2.7.2.3.4 アカラブルチニブの薬力学的作用、薬物動態／薬力学関係及び曝露量－反応関係

2.7.2.3.4.1 薬力学、薬物動態／薬力学関係

BTK は BCR シグナル伝達経路に不可欠なキナーゼであり、細胞の増殖及び生存の重要な調節因子として B 細胞性腫瘍の形成を促進する（Hendriks et al 2014）。BTK 経路内の変異により耐性機序が発現することがイブルチニブで報告されている（Woyach et al 2014a、Tucker and Rule 2015）。ほぼ完全かつ継続的な BTK の阻害を達成できれば、臨床的ベネフィットに加え、BTK 阻害剤に対する耐性発現の可能性を抑制できると考えられる。

このため、初期臨床試験では各投与間隔で小さい個体間変動及び高い BTK 占有率が得られ、忍容性が良好な用法・用量を特定することに重点を置いた。アカラブルチニブ及び活性代謝物 ACP-5862 は BTK に共有結合する。アカラブルチニブの類縁体を基質として使用して非占有の BTK を測定する分析法を確立した（試験 R2017004 参照）。アカラブルチニブが一旦共有結合すると、個々の BTK 蛋白は恒久的に不活化されるため、機能を回復するには新たな BTK 蛋白の合成が必要となる。BTK の合成速度は B 細胞性腫瘍患者の間で差があるため、各投与間隔を通して個体間変動が小さく高い BTK 占有率が維持される用法・用量を用いることで、より多くの患者で臨床的ベネフィットが得られると考えられる。ほぼ完全な BTK 占有が得られる用法・用量が特定されれば、それ以上に曝露量を増加させても BTK 阻害は増強されず、標的外作用が発現する可能性がある。そのため、最大耐量（MTD）まで投与する必要はない。

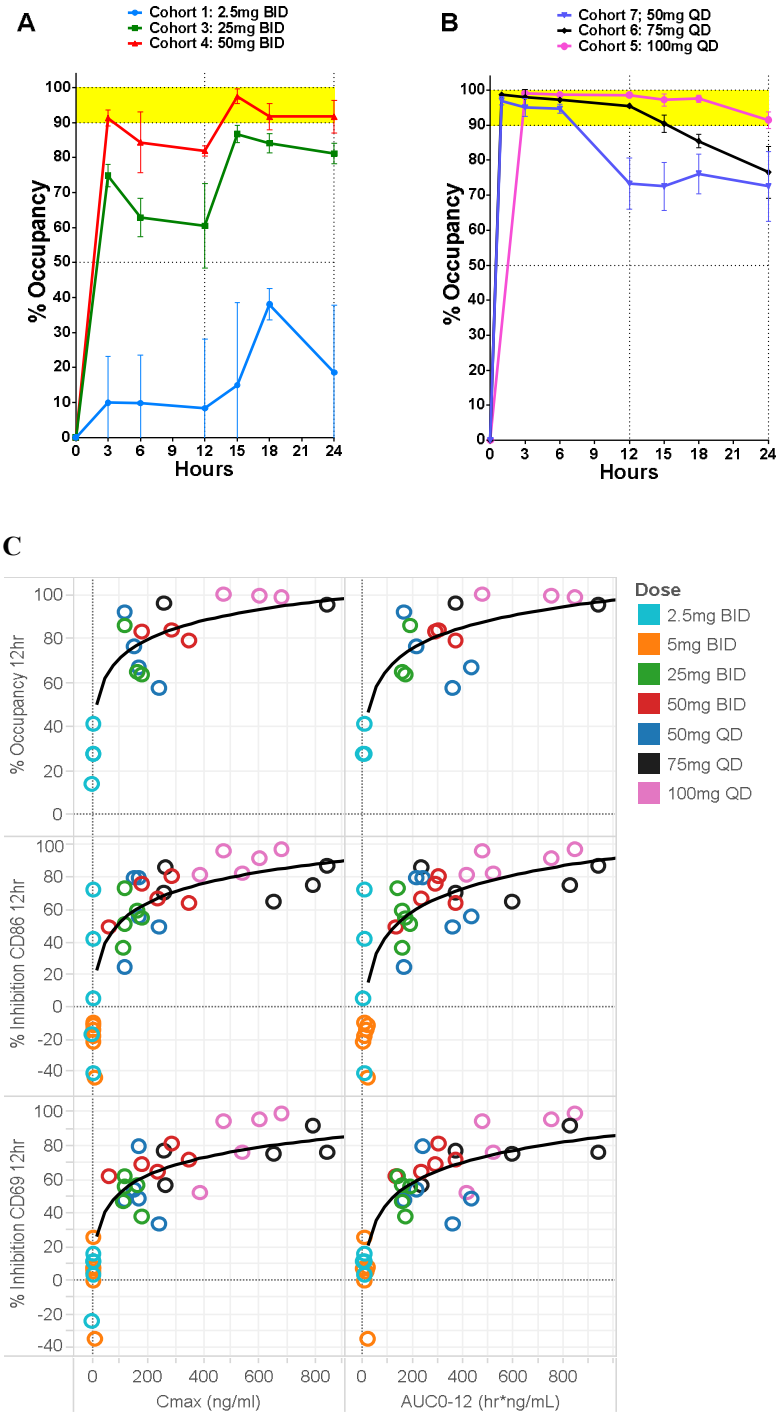
2.7.2.3.4.2 薬物動態／BTK 占有率の関係

2.7.2.3.4.2.1 健康被験者

ACE-HV-001 試験では、アカラブルチニブ 2.5～50 mg を 12 時間間隔で 1 日 2 回経口投与したとき、並びに 50、75 及び 100 mg を単回経口投与したときの薬物動態及び薬力学を評価した。末梢血細胞を採取して、BTK 占有率及び B 細胞活性化マーカーである CD69 及び CD86 の発現に対する阻害率を経時的に測定した。初回投与後に用量反応性が認められ（図 33 A 及び B 参照）、100 mg 単回投与で BTK 占有率は最高値（91.5%）を示した。1 日 2 回投与時、BTK 占有率は投与後 12 時間でも 0 にはならず、次投与により増加した。BTK 占有率と初回投与時の血漿中濃度との間に関連性は E_{max} モデルにより良好に記述された（図 33 C 参照）。

標的と共有結合を形成しない薬剤と比較して、アカラブルチニブ等の標的に共有結合する薬剤では、薬力学的作用の持続は、薬物濃度への依存性は低く、標的蛋白のターンオーバー速度（de novo 合成速度）への依存性が高かった（Barf and Kaptein 2012）。

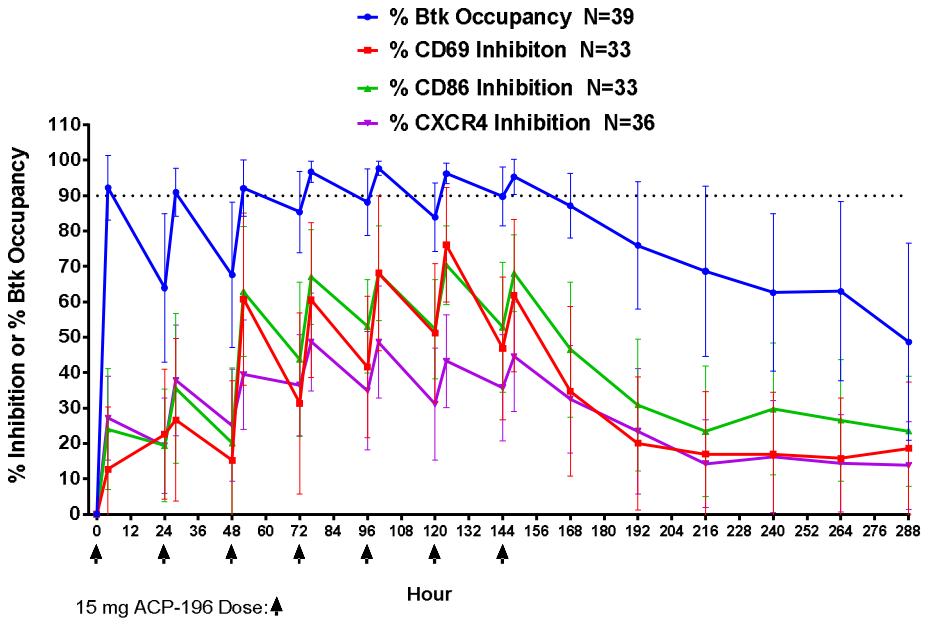
図 33　　アカラブルチニブ 2.5～100 mg を経口投与後 24 時間における BTK 占有率及び CD69 又は CD86 発現阻害率（ACE-HV-001 試験）



Source: ACE-HV-001 CSR in-text figures 11-4 and 11-6

ACE-HV-007 試験において、健康被験者にアカラブルチニブ 15 mg を 7 日間反復投与した後、6 日間休薬したときの薬物動態／薬力学関係を評価した。BTK 占有率は投与開始後約 4 日で定常状態に到達し、投与中止により低下した（図 34 参照）。

