% and 247%, respectively). One of 6 subjects in the moderate hepatic impairment group had mean gamma-glutamyltransferase, ALT, and glucose levels above the reference range at both baseline and day 3. One

Table 5. Incidence of TEAEs (Safety Analysis Population)

		Hepatic Impairment			
	Control (n = 14)	Mild (n = 6)	Moderate (n = 6)	Severe (n = 8)	Overall (N = 34)
Number (%) of subjects with TEAEs	0	2 (33)	0	1 (13)	3 (9)
Gastrointestinal disorders					
Dyspepsia	0	1 (17)	0	0	1 (3)
Metabolism and nutrition disorders					
Hypokalemia	0	0	0	1 (13)	1 (3)
Hypomagnesemia	0	0	0	1 (13)	1 (3)
Nervous system disorders					
Headache	0	1 (17)	0	0	1 (3)

TEAEs, treatment-emergent adverse events.
Subjects with ≥2 TEAEs are counted only once within a category. The same subject may appear in different categories.

potential explanation for the high intersubject variability is that this subject transitioned to severe hepatic impairment sometime between subject screening and study conduct. It is recognized that at steady state, the change in volume of distribution will depend on the relationship of drug binding in plasma, BTK covalent binding, and tissue partitioning. If the fraction bound in plasma decreases (as in severe hepatic impairment), it is predicted that more drug will enter tissues, and the volume of distribution will increase. However, in this single-dose study, apparent volume of distribution decreases, which may be a reflection of the impact of severe hepatic impairment compromising blood flow to the liver and the potential cross-talk between impaired hepatic distribution and increased bioavailability of this high-extraction-ratio drug; thus, variable bioavailability may be driving this observation. Currently, acalabrutinib should be avoided in patients with cancer with severe hepatic impairment, as the safety has not been investigated.

In vitro protein binding of acalabrutinib is 97.5% in human plasma and is 93.7% bound in human serum albumin solution and 41.1% bound in α1-acid glycoprotein solution. The same ex vivo percentage was observed in plasma obtained from subjects participating in the mass-balance study.[12] There was no concentration dependency in the plasma protein binding at the concentrations tested. The 2.5% free fraction (percentage unbound) of acalabrutinib in humans is related mainly to albumin binding (data not shown). The in vitro protein binding of the major circulating metabolite, ACP-5862, was determined at plasma concentrations of 1 and 10 μM (0.482 and 4.82 μg/mL, respectively) to be 98.7% and 98.6%, respectively, in human plasma. As such, the free fraction (percentage unbound) of ACP-5862 in vitro is about half that of acalabrutinib. In this study, the lower protein binding observed in subjects with severe hepatic impairment compared with healthy matched controls resulted in an increase in free fraction and thus higher exposure to unbound acalabrutinib compared with control subjects. Acalabrutinib is covalently bound to target BTK and its metabolism results in an active metabolite, both representing exceptions to the free drug hypothesis as it relates to the impact of free fraction on in vivo efficacy.[24] Clinically significant changes in total BTK occupancy (pharmacodynamics), which is primarily driven by resynthesis rate of BTK, are not anticipated with continuing administration of acalabrutinib. Higher bilirubin levels and prothrombin time values were associated with higher total acalabrutinib exposure parameters, while higher albumin levels were associated with lower total acalabrutinib exposure parameters. Increases in exposure of 13-fold with hepatic impairment have been seen for other BTK inhibitors that are eliminated through hepatic metabolism.[23]

In the severe hepatic impairment group and corresponding control subjects, where urine acalabrutinib and ACP-5862 were measured, renal clearance represented a very small contribution to total clearance. The acalabrutinib renal excretion results were consistent with the acalabrutinib mass-balance study.[12] Overall, renal excretion is a minor elimination pathway of acalabrutinib and its metabolite in subjects with hepatic impairment.

The metabolism of acalabrutinib was affected by severe hepatic impairment, leading to increased systemic exposure and decreased systemic clearance. However, the total and peak exposure to total and unbound ACP-5862 was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. This is likely due to prehepatic, first-pass metabolism occurring in the small intestine. Interestingly, the formation of ACP-5862 was not hindered in severe hepatic impairment (Figure 2); however, the mean metabolite-to-parent C_{max} ratios decreased from 1.15 in control subjects to 0.247 in subjects with severe hepatic impairment, and the

metabolite-to-parent:$AUC_{0\text{-inf}}$ ratio decreased from 3.59 to 0.841. No apparent trends were observed between Child-Pugh scores, albumin or bilirubin levels, aspartate aminotransferase, and ALT (Figures S1 and S2).

