acalabrutinib

NDA 210259 **32 entries** HI Study approval date: 2017

Therapeutic class	Kinase Inhibitors
Molecular weight	465.5147 g/mol
Biopharmaceutics class	Class II: High permeability - Low solubility reference: NDA Multi-discipline Review (page 60)

DDI summary

DDI risk level as object **I (High)**

DDI risk level as precipitant **III (No or Low)**

Acalabrutinib is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy. The recommended dose is 100 mg orally BID.

Acalabrutinib is predominantly metabolized by CYP3A enzymes to the active metabolite ACP-5862. Acalabrutnib was identified as a sensitive substrate of CYP3A through clinical evaluations. Co-administration with itraconazole, a strong CYP3A inhibitor, increased acalabrutinib AUC 5.0-fold in healthy subjects. Clarithromycin, also a strong CYP3A inhibitor, was predicted to increase acalabrutinib exposure 3.3-fold. Based on these observations, co-administration of acalabrutnib with strong CYP3A inhibitors should be avoided. Alternatively, if the inhibitor will be used for a short term, use of acalabrutinib should be interrupted (CALAQUENCE Product Label). The effects of moderate and weak CYP3A inhibitors on the pharmacokinetics of acalabrutinib were predicted using PBPK simulations. Co-administration of the moderate CYP3A inhibitors erythromycin, diltiazem, or fluconazole was predicted to increase acalabrutinib (100 mg BID) AUC 2- to 3-fold, while a much lower increase (< 1.4-fold) was predicted for acalabrutinib 100 mg QD. According to the Product Label, when acalabrutinib is co-administered with moderate CYP3A inhibitors, acalabrutinib dose should be reduced to 100 mg QD. The weak CYP3A inhibitor fluvoxamine was predicted to only increase acalabrutinib 1.4-fold, which was not considered clinically significant.

On the other hand, acalabrunitib is sensitive to induction. Co-administration with the strong CYP3A inducer rifampin decreased acalabrutinib AUC by 77% in healthy subjects. Likewise, carbamazepine, also a strong CYP3A inducer, was predicted to cause a 61% decrease in the exposure of co-administered acalabrutinib. Based on these results, co-administration of acalabrutinib with strong CYP3A inducers should be avoided. If a strong CYP3A inducer cannot be avoided, acalabrutinib dose should be increased to 200 mg BID (CALAQUENCE Product Label). A 61% decrease in the AUC of acalabrutinib was predicted with co-administration of efavirenz, a moderate CYP3A inducer. However, considering that the exposure to the adjusted free total moiety (acalabrutinib and ACP-5862) was predicted to decrease only 31-36%, no dose adjustment is needed for concomitant use of moderate CYP3A inducers.

As a perpetrator, acalabrutinib inhibited CYP2C8 and CYP3A in vitro. However, PBPK simulations predicted no interactions with rosiglitazone (a moderate sensitive substrate of CYP2C8) and midazolam (a sensitive substrate of CYP3A) after repeated doses of acalabrutinib. In addition, weak inhibition (CYP2C9 and CYP2C19) and induction (CYPA2, CYP2B6, and CYP3A) were observed toward some CYPs in vitro. Overall, based on in vitro data and PBPK modeling, no interaction of acalabrutinib with co-administered drugs that are CYP substrates is expected at clinically relevant concentrations (CALAQUENCE Product Label).

With regards to transporters, acalabrutinib is likely to inhibit intestinal BCRP based on in vitro results. According to the Product Label, acalabrutinib may increase the exposure of concomitant BCRP substrates (e.g., methotrexate) via inhibition of intestinal BCRP. However, the effects of acalabrutnib on co-administered BCRP substrates were not evaluated.

Acalabrutinib undergoes minimal renal elimination. Based on clinical studies and population PK analyses, no clinically relevant pharmacokinetic difference was observed in patients with mild or moderate hepatic or renal impairment compared to normal controls. Therefore, dosage adjustment is not necessary for these patient populations (CALAQUENCE Product Label). Acalabrutinib pharmacokinetics has not been evaluated in patients with severe hepatic or renal impairment or renal impairment requiring dialysis. The sponsor has been requested to conduct a clinical pharmacokinetic trial to determine the appropriate dose of acalabrutnib in patients with severe hepatic impairment as a post-marketing requirement.