図 34　　健康被験者にアカラブルチニブ 15 mg を 1 日 1 回 7 日間反復投与したときの BTK 占有率並びに CD69 及び CD86 阻害率

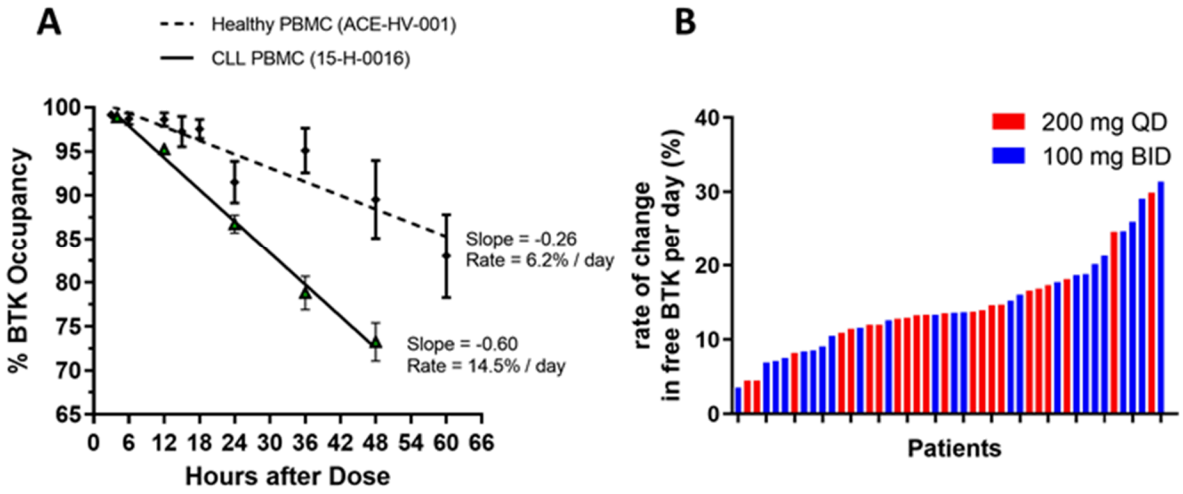


Source: ACE-HV-007 CSR Figure 11-13

2.7.2.3.4.2.2　患者

15-H-0016 試験において、アカラブルチニブの投与中止後に CLL 患者から PBMC サンプルを採取し、BTK 占有率を測定したところ、BTK 占有率の低下が認められた（図 35 A）。投与中止後の BTK 占有率の低下速度は BTK 再合成速度に依存すると推察される。線形回帰分析により、CLL 患者における BTK 再合成速度は 14.5%/日と推定された。この値は、ACE-HV-001 試験における健康被験者での BTK 再合成速度（6.2%/日）と比較して高かった（図 35 A）。また、非占有 BTK の増加速度には個体間で大きな変動が認められたが（図 35 B）、CLL の生物学的不均一性が寄与している可能性が考えられた。また、一部の MCL 患者で採取した PBMC で速やかな BTK 再合成が認められた（ACE-LY-004 試験）。血漿中アカラブルチニブ濃度の $t_{½}$は概ね短いことから、投与間隔における BTK 占有率の維持は主に BTK 再合成速度に依存すると考えられる。

図 35　　アカラブルチニブ投与中止後に認められる BTK 占有率及び BTK 再合成速度（CLL 患者 46 例のデータを A 及び B に、健康被験者 4 例のデータを A に示す）



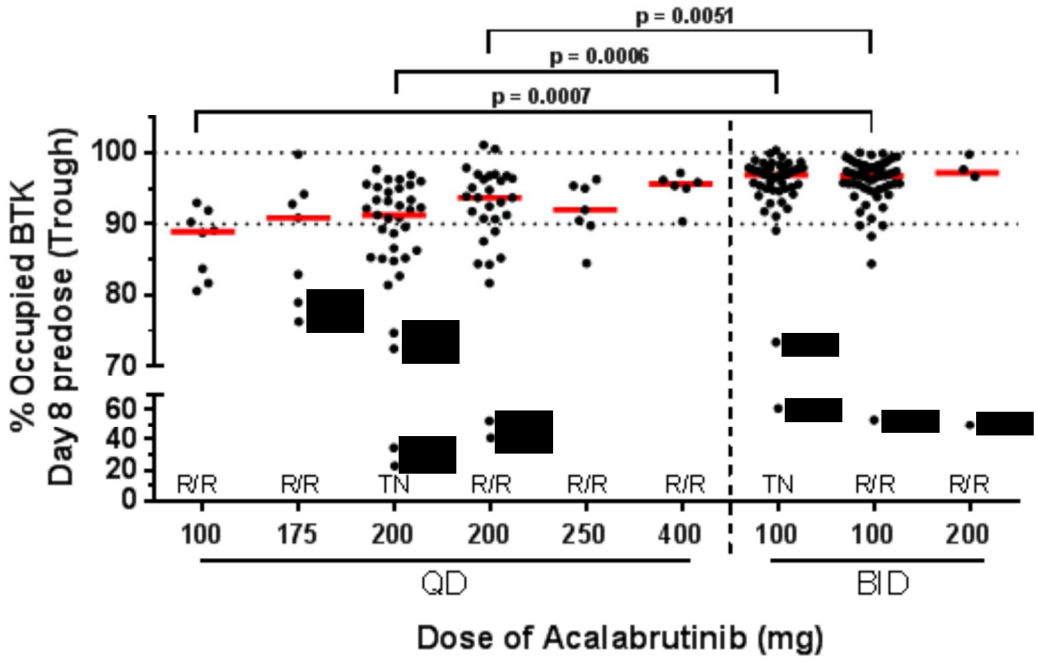
CLL=chronic lymphocytic leukemia; BTK=Bruton tyrosine kinase; n=number of healthy subjects/subjects; PBMC=peripheral blood mononuclear cells; SEM=standard error of the mean.

Note:　Panel A: Linear regression of the median BTK occupancy for subjects with CLL (solid line) or healthy subjects (dashed line).　Error bars show SEM.　Panel B shows individual BTK resynthesis rates from subjects in Study 15-H-0016.

Source: Studies 15-H-0016 (subjects with CLL) and ACE-HV-001 (healthy subjects)

ACE-CL-001 試験において、R/R 又は未治療 CLL 患者にアカラブルチニブを 7 日間反復投与し、患者から採取した PBMC を用いて BTK 占有率を測定した。1 日 2 回投与、1 日 1 回投与ともに、投与前、投与後約 12 時間及び 24 時間で採血を行い、PBMC を採取した。その結果から、図 36 に示すように、100 mg 1 日 2 回投与において、BTK 占有率のトラフ値（反復投与における投与前値）は高く、個体間変動が小さいことが示唆された。なお、100 mg 1 日 2 回投与したとき、95%の患者で BTK 占有率のトラフ値は 90%を超えていた。一方、同じ 1 日用量を 1 日 1 回（200 mg 1 日 1 回）で投与したときは、BTK 占有率のトラフ値が 90%を上回っていた患者の割合は 66%であった。用量を 100 mg 1 日 2 回から 200 mg 1 日 2 回に増加しても定常状態における BTK 占有率のトラフ値は増加しないと考えられたことから、CLL 治療に対する推奨用法・用量を 100 mg 1 日 2 回とする妥当性が示された。

図 36　　R/R 又は未治療 CLL 患者における BTK 占有率 [a]（トラフ値）（%）

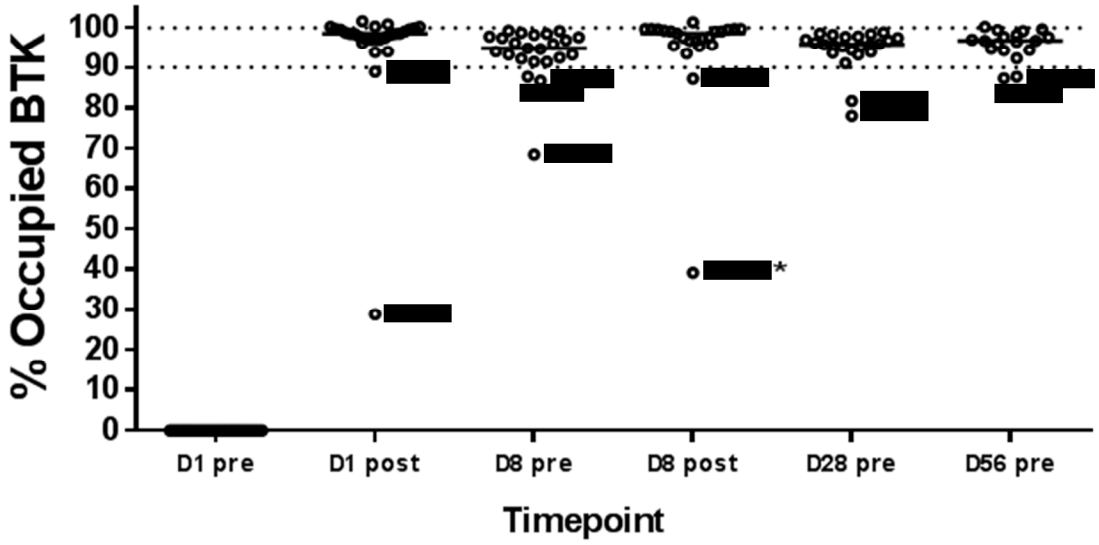


	Percent BTK occupancy at trough on Day 8								
	100 mg QD R/R	175 mg QD R/R	200 mg QD TN	200 mg QD R/R	250 mg QD R/R	400 mg QD R/R	100 mg BID TN	100 mg BID R/R	200 mg BID R/R
Median	89.0	90.9	91.3	93.7	92.0	95.7	96.9	96.8	97.2
Mean	87.4	88.0	86.6	89.8	91.9	95.0	95.3	95.3	86.0
SD	4.7	8.7	15.7	12.9	4.1	2.4	6.3	6.2	24.2
CV%	5.4	9.9	18.1	14.4	4.5	2.5	6.6	6.5	28.1
n	8	7	35	29	7	6	51	62	4

Source: Study ACE-CL-001
a　Horizontal lines depict median values; (unpaired, parametric, 2 tailed t-test used for statistical testing); values in red are p-values <0.05.　Abbreviations: BID = twice daily; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; Cmax, ss = maximal plasma concentration at steady state; CV = coefficient of variation; n = number of subjects; QD = once daily; R/R = relapsed/refractory; SD = standard deviation; TN = treatment naive

ACE-LY-004 試験において、MCL 患者にアカラブルチニブ 100 mg を 1 日 2 回投与したとき、投与前及び投与後 4 時間における BTK 占有率はいずれの評価日においても高かった。図 37 に示すように、MCL 患者における投与前及び投与 4 時間後の BTK 占有率は全ての時点で 95%以上であった。