A physiologically based PK (PBPK) model has been developed for acalabrutinib and its active metabolite, ACP-5862, and was successfully used to simulate drug interaction potential.[25] PBPK modeling was undertaken to predict the effects of hepatic impairment by accounting for known acalabrutinib disposition pathways and clinical PK properties and the physiologic alterations due to hepatic impairment. The observed magnitude of increase of acalabrutinib exposure in subjects with mild and severe hepatic impairment is close to that predicted by the PBPK model, which supported the selection of the lower acalabrutinib dose (50 mg) in the present analyses. However, the PBPK model overpredicted the effect of acalabrutinib in moderate hepatic impairment and underpredicted the effect of the metabolite ACP-5862 in severe hepatic impairment. Possible reasons for these discrepancies are the high sensitivity of acalabrutinib to the effect of portacaval shunting, reduced liver volume, and reduced CYP3A abundance. hepatic impairment may affect the exposure to hepatically metabolized agents through various mechanisms, including alterations in liver blood flow, binding to plasma proteins, and reduced hepatic intrinsic clearance due to lower expression of CYP enzymes, among other factors. Previous investigations have supported that acalabrutinib is subject to high hepatic extraction.[13] The effect of portacaval shunting has not been validated based on clinical data for other compounds with high hepatic extraction.

Overall, a single dose of acalabrutinib was well tolerated in various degrees of hepatic impairment. Only grade 1 treatment-emergent toxicities were observed in subjects with mild and severe hepatic impairment. No serious AEs, deaths, or discontinuations due to an AE were reported. There were no clinically relevant changes in other laboratory findings, vital signs, or physical examinations. The safety profile appeared consistent with the AE profile expected in subjects with varying levels of hepatic impairment.

A limitation of this study is the absence of ACP-5862 PK and protein-binding data in study 1; at the time of study conduct, the role of this metabolite in acalabrutinib disposition had not yet been fully elucidated. In addition, because the study was conducted in 2 parts, different healthy control subjects were included in each study; however, this difference should not affect the study conclusions because no notable differences between the healthy control groups were observed between studies.

Conclusions

In this study of the effect of hepatic impairment on the PK of acalabrutinib and its major active metabolite ACP-5862, mild to moderate hepatic impairment did not significantly affect systemic exposure of acalabrutinib. However, mean acalabrutinib exposure increased by up to 5-fold in subjects with severe hepatic impairment. No apparent trends were observed between Child-Pugh scores, albumin levels, or bilirubin levels and acalabrutinib $AUC_{0\text{-inf}}$ and C_{max} values. Based on these results, no starting dose adjustment for acalabrutinib (normal dosing regimen, 100 mg twice daily) is necessary in subjects with mild to moderate hepatic impairment, and administration of acalabrutinib in subjects with severe hepatic impairment is not recommended.

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Conflicts of Interest

This study was sponsored by Acerta Pharma, a member of the AstraZeneca group. S.S. and K.V. are employees and stockholders of AstraZeneca. Y.X., H.N., A.K., H.K., and J.M. were employees of Acerta Pharma during the time the research was conducted. J.A.W. was an employee of Acerta Pharma during the time the research was conducted and is a stockholder of AstraZeneca. G.S. was an employee of Acerta Pharma during the time the research was conducted and is a stockholder of Acerta Pharma and AstraZeneca. R.I. was an employee of Acerta Pharma during the time the research was conducted, is a patent holder for acalabrutinib, and is a stockholder of Acerta Pharma and AstraZeneca. T.P. was an employee of Acerta Pharma during the time the research was conducted, is a patent holder for acalabrutinib, is a stockholder of AstraZeneca, and is a remunerated consultant for Acerta Pharma BV. T.M. is an employee and equity owner of Orlando Clinical Research Center. R.A.P. reports a grant for the present study paid to his institution by Acerta Pharma. W.S. has no disclosures to report.

Data Availability Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing

policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Supplemental Information

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