A high-fat/high-calorie meal did not significantly alter the pharmacokinetics of acalabrutinib compared to fasted conditions and acalabrutinib can be taken with or without food (CALAQUENCE Product Label). However, acalabrutinib AUC was decreased by 16% and 38% when taken

with grapefruit juice and orange juice, respectively. Due to the overall exposure decrease, acalabrutinib should be taken with water (CALAQUENCE Multi-discipline Review).

Acalabrutinib solubility decreases with increasing pH. Co-administration with the proton pump inhibitor omeprazole decreased acalabrutinib AUC by 43%. According to the Product Label, concomitant use with proton pump inhibitors should be avoided. Co-administration with the antacid calcium carbonate decreased acalabrutinib AUC by 53% in healthy subjects. Based on this result, it is recommended to stagger dosing with antacids and H2-receptor antagonists (CALAQUENCE Product Label).

Main routes of elimination

Extensive Metabolism

Acalabrutinib is metabolized in the liver, primarily by CYP3A. ACP-5862 was identified as the major active metabolite (approximately 50% less potency for bruton tyrosine kinase inhibition than acalabrutinib) in plasma with a mean exposure (AUC) approximately 2- to 3-fold higher than that of acalabrutinib. In a mass balance study, following administration of a single oral dose of 100 mg radiolabeled acalabrutinib in healthy subjects, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine, with less than 1% of the dose excreted as unchanged acalabrutinib.

Hepatic impairment: In a hepatic impairment study, compared to subjects with normal liver function (N = 6), acalabrutinib exposure (AUC) was increased by less than 2-fold in subjects with mild (N = 6) and moderate (N = 6) hepatic impairment. In a population pharmacokinetic analysis, no clinically relevant pharmacokinetic difference was observed in subjects with mild (N = 41) or moderate (N = 3) hepatic impairment relative to subjects with normal hepatic function (N = 527). Therefore, dosage adjustment is not necessary for these patient populations (CALAQUENCE Product Label). Acalabrutinib pharmacokientics has not been evaluated in patients with severe hepatic impairment. The sponsor has been requested to conduct a clinical pharmacokinetic trial to determine the appropriate dose of acalabrutnib in this patient population as a post-marketing requirement.

Renal impairment: Acalabrutinib undergoes minimal renal elimination. Based on a population pharmacokinetic analysis, no clinically relevant pharmacokinetic difference was observed in 268 patients with mild or moderate renal impairment. No dosage adjustment is required for these patient populations (CALAQUENCE Product Label). Acalabrutinib pharmacokinetics has not been evaluated in patients with severe renal impairment or renal impairment requiring dialysis.

Food effect: In healthy subjects, administration of a single 75 mg dose of acalabrutinib with a high-fat/high-calorie meal did not affect the mean AUC compared to dosing under fasted conditions, while Cmax was decreased by 73% and Tmax was delayed 1-2 hours. However, these changes were not considered clinically relevant and acalabrutinib can be taken with or without food (CALAQUENCE Product Label). The effects of acidic beverages on acalabrutinib exposure were also evaluated. Acalabrutinib (100 mg SD) AUC was decreased by 16% and 38% when taken with grapefruit juice (240 mL SD) and orange juice (240 mL SD), respectively. Due to the overall exposure decrease, acalabrutinib should be taken with water (CALAQUENCE Multi-discipline Review).

Main enzymes and associated interactions

CYP3A

In vitro studies suggest that acalabrutinib is predominantly metabolized by CYP3A, and to a minor extent, by glutathione conjugation and amide hydrolysis.