図 37　　R/R MCL 患者にアカラブルチニブ 100 mg 1 日 2 回投与したときの BTK 標的部位占有率（%）

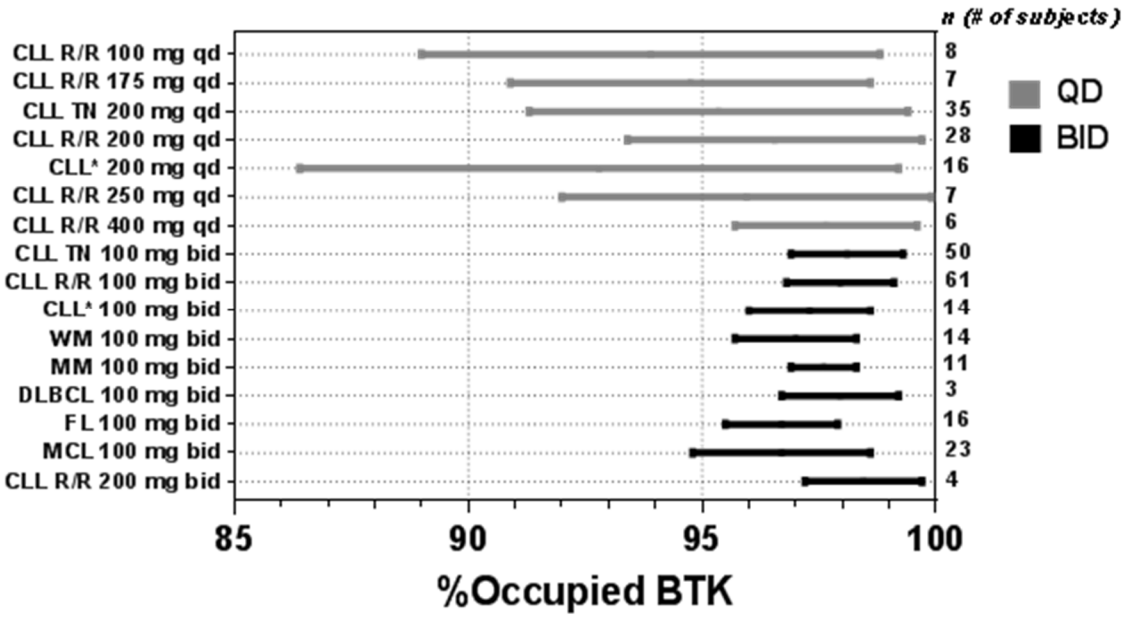


	BTK occupancy (%)					
	Day 1 Pre	Day 1 Post	Day 8 Pre	Day 8 Post	Day 28 Pre	Day 56 Pre
Median	0.0	95.5	94.8	98.6	95.8	96.7
Mean	0.0	95.5	93.7	95.1	94.6	95.9
SD	0.0	13.6	6.5	12.5	5.1	3.7
CV (%)	0.0	14.2	7.0	13.2	5.4	3.8
N	27	27	23	23	23	18

Source: Study ACE-LY-004; Report R2016003
[a] Horizontal lines depict median values
* Occupancy for Day 8 pre was 92.6% for Subject [redacted], suggesting that the pre- and post-dose samples may have been switched (no remaining sample was available to repeat the testing).
Abbreviations: BTK = Bruton tyrosine kinase; CV = coefficient of variation; N = number of subjects; Post = postdose (4h after dosing); Pre = predose (timepoint prior to next dose; trough level); SD = standard deviation

更に、B 細胞性腫瘍患者を対象とした臨床試験（ACE-CL-001 試験、15-H-0016 試験、ACE-WM-001 試験、ACE-MY-001 試験、ACE-LY-002 試験、ACE-LY-003 及び ACE-LY-004）で認められた定常状態（8 日目）における BTK 占有率を図 38 に示す。横線は各コホートで認められた BTK 占有率の範囲を示し、左端がトラフ値（投与前）の中央値、右端が最高値（投与後 4 時間）の中央値である。概して、他の用法・用量と比較して、100 mg 1 日 2 回投与では投与間隔（1 日）内における BTK 占有率の変動が小さかった。アカラブルチニブ 100 mg を 1 日 2 回投与したときの BTK 占有率は種々の B 細胞性腫瘍で一貫して高かった（95%以上）。1 日用量を増加しても（例えば、200 mg 1 日 2 回）、BTK 占有率は大きく増加しなかった。

図 38　　B 細胞性腫瘍患者を対象とした臨床試験で認められた定常状態における BTK 占有率（中央値）の 1 日の変動範囲



BID=twice daily; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; MM=multiple myeloma; QD=once daily; R/R=relapsed/refractory; TN=treatment naive; WM=Waldenström Macroglobulinemia.

Notes:　Grey lines represent QD dosing; black lines BID dosing.

The y-axis shows the B-cell malignancy and acalabrutinib dose for each study cohort.　Percent of occupied BTK is displayed on the x-axis.

2.7.2.3.4.3　曝露量－反応解析

アカラブルチニブを単独又は併用投与した B 細胞性腫瘍患者を対象として、曝露量－有効性及び曝露量－安全性の関係を評価した。

曝露量－有効性解析は、ACE-CL-007 試験の未治療 CLL 患者（274 例）のデータを用いて実施した。

曝露量－安全性解析は、表 11 に記載する 8 試験の併合データを用いて実施した。全解析対象集団には、計 573 例の B 細胞性腫瘍患者が含まれた。また、当該解析では、以下の部分解析対象集団を設定した。

(a) 未治療 CLL 患者集団（328 例）：アカラブルチニブを単独又はオビヌツズマブと併用投与された未治療 CLL 患者集団

(b) 全 CLL 患者集団（443 例）：アカラブルチニブを単独又は併用投与された未治療 CLL 患者並びに R/R CLL 患者を併合した全 CLL 患者集団

(c) 単独投与を受けた CLL 患者集団（301 例）：アカラブルチニブを単独投与された CLL 患者集団

(d) 併用投与を受けた CLL 患者集団（142 例）：アカラブルチニブをオビヌツズマブと併用投与された CLL 患者集団

(e) 単独投与を受けた血液学的悪性腫瘍患者集団（431 例）：アカラブルチニブを単独投与された血液学的悪性腫瘍患者集団

解析には $AUC_{ss,(0\text{-}24)}$及び $C_{ss,max}$ を用いた。また、活性代謝物 ACP-5862 の有効性及び安全性に及ぼす影響を評価するために、以下の式に示すように、アカラブルチニブ及び ACP-5862 のモル濃度を分子量、BTK 阻害活性及び蛋白結合率で補正した上でアカラブルチニブ及び ACP-5862 の $AUC_{ss,(0\text{-}24)}$又は $C_{ss,max}$ の総和（すなわち、活性成分の $AUC_{ss,(0\text{-}24)}$又は $C_{ss,max}$）を算出した。

$$Total\ Active\ Concentration = C_{parent} * fu_{parent} + C_{metabolite} * fu_{metabolite} * 0.5$$

ここで、C_{parent} 及び $C_{metabolite}$ はそれぞれアカラブルチニブ及び ACP-5862 のモル濃度、fu_{parent} はアカラブルチニブの非結合形分率（0.025）、$fu_{metabolite}$ は ACP-5862 の非結合形分率（0.013）で、係数 0.5 はアカラブルチニブに対する ACP-5862 の BTK 阻害活性の比である。

表 11 の 8 試験では、アカラブルチニブは 100、175、200 及び 250 mg 1 日 1 回又は 100 mg 及び 200 mg 1 日 2 回投与された。

表 11　　曝露量－反応解析に含まれる試験一覧

Study	Study Description	PK Sample Collection	Acalabrutinib N with PK Data (all/100 mg BID)	ACP-5862 N with PK Data (all/100 mg BID)
ACE-CL-001	Phase 1/2 study in subjects with R/R or previously untreated CLL, Richter's Syndrome or PLL	Cycle 1: Days 1, 8, 15, 22 and 28	161/130	18/18
ACE-CL-003	Phase 1b study in subjects with R/R CLL	Cycle 1: Day 1	8/8	-
ACE-CL-007	Phase 3 study in subjects with previously untreated CLL	Cycle 1 and Cycle 2: Day 1	274/264	274/264
ACE-LY-002	Phase 1b study in subjects with R/R de novo activated B-cell subtype of DLBCL	Cycle 1: Days 1, 8, 15, 22 Cycle 2: Day 1	15/15	-
ACE-LY-003	Phase 1b study of acalabrutinib alone or in combination with rituximab in subjects with FL	Cycle 1: Days 1, 8, 15, 22 and 28	7/7	-
ACE-LY-004	Phase 2 study in subjects with MCL	Cycle 1: Days 1, 8, 15, 22 and 28	45/45	-
ACE-WM-001	Phase 1/2 in subjects with WM	Cycle 1: Days 1, 8, 15, 22 and 28	50/49	-
ACE-MY-001	Phase 1b study of acalabrutinib or in combination with dexamethasone in subjects with MM	Cycle 1: Days 1, 8, 15, 22 and 28	13/13	-
Total			573/531	292/282

BID=twice daily; CLL=chronic lymphocytic leukemia; DLBCL=Diffuse Large B-cell Lymphoma; MCL=mantle cell lymphoma; N=number of subjects; PLL=prolymphocytic leukemia; WM=Waldenström macroglobulinemia; FL=follicular lymphoma; MM=multiple myeloma.

Note: The most prevalent dosing regimen, administered to individuals for the duration of the clinical study is shown.

Source: D8223C00004

2.7.2.3.4.3.1　曝露量と有効性との関連性

未治療 CLL 患者（274 例）を対象として進行中の有効性及び安全性を評価する主要な臨床試験 ACE-CL-007 から得られたデータを用いて、有効性に関する曝露量－反応解析を実施した。なお、ACE-CL-007 試験では、アカラブルチニブ 100 mg を 1 日 2 回反復投与した。

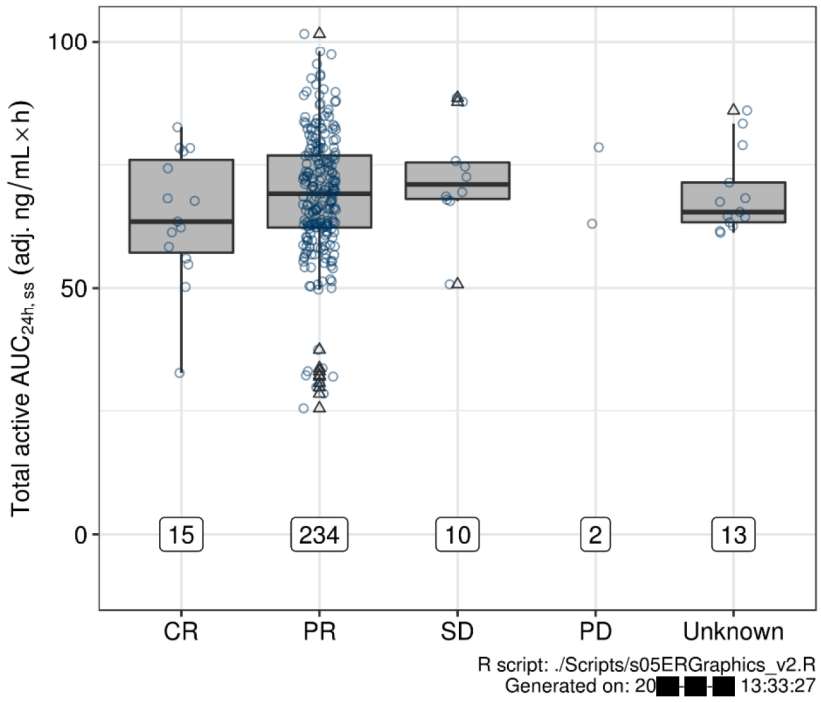
解析には、アカラブルチニブ、ACP5862 及び活性成分の $AUC_{ss,(0-24)}$及び $C_{ss,max}$ を用いた。有効性の評価項目としては、BOR（IRC 評価）、PFS（IRC 評価）及び腫瘍縮小効果（最長径のベースライン値からの変化率［%］を評価）であった。BOR は、奏効例（完全奏効［CR］又は部分

奏効［PR］）及び非奏効例（安定［SD］又は病勢進行［PD］）に分類した。なお、奏効に関する情報が得られなかった被験者は全て「不明」に分類した。

本項には、活性成分の $AUC_{ss,(0-24)}$を用いた曝露量－有効性解析の結果のみを記載し、活性成分の $C_{ss,max}$、アカラブルチニブ及び ACP-5862 の $AUC_{ss,(0-24)}$及び $C_{ss,max}$ を用いた解析は D8223C00003 解析の報告書を参照のこと。また、本項には併合データ（アカラブルチニブ及びオビヌツズマブの併用投与群［B 群］並びにアカラブルチニブ単独投与群［C 群］のデータを併合）を用いた解析結果のみを示し、個別の投与群（B 群又は C 群）のデータを用いた解析結果は D8223C00003 解析の報告書を参照のこと。

活性成分の $AUC_{ss,(0-24)}$を BOR 別に図 39 に示す。図 39 から、活性成分の $AUC_{ss,(0-24)}$の中央値は BOR に依らずほぼ一定であり、活性成分の $AUC_{ss,(0-24)}$と BOR との間に関連性がないことが示された。

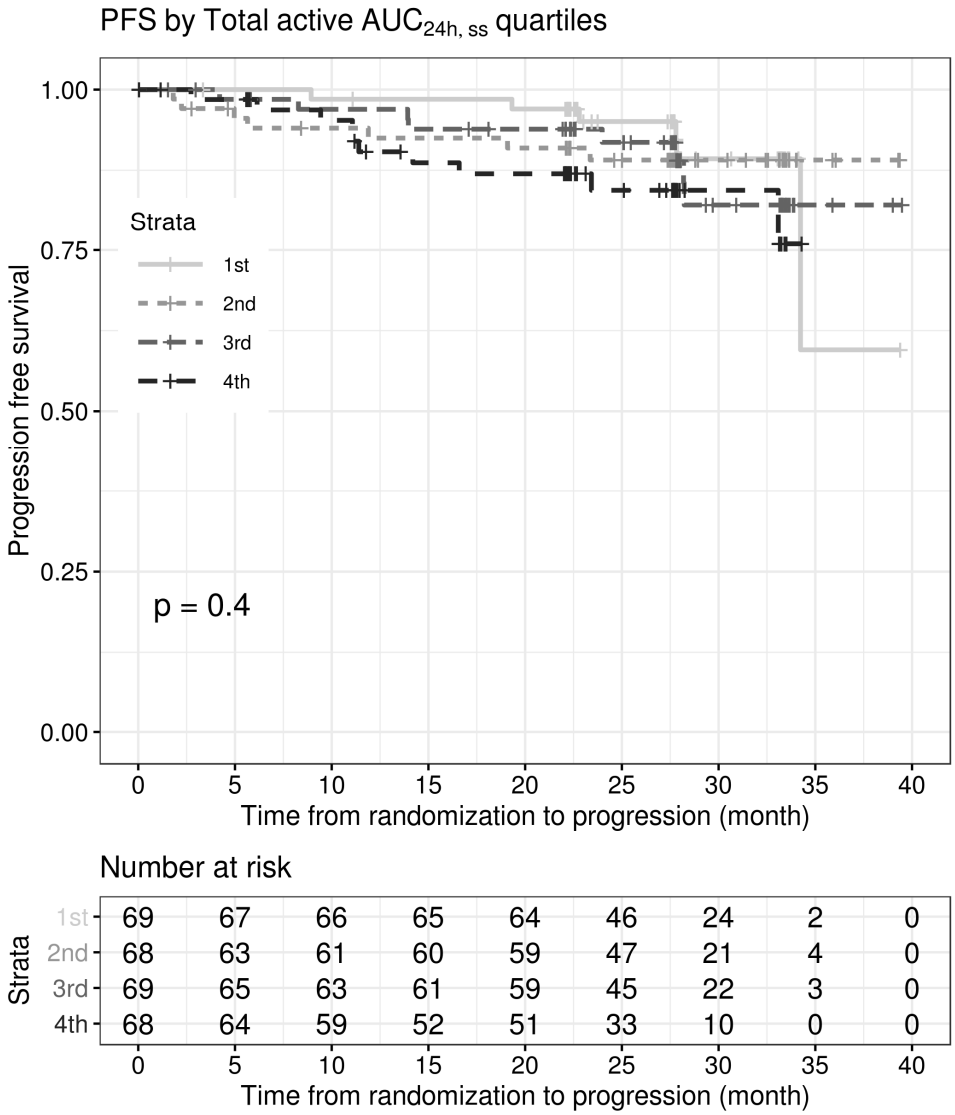
図 39　　BOR 別に示した活性成分の $AUC_{ss,(0-24)}$の箱ひげ図（併合データ）



CR=complete response; PR=partial response; PD=progressive disease; Total active AUC24h,ss=area under the plasma concentration-time curve from time 0 to 24 hours (2 dosing intervals) at steady state for the total active moiety (i.e., acalabrutinib + ACP-5862 adjusted for molecular weight, potency and protein binding).
Note:　The numbers above the categories on the x-axis indicate the number of subjects in each category. Information about response was missing for 13 subjects (categorized as unknown).
Open circles represent estimated AUC24h,ss in each response category and open triangles represent outliers.
Source: D8223C00003.

活性成分の $AUC_{ss,(0-24)}$の四分位点に基づき患者を 4 群に層別して作成した PFS の Kaplan-Meier プロットを図 40 に示す。PFS に活性成分の $AUC_{ss,(0-24)}$の増加に伴う延長傾向は認められず、活性成分の $AUC_{ss,(0-24)}$と PFS との間に明らかな関連性は認められなかった。

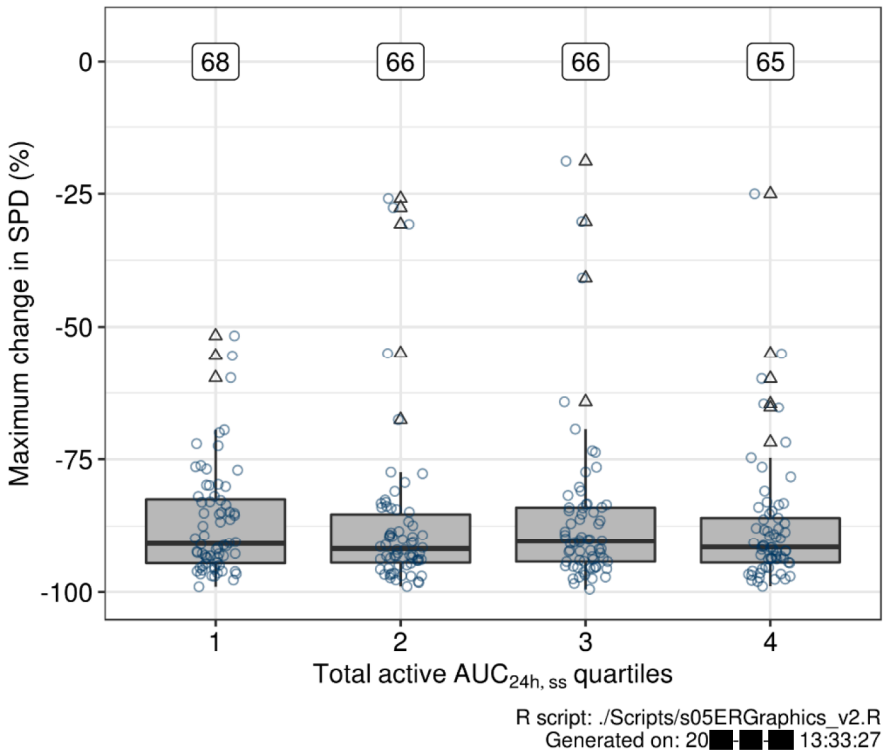
図 40　　活性成分の $AUC_{ss,(0-24)}$に基づき層別した各患者群（4 群）における PFS の Kaplan-Meier プロット（併合データ）



Note:　Total active AUC24h,ss=area under the plasma concentration-time curve from time 0 to 24 hours (2 dosing intervals) at steady state for the total active moiety (i.e., acalabrutinib + ACP-5862 adjusted for molecular weight, potency, and protein binding).　The p-value represents the results of log rank test comparing the probabilities across quartiles.　The table below the Kaplan-Meier curves represents the number of subjects available for the analyses (i.e. not censored or discontinued).
Source: D8223C00003.