Acalabrutnib was identified as a sensitive substrate of CYP3A through clinical evaluations. Co-administration of the strong CYP3A inhibitor itraconazole (200 mg BID for 6.5 days) with acalabrutinib (50 mg SD) increased the acalabrutinib Cmax 3.9-fold and AUC 5.0-fold in healthy subjects. A similar result with itraconazole (200 mg BID) was predicted using PBPK simulations, where a 4.8- and 4.6-fold increase in acalabrutinib AUC was predicted when acalabrutinib was administered at 50 mg SD and 100 mg BID, respectively. Clarithromycin (500 mg QD), also a strong CYP3A inhibitor, was predicted to increase acalabrutinib (100 mg BID) exposure 3.3-fold (of note, in both DDI predictions, the increases in the exposure to adjusted free total active moiety, which combines both parent and ACP-5862, were less than 2-fold). Based on these observations, co-administration of acalabrutnib with strong CYP3A inhibitors should be avoided. Alternatively, if the inhibitor will be used for a short term, use of acalabrutinib should be interrupted (CALAQUENCE Product Label). The effects of moderate and weak CYP3A inhibitors on the pharmacokinetics of acalabrutinib were also predicted using PBPK simulations. Co-administration of the moderate inhibitors erythromycin (500 mg TID), diltiazem (90 mg TID), or fluconazole (200 mg QD) was predicted to increase acalabrutinib (100 mg BID) AUC 2.8-, 2.3-, and 2.4-fold, respectively (the exposure to adjusted free total active moiety was only 1.5- to 1.6-fold higher). A 1.1- to 1.4-fold increase in acalablutinib AUC and a 25-30% decrease in the AUC of the adjusted free total active moiety were predicted when acalabrutinib was administered as 100 mg QD with the inhibitors (100 mg BID for control group). According to the Product Label, when acalabrutinib is co-administered with moderate CYP3A inhibitors, acalabrutinib dose should be reduced to 100 mg QD. In addition, the weak CYP3A inhibitor

fluvoxamine (150 mg QD) was predicted to increase acalabrutinib (100 mg BID) 1.4-fold, which was not considered clinically significant.

On the other hand, acalabrunitib is sensitive to induction. Co-administration with the strong CYP3A inducer rifampin (600 mg QD for 9 days) decreased acalabrutinib (100 mg SD) Cmax by 68% and AUC by 77% in healthy subjects. A similar result with rifampin (600 mg QD) was predicted using PBPK simulations, where a 83% and 65% decrease in acalabrutinib AUC was predicted when acalabrutinib was administered at 100 mg BID and 200 mg BID, respectively (a 61% and 32% decrease in the AUC of adjusted free total active moiety, respectively). Likewise, carbamazepine (400 mg QD), also a strong CYP3A inducer, was predicted to result in a 61% decrease in the exposure of co-administered acalabrutinib (100 mg BID; a 32% decrease in the AUC of adjusted free total active moiety). Based on these results, co-administration of acalabrutinib with strong CYP3A inducers should be avoided. If a strong CYP3A inducer cannot be avoided, acalabrutinib dose should be increased to 200 mg BID (CALAQUENCE Product Label). A 61% decrease in the AUC of acalabrutinib (100 mg BID) was predicted with co-administration of efavirenz (600 mg QD), a moderate CYP3A inducer. However, considering the small (36%) decrease in the AUC of adjusted free total active moiety, no dose adjustment is needed for concomitant use of moderate CYP3A inducers.

Main transporters and associated interactions

P-gp (ABCB1)

In vitro studies suggest that acalabrutinib is a substrate of P-gp. Therefore, it is possible that P-gp was also involved in the drug interactions discussed above because all the perpetrators except fluconazole are inhibitors or inducers of P-gp.

In vitro, acalabrutinib is also a substrate of BCRP. The clinical relevance of this finding was not evaluated. In vitro, acalabrutinib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

Inhibition profile

Enzymes

In vitro, acalabrutinib showed reversible and non-reversible inhibition of CYP3A (Ki = 23.9 μM; KI = 10.1 μM and Kinact = 1.11 /h). A PBPK simulation predicted no interaction with midazolam, a sensitive substrate of CYP3A, after repeated doses of acalabrutinib 100 mg BID.