活性成分の $AUC_{ss,(0-24)}$に基づき層別した患者群（4 群）別に腫瘍縮小効果を図 41 に示す。最長径のベースライン値からの変化率は 4 群で同程度あり、活性成分の $AUC_{ss,(0-24)}$と腫瘍縮小効果との間に関連性はないことが示された。

図 41　　活性成分の $AUC_{ss,(0-24)}$に基づき層別した患者群（4 群）別に示した腫瘍縮小効果（最長径のベースライン値からの変化率）（併合データ）



Note:　Total active AUC24h,ss=area under the plasma concentration-time curve from time 0 to 24 hours (2 dosing intervals) at steady state for the total active moiety (i.e., acalabrutinib + ACP-5862 adjusted for molecular weight, potency and protein binding).　The numbers above the categories on the x-axis indicate the number of subjects in each category.　Open circles represent estimated AUC24h,ss in each response category and open triangles represent outliers.
Source: D8223C00003

活性成分の $AUC_{ss,(0-24)}$を用いた曝露量－有効性解析の結果は、活性成分の $C_{ss,max}$、アカラブルチニブ又は ACP-5862 の $AUC_{ss,(0-24)}$及び $C_{ss,max}$ を用いたときの結果と同様であった。また、個別の投与群（B 群：アカラブルチニブ及びオビヌツズマブの併用投与群並びに C 群：アカラブルチニブ単独投与群）のデータを用いて解析を行った結果においても、曝露量と有効性との間に関連性は認められなかった（D8223C00003 解析参照）。

曝露量－有効性解析の結果から、ACE-CL-007 試験においてアカラブルチニブ又は ACP-5862 の曝露量と種々の有効性評価項目との間に関連性はないことが示され、アカラブルチニブ 100 mg の 1 日 2 回投与により、一貫した高い臨床効果が得られることが示唆された。

解析対象集団におけるアカラブルチニブの $AUC_{ss,(0-24)}$の中央値は 1674 ng·hr/mL であった。第 1 四分範囲に含まれる患者集団（Q1）での中央値は 1336 ng·hr/mL であり、2.5 及び 97.5 パーセンタイル点はそれぞれ 669 ng·hr/mL 及び 1442 ng·hr/mL であった。第 4 四分範囲に含まれる患者集団（Q4）における中央値は 2174 ng·hr/mL であり、2.5 及び 97.5 パーセンタイル点はそれぞれ 2007 ng·hr/mL 及び 2704 ng·hr/mL であった。一方、解析対象集団における ACP-5862 の $AUC_{ss,(0-24)}$の中央値は 4138 ng·hr/mL であった。Q1 における中央値は 3576 ng·hr/mL であり、2.5 及び 97.5 パーセンタイル点はそれぞれ 1669 ng·hr/mL 及び 3847 ng·hr/mL であった。Q4 における中央値は

4818 ng·hr/mL であり、2.5 及び 97.5 パーセンタイル点はそれぞれ 4514 ng·hr/mL 及び 5648 ng·hr/mL であった。以上のように、アカラブルチニブ及び ACP-5862 の曝露量には大きな個体間変動が認められた（Q4 と Q1 の中央値の間に約 2 倍の差が認められ、かつ、Q4 の 97.5 パーセンタイル点と Q1 の 2.75 パーセンタイルとの間に約 4 倍の差が認められた）。曝露量－有効性解析の結果から、検討した曝露量範囲において、アカラブルチニブ又は ACP-5862 の曝露量と有効性との間に関連性が認められず、検討した内因性及び外因性要因が曝露量に及ぼす影響が僅かであること（2.7.2.3.2 項及び 2.7.2.3.3 項参照）を考慮すると、これら内因性及び外因性要因がアカラブルチニブの体内動態に及ぼす影響は臨床上問題とはならないと考えられた。

母集団薬物動態解析の結果、アカラブルチニブ及び ACP-5862 の曝露量には、R/R CLL 患者、未治療 CLL 患者及び種々の B 細胞性腫瘍（CLL、MCL、DLBCL、FL、WM 及び MM）患者間で明らかな差異は認められなかった。また、R/R CLL 患者及び未治療 CLL 患者の両方で高い ORR が認められた。すなわち、R/R CLL 患者での ORR は 81.3%であり、未治療 CLL 患者における ORR はアカラブルチニブ単独投与群で 85.5%、オビヌツズマブ併用投与群で 93.9%であった。

アカラブルチニブ 100 mg 1 日 2 回投与により R/R CLL 患者及び未治療 CLL 患者ともに高い臨床効果が確認されていること、これら患者群間でアカラブルチニブ及び ACP-5862 の曝露量に顕著な差異がないこと、及び、広範な曝露量範囲において曝露量と有効性との間に明確な関連性がないことを考慮し、R/R 又は未治療 CLL 患者に対するアカラブルチニブの推奨用法・用量は 100 mg 1 日 2 回投与が妥当であると判断した。

2.7.2.3.4.3.2　曝露量と安全性との関連性

曝露量－安全性解析は、アカラブルチニブを単独又は併用投与した B 細胞性腫瘍患者から得られた併合データセット（全解析対象集団 567 例、8 試験）及び事前に規定した部分解析対象集団（2.7.2.3.4.3 項参照）を用いて実施した。解析にはアカラブルチニブ、ACP-5862 及び活性成分の $AUC_{ss,(0\text{-}24)}$及び $C_{ss,max}$ を用いた（2.7.2.3.4.3 項参照）。血漿中 ACP-5862 濃度を測定した患者は全解析対象集団（567 例）の半数程度（292 例）であったことから、アカラブルチニブの $AUC_{ss,(0\text{-}24)}$ 及び $C_{ss,max}$ を主要な指標とした。血漿中 ACP-5862 濃度を測定していない患者については、代表的な母集団薬物動態パラメータ（最終モデルに基づき推定した平均的な薬物動態パラメータ）を用いて ACP-5862 の曝露量を予測した。

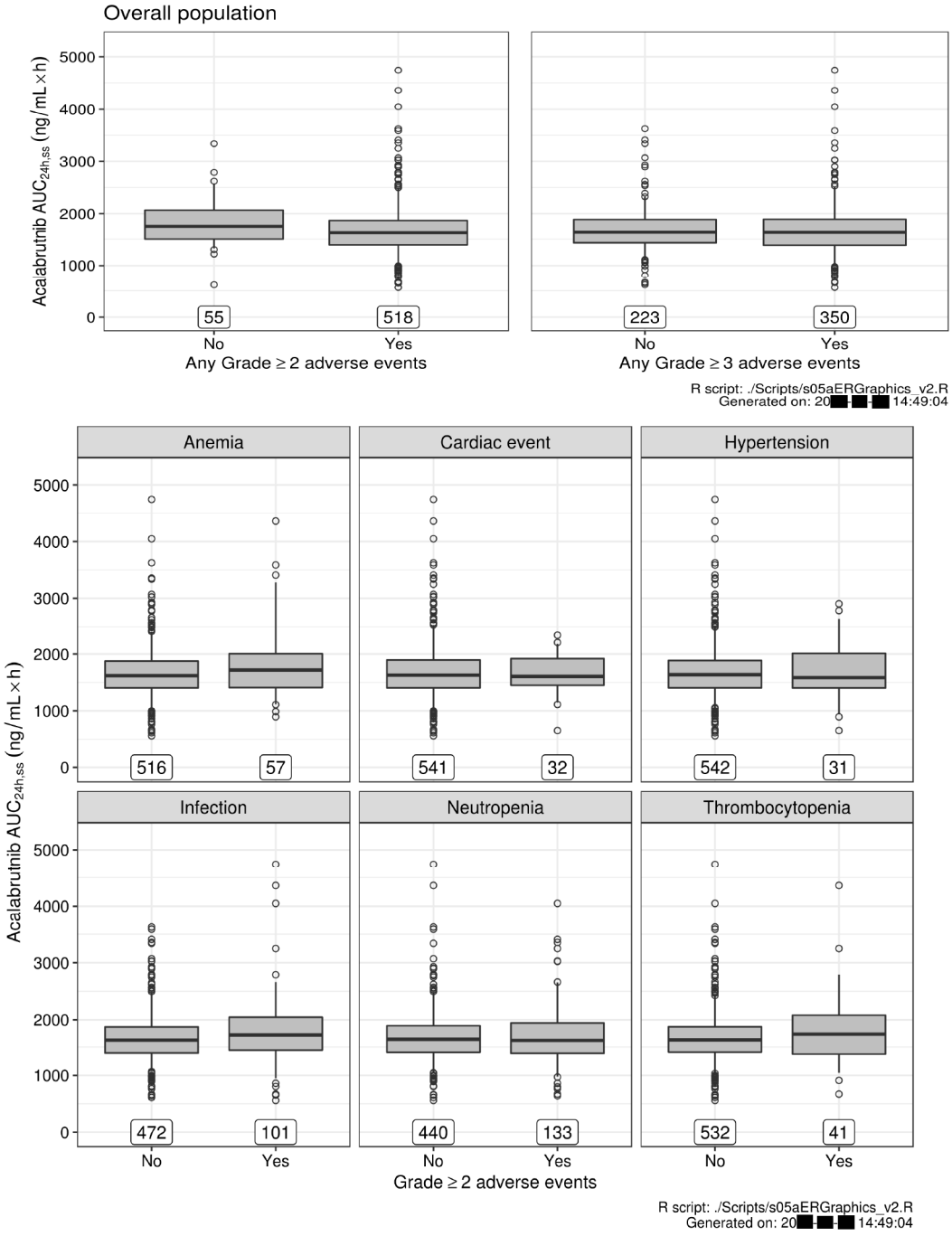
本項には、アカラブルチニブ及び ACP-5862 の曝露量は単独投与時及び併用投与時の間で同程度であることを考慮して、全解析対象集団のデータを用いてアカラブルチニブの $AUC_{ss,(0\text{-}24)}$と有害事象との関連性を評価した結果のみを記載する。なお、個々の部分解析対象集団（(a) 未治療 CLL 患者集団、(b) 全 CLL 患者集団、(c) 単独投与を受けた CLL 患者集団、(d) 併用投与を受けた CLL 患者集団及び(e) 単独投与を受けた血液学的悪性腫瘍患者集団）を対象として、アカラブルチニブ、ACP-5862 及び活性成分の $AUC_{ss,(0\text{-}24)}$及び $C_{ss,max}$ と有害事象との関連性を評価した結果は D8223C00004 解析の報告書を参照のこと。

解析の対象とした有害事象は、グレード 2 以上の有害事象、グレード 3 以上の有害事象及びグレード 2 以上の注目すべき有害事象（貧血、心血管系事象、下痢、頭痛、出血、肝臓関連事象、高血圧、感染症、好中球減少症および血小板減少症）であった。曝露量－安全性プロファイルに潜在的な差異があるか否かを評価するため、有害事象発現率についてはグレード 2 以上とグレード 3 以上の 2 種類のグレードについて検討した。解析の結果、グレード 2 以上の有害事象とグレード 3 以上の有害事象とで曝露量－安全性関係は同様であったことから、グレード 2 以上の注目すべき有害事象のみを評価した。なお、グレード 2 以上の注目すべき有害事象のうち、下痢（1.9%［11 例/573 例］)、頭痛（0.7%［4 例/573 例］）、出血（2.1%［12 例/573 例］）及び肝臓

関連事象（2.8%［16 例/573 例］）の発現率は 5%未満であったため、これらの有害事象は以降の曝露量－安全性解析の対象から除外した。

特定の有害事象について、その発現率とアカラブルチニブの $AUC_{ss,(0-24)}$との関係を図 42 に示す。アカラブルチニブの $AUC_{ss,(0-24)}$はグレード 2 以上の有害事象を発現した患者と発現していない患者とで同程度であり、同様にグレード 3 以上の有害事象を発現した患者と発現していない患者とで同程度であった。グレード 2 以上の貧血及び高血圧を除いて、アカラブルチニブの曝露量とグレード 2 以上の注目すべき有害事象の発現との間に明らかな傾向は認められなかった。これらの全解析対象集団における解析結果は、部分解析対象集団（(a) 未治療 CLL 患者集団、(b) 全 CLL 患者集団、(c) 単独投与を受けた CLL 患者集団、(d) 併用投与を受けた CLL 患者集団及び(e) 単独投与を受けた血液学的悪性腫瘍患者集団）における解析結果（D8223C00004 解析参照）と一貫していた。

図 42　　グレード 2 以上の有害事象、グレード 3 以上の有害事象及びグレード 2 以上の注目すべき有害事象発現の有無別に示したアカラブルチニブの $AUC_{ss,(0-24)}$（全解析対象集団）

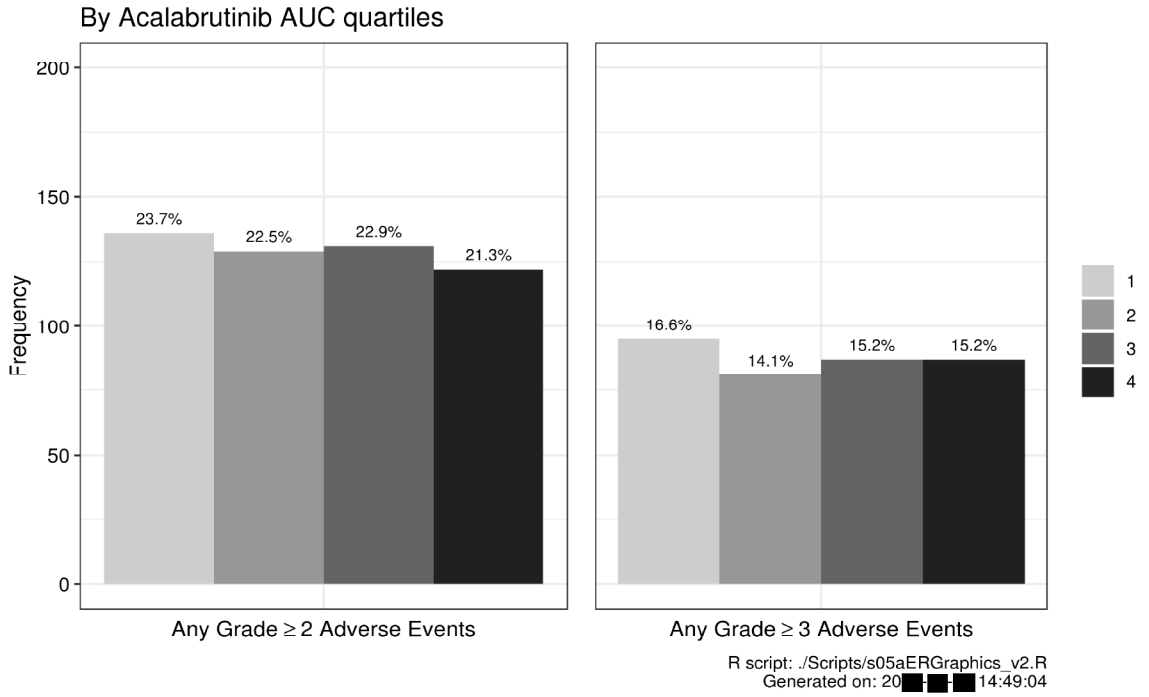


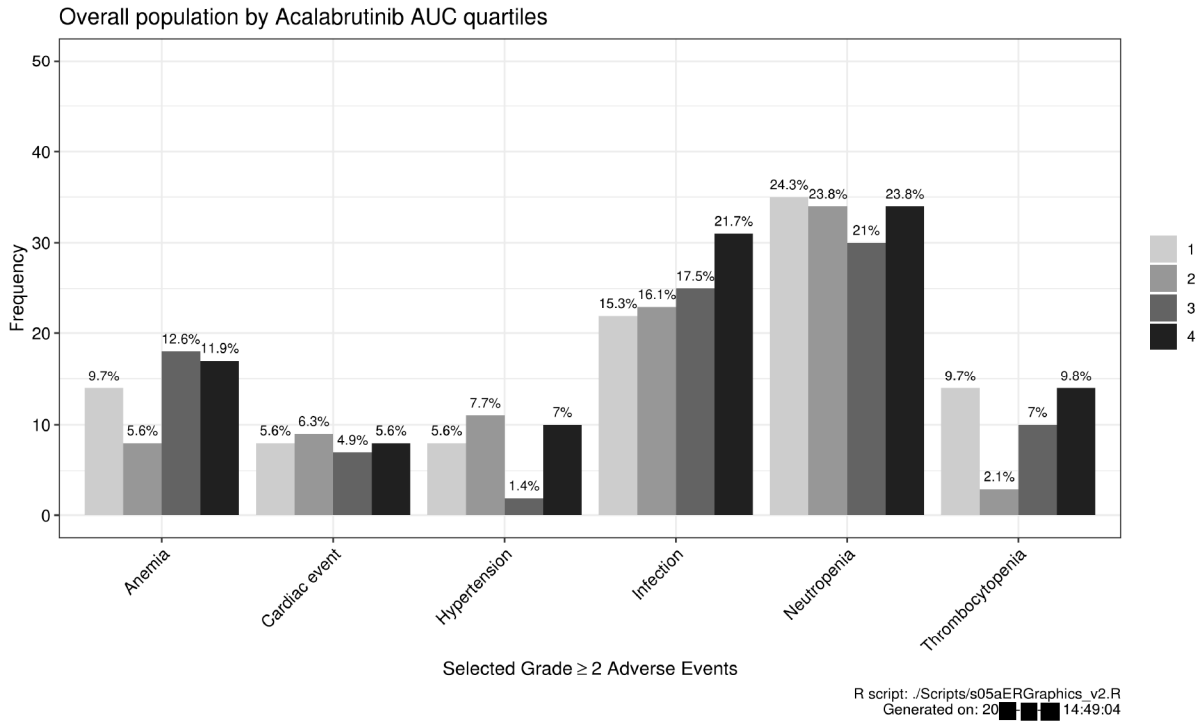
AE=adverse event; ECI= event of clinical interest.

Note: The numbers under the categories on the x-axis indicate the number of subjects experiencing the selected AE (Yes), and the number of subjects without experiencing the AE (No). Top Panel: shows Grade ≥2 and Grade ≥3 Any AEs, Bottom Panel: shows ECIs.
Source: D8223C00004.

更に、アカラブルチニブの $AUC_{ss,(0-24)}$の四分位点に基づき患者を 4 群に分け、各群における有害事象の発現率を評価することにより曝露量－安全性解析を実施した（図 43 参照）。グレード 2 以上の貧血および高血圧の発現率が第 4 四分範囲に含まれる患者集団（Q4）のほうが他の患者集団（Q1～Q3）に比べて高かったことを除き、検討した有害事象の発現率とアカラブルチニブの $AUC_{ss,(0-24)}$との間に特に傾向は認められなかった。これらの全解析対象集団における解析結果は、部分解析対象集団における解析結果（D8223C00004 解析参照）と一貫していたことから、以降のロジスティック回帰分析は全解析対象集団のデータのみを用いて実施した。

図 43　　アカラブルチニブの $AUC_{ss,(0-24)}$の四分位点に基づき層別した各患者集団におけるグレード 2 以上の有害事象、グレード 3 以上の有害事象及びグレード 2 以上の注目すべき有害事象の発現率（全解析対象集団）