In vitro, acalabrutinib showed reversible inhibition of CYP2C8 (Ki = 20.6 μM) and the active metabolite ACP-5862 showed non-reversible inhibition of CYP28 (KI = 4.0 μM and Kinact = 0.72 /h). The clinical relevance was predicted using PBPK simulations. No interaction with rosiglitazone, a moderate sensitive substrate of CYP2C8, was predicted after repeated doses of acalabrutnib 100 mg BID. Additionally, using Ki and KI values of 1/10 of the in vitro values for CYP3A and CYP2C8, the model predicted minimal change (16-36% increase) in the AUC of midazolam and rosiglitazone, further confirming the absence of clinically relevant interactions.

In vitro, acalabrutinib also inhibited CYP2C9 (Ki = 11.3 μM), while ACP-5862 inhibited CYP2C9 (Ki = 3.3 μM) and CYP2C19 (Ki = 8.5 μM). However, these results were not considered clinically relevant by the sponsor. In contrast, acalabrutinib did not inhibit CYP1A2, CYP2B6, CYP2C19, or CYP2D6, and ACP-5862 did not inhibit CYP1A2, CYP2B6, CYP2D6, or CYP3A4/5. Overall, based on in vitro data and PBPK modeling and simulations, no interactions with drugs that are CYP substrates are expected with acalabrutinib at clinically relevant concentrations.

Transporters

BCRP (ABCG2)

Acalabrutinib does not inhibit P-gp at clinically relevant concentrations, per calculations of [I]1/IC50 < 0.1 and [I]2/IC50 < 10 (in vitro inhibition details not available).

Acalabrutinib is a weak BCRP inhibitor at the intestinal level, per calculations of [I]2/IC50 = 21 ([I]1/IC50 < 0.1). According to the Product Label, acalabrutinib may increase the exposure of concomitant BCRP substrates (e.g., methotrexate) via inhibition of intestinal BCRP. However, the effects of acalabrutnib on co-administered BCRP substrates were not evaluated.

In vitro studies suggest that acalabrutinib is not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 at clinically relevant concentrations.

Induction profile

Enzymes

In vitro, acalabrutinib is a weak inducer of CYP1A2, CYP2B6, and CYP3A4, and ACP-5862 weakly induces CYP3A4 (details not available).

Transporters

The induction of acalabrutinib on transporters was not evaluated.

Other DDIs

Gastric acid reducing agents: Acalabrutinib solubility decreases with increasing pH. Co-administration with the proton pump inhibitor omeprazole (40 mg QD for 5 days) decreased acalabrutinib (100 mg SD) AUC by 43%. According to the Product Label, concomitant use with proton pump inhibitors should be avoided. Co-administration with the antacid calcium carbonate (1 g SD) decreased acalabrutinib (100 mg SD) AUC by 53% in healthy subjects. Based on this result, it is recommended to separate dosing by at least 2 h. Also, it is recommended to take acalabrutinib 2 h before taking a H2-receptor antagonist (CALAQUENCE Product Label).

QT summary

Sources

Drugs@FDA - Clinical Reviews **Drugs@FDA - Product Labels**

Preclinical data

Acalabrutinib inhibited hERG tail current by 8.2% at 1 μM and 24.9-25.1% at 10 μM in transfected HEK293 or CHO-K1 cells.

Clinical data

No QTc prolongation — Thorough QT (TQT) study

Measurement Means (CI)	**Test**	**Positive control** moxifloxacin
Dose Regimen	100 mg or 400 mg SD orally	400 mg single dose orally
Population	healthy volunteers	healthy volunteers
Mean change in QTc Fridericia (msec)	100 mg and 400 mg: 1.7 (-0.3, 3.7)	13.4 (11.4, 15.4)

The effect of acalabrutinib on the QTc interval was evaluated in a randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover thorough QT study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is 4-fold maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent.

Pharmacokinetic profile

Molecular weight	465.5147 g/mol
C_{max}	323 ng/mL 0.694 μmol/L
Dose / duration	PopPK prediction based on a dose range of 75-250 mg (recommended dose: 100 mg BID)
Oral bioavailability	25%
Plasma protein binding	97.5%
Clearance	159 L/h
Vd	34 L
$T_{1/2}$	0.9 (0.6, 2.8) h
Reference	NDA#210259; Acalabrutinib Product Label