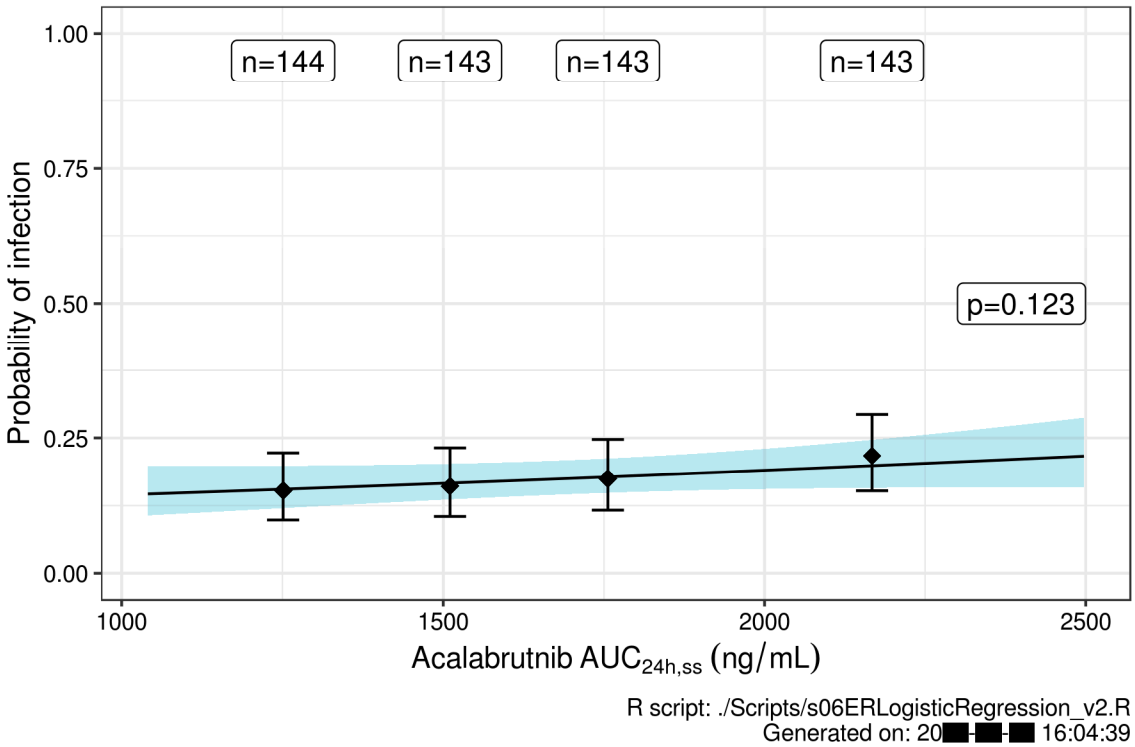


AE=adverse event; ECI=event of clinical interest.

Note:　Y-axis represents the number of subjects experiencing the selected AE; The shaded bars represent the four quantiles (quartiles) of $AUC_{ss,(0-24)}$ with 1=first quartile, 2=second quartile, 3=third quartile, and 4=fourth quartile. Top Panel: shows Grade ≥2 and Grade ≥3 Any AEs, Bottom Panel: shows ECIs.
Source: D8223C00004.

以上の解析結果を踏まえ、アカラブルチニブの $AUC_{ss,(0-24)}$ とグレード 2 以上の感染症の発現率との関連性をロジスティック回帰分析により評価した。ロジスティック回帰分析の結果、グレード 2 以上の感染症の発現率とアカラブルチニブの $AUC_{ss,(0-24)}$ との間には統計学的に有意な相関は認められず（p=0.123）、曝露量は感染症の鋭敏な予測因子ではないことが示された（図 44 参照）。

図 44　　アカラブルチニブの $AUC_{ss,(0-24)}$ の四分位点に基づき層別した 4 群におけるグレード 2 以上の感染症の発現率（点推定値及び 95% CI）



AE=adverse event; AUC24h,ss=area under the plasma concentration-time curve from time 0 to 24 hours (2 dosing intervals) at steady state.
Note:　The point estimate (solid diamond) and 95% CIs (error bars) estimated for the selected AEs in each quartile of acalabrutinib AUC24h,ss are shown. Shaded region represents the 90% CI for the regression line. Numbers shown in boxes represent the p-values estimated for the exposure-AE relationship and the number of subjects per quartile of acalabrutinib exposures.
Source: D8223C00004.

全解析対象集団において、ACP-5862 又は活性成分の $AUC_{ss,(0-24)}$及び $C_{ss,max}$ を用いた曝露量－安全性解析からも、アカラブルチニブの $AUC_{ss,(0-24)}$を用いた解析と一貫した結果が得られた。また、部分解析対象集団（(a) 未治療 CLL 患者集団、(b) 全 CLL 患者集団、(c) 単独投与を受けた CLL 患者集団、(d) 併用投与を受けた CLL 患者集団及び(e) 単独投与を受けた血液学的悪性腫瘍患者集団）における解析からも同様の結果が得られた（D8223C00004 解析参照）。

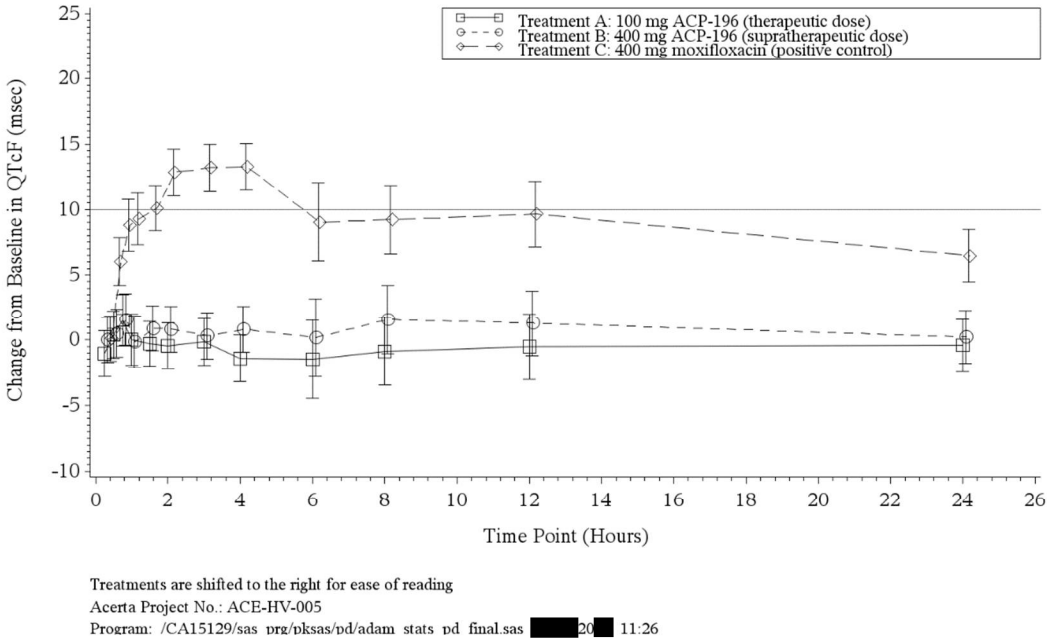
全解析対象集団において、アカラブルチニブの $AUC_{ss,(0-24)}$の 2.5 パーセント点、第 1 四分範囲（Q1）の中央値、中央値、第 4 四分範囲（Q4）の中央値及び 97.5 パーセント点はそれぞれ 659、1251、1626、2167 及び 3604 ng·hr/mL で あった。一方、ACP-5862 の $AUC_{ss,(0-24)}$の 2.5 パーセント点、Q1 の中央値、中央値、Q4 の中央値及び 97.5 パーセント点はそれぞれ 1796、3326、4091、4808 及び 8880 ng·hr/mL であった。Q4 と Q1 の中央値の間に約 2 倍の差が認められ、かつ、Q4 の 97.5 パーセンタイル点と Q1 の 2.75 パーセンタイルとの間に約 5 倍の差が認められた。検討した曝露量範囲において、アカラブルチニブ又は ACP-5862 の曝露量と安全性との間に関連性が認められず、検討した内因性及び外因性要因が曝露量に及ぼす影響が僅かであること（2.7.2.3.2 項及び 2.7.2.3.3 項参照）を考慮すると、これら内因性及び外因性要因がアカラブルチニブの体内動態に及ぼす影響は臨床上問題とはならないと考えられた。

以上の結論として、曝露量－安全性解析結果からも、R/R CLL 患者及び未治療 CLL 患者に対するアカラブルチニブの臨床推奨用量を 100 mg 1 日 2 回投与とすることの妥当性が示唆された。

2.7.2.3.4.3.3　曝露量と QT 間隔延長との関係

健康被験者を対象とした QT/QTc 評価試験（ACE-HV-005 試験）において、陽性対照のモキシフロキサシン 400 mg を単回投与したときにはプラセボで補正した QTcF 間隔に延長が認められたのに対し、アカラブルチニブを単回投与したときには推奨用量（100 mg）及び治療量域を超える用量（400 mg）のいずれにおいてもプラセボで補正した QTcF 間隔への影響は認められなかった（図 45 参照）。アカラブルチニブ 100 mg 及び 400 mg を投与した後 24 時間まで QTcF 間隔を評価したところ、QTcF 間隔のベースラインからの変化量をプラセボで補正した値（ddQTcF：アカラブルチニブとプラセボとの LSM の差）はそれぞれ-1.468～+1.531 ms 及び-0.139～+1.569 ms であった。モキシフロキサシン投与群では、投与後 4 時間で最大延長が認められた（ddQTcF：+13.153 ms）。アカラブルチニブ 100 mg 及び 400 mg を投与したときの ddQTcF の両側 90% CI の上限は、全ての測定時点（12 時点で測定）において 10 ms 未満であった。

図 45　　モキシフロキサシン 400 mg、アカラブルチニブ 100 mg 又はアカラブルチニブ 400 mg を投与したときの各測定時点における QTcF 間隔のベースラインからの変化量（ddQTcF：実薬とプラセボとの LSM の差及び 90% CI）（ACE-HV-005 試験）

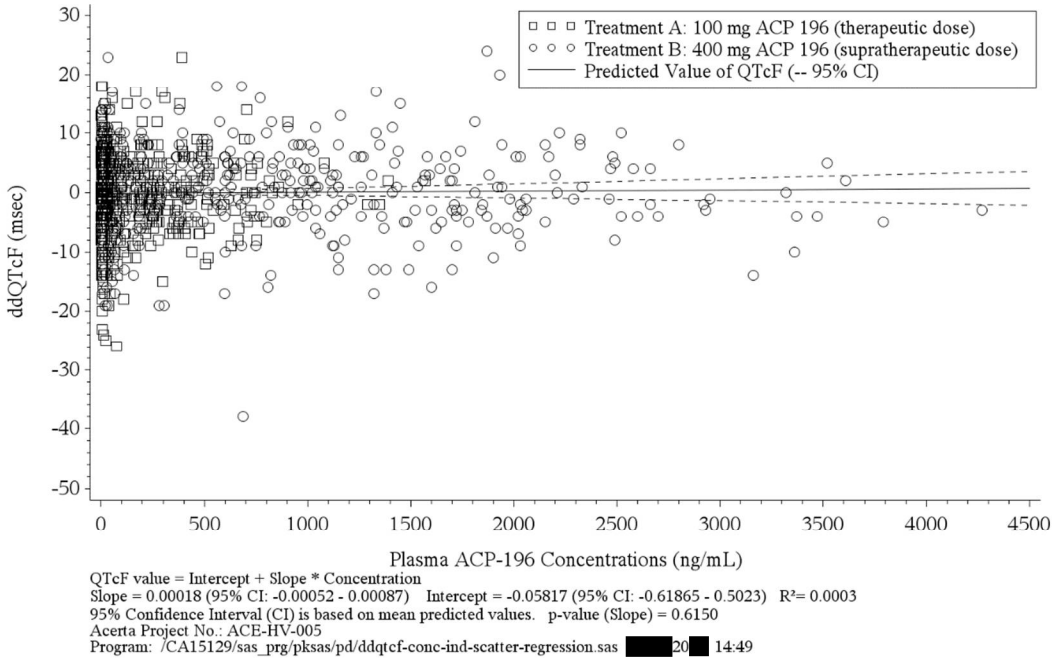


Source: ACE-HV-005 CSR Figure 11-9

QT、PR、QRS 及び RR 間隔のベースラインからの変化量（LSM）は、アカラブルチニブ群とプラセボ群で同程度であった。

QTcF 間隔のベースラインからの変化量（プラセボ補正値：ddQTcF）と血漿中アカラブルチニブ濃度の関係を図 46 に示す。ddQTcF と血漿中アカラブルチニブ濃度の間に関連性は認められなかった。100 mg 及び 400 mg 投与時のアカラブルチニブの C_{max}（幾何平均値）に対して予測される ddQTcF はそれぞれ 0.025 ms（両側 90% CI：+0.369～+0.419 ms）及び 0.240 ms（両側 90% CI：-0.579～+1.059 ms）であり、両側 90% CI の上限値はいずれの用量でも 10 ms 未満であった。

図 46　　QTcF 間隔のベースラインからの変化量（プラセボ補正値：ddQTcF）と血漿中アカラブルチニブ濃度との関係（曝露量－反応解析、ACE-HV-005 試験）



Source: ACE-HV-005 CSR Figure 11-10

100～400 mg の用量範囲ではアカラブルチニブの AUC は用量比を若干上回る増加を示したことから、QT/QTc 評価試験では、治療量域を超える高用量までアカラブルチニブの曝露量と QTc 間隔との関係を評価することが適切であると考えられた。B 細胞性腫瘍患者にアカラブルチニブ 100 mg を 1 日 2 回投与したときの C_{max} には 265～686 ng/mL（投与 1 日目での幾何平均値）と投与群間で大きな変動が認められた（表 13 参照）。当該 QT/QTc 評価試験（ACE-HV-005 試験）においてアカラブルチニブ 100 mg を単回経口投与したときの C_{max}（幾何平均値）は 465.9 ng/mL（44 例）であり、400 mg 単回経口投与時の C_{max}（幾何平均値）は 1672 ng/mL（43 例）と、上記の変動上限を十分に超えていた。

健康被験者を対象とした ACE-HV-001 試験及び CLL、SLL、RS 又は PLL 患者を対象とした ACE-CL-001 試験においても、アカラブルチニブが QT 間隔に影響を及ぼす可能性を評価した。

ACE-HV-001 試験では、アカラブルチニブ 50 mg を 12 時間間隔で 1 日 2 回投与された被験者（コホート 4）、アカラブルチニブ 100mg を単回投与された被験者（コホート 5）及びアカラブルチニブ 50 mg を単独投与又はイトラコナゾール（反復投与）と併用投与された被験者（コホート 7）を対象に、ホルター心電図の検査結果と血漿中アカラブルチニブ濃度との関係をついて詳細に解析した。本解析から、QTcF（Fridericia 補正法）又は QTcB（Bazett 補正法）のいずれについても血漿中アカラブルチニブ濃度と QTc 間隔の変化と関連性は認められなかった。更に、心拍数及び 12 誘導心電図に対するアカラブルチニブの影響もみられなかった。

これらの結果は、以下に示すように、B 細胞性腫瘍患者（ACE-CL-001 試験、118 例）の心電図の検査結果とも合致していた（臨床的安全性 2.7.4 参照）。ACE-CL-001 試験において、心拍数に対する明らかな影響は認められなかった。PR 及び QRS 間隔の評価結果から、房室伝導又は心筋の脱分極に対する影響を示唆するデータは得られなかった。QTcF 間隔の評価結果から、心筋

の再分極に対する臨床上問題となる顕著な影響は認められなかった。また、アカラブルチニブの曝露量－反応解析から、血漿中アカラブルチニブ濃度と ddQTcF との相関の傾き（点推定値：0.00018、95% CI：-0.00052～0.00087、図 46 脚注参照）から判断し、心筋の再分極に対して臨床上問題となる顕著な影響はないことが示され、アカラブルチニブの C_{max} で予測される QTcF 間隔への影響も認められなかった。更に、アカラブルチニブ投与に関連して、臨床的に重大な新たな波形の変化も認められなかった。

上述のように、QT/QTc 評価試験（ACE-HV-005 試験）から、アカラブルチニブの治療量（100 mg）及び治療量域を超える高用量（400 mg）を投与したときに臨床上問題となる QTc 間隔の延長は認められなかった。これらは、健康被験者（ACE-HV-001 試験）及び CLL、SLL、RS 又は PLL 患者（ACE-CL-001 試験）を対象に実施した心電図検査と一貫する結果であった。アカラブルチニブの臨床薬理学的特性及び心臓関連の安全性の要点を表 18 に要約する。

2.7.2.3.4.3.4　アカラブルチニブの用量設定根拠

BTK は BCR シグナル伝達経路に不可欠なキナーゼであり、細胞の増殖及び生存の重要な調節因子として B 細胞性腫瘍の形成を推進する（Hendriks et al 2014）。そのため、MCL 及び CLL 等の B 細胞性腫瘍に対する治療として BTK を標的とすることの妥当性が示されている（Advani et al 2013、Byrd et al 2014）。一方、イブルチニブによる治療において、BTK 変異又は BTK シグナル伝達の下流の活性型変異が出現し、病勢進行に至ることが報告されている（Burger et al, 2016、Tucker and Rule, 2015、Woyach 2015、Woyach et al 2014b）。BTK 阻害が持続的でない又は部分的な場合に補完的な耐性経路の発現が促進される可能性があるため、投与間隔を通じてほぼ完全な BTK 阻害が得られる用量を探索した。アカラブルチニブの用量設定試験（ACE-CL-001 試験）は、個体間変動が小さく、かつ高い BTK 阻害効果が持続して得られるとともに、忍容性が良好な用法・用量を特定することを目的として計画した。アカラブルチニブ 100 mg を 1 日 2 回投与することで、高い BTK 占有率が持続的に得られ、1 日用量は同一であるが、200 mg を 1 日 1 回投与したときと比較して、薬力学の個体間変動は小さく、高い BTK 占有率（トラフ値）が維持されることが示された（ACE-CL-001 試験、図 36 参照）。CLL 患者にアカラブルチニブを 100 mg の用量で 1 日 2 回投与したときの許容可能な安全性プロファイルが認められた。

アカラブルチニブ及びその活性代謝物 ACP-5862 の体内動態を評価し、またアカラブルチニブ 100 mg 1 日 2 回投与による CLL 患者に対する治療のリスク・ベネフィット評価を補強するために、母集団薬物動態解析、PBPK モデル解析及び曝露量－反応解析を実施した。

アカラブルチニブを投与された健康被験者（138 例）及び B 細胞悪性腫瘍患者（575 例）のデータを用いて母集団薬物動態解析を実施し、内因性及び外因性の共変量がアカラブルチニブの体内動態に及ぼす影響を検討した。また、PBPK モデルを構築し、CYP 阻害剤又は誘導剤の併用がアカラブルチニブ及び ACP-5862 の体内動態に及ぼす影響を検討した。

曝露量－有効性解析では、未治療 CLL 患者（ACE-CL-007 試験、274 例）のデータを用いてアカラブルチニブ又は ACP-5862 の曝露量と有効性との関連性を評価した。曝露量－安全性解析では、種々の B 細胞性腫瘍患者（1 日投与量 100～400 mg のアカラブルチニブを投与された患者 573 例の併合データ、計 8 試験）を用いてアカラブルチニブ又は ACP-5862 の曝露量と臨床的に注目すべき有害事象との関連性を評価した。

アカラブルチニブの推奨用法・用量を 100 mg 1 日 2 回投与とした根拠を以下に示す。

- アカラブルチニブ及び ACP-5862 は BTK への共有結合により、R/R 又は未治療 CLL に対する薬力学的作用は長時間持続する。100 mg 1 日 2 回投与により、12 時間の投与間隔

を通してほぼ完全に BTK の占有が維持され、かつ個体間変動も小さかった（2.7.2.3.4.2.2 項参照）。

- B 細胞性腫瘍（MCL、FL、DLBCL、WM 及び MM 等）患者にアカラブルチニブ 100 mg を 1 日 2 回投与したとき、投与間隔を通してほぼ完全な BTK 占有が維持された。また、母集団薬物動態解析の結果、アカラブルチニブ及び ACP-5862 の体内動態は種々の B 細胞性腫瘍間で類似していた。したがって、アカラブルチニブ 100 mg を 1 日 2 回投与したときの曝露量－反応（有効性又は安全性）関係は異なる癌腫においても概ね同様であると予想される。
- 曝露量－反応解析の結果から、CLL 患者にアカラブルチニブ 100 mg を 1 日 2 回投与したとき、アカラブルチニブ又は ACP-5862 の曝露量（$AUC_{ss,(0-24)}$）と有効性の評価項目（BOR、PFS 及び腫瘍縮小効果、2.7.2.3.4.3.1 項参照）との間に関連性は認められなかった。これは、100 mg 1 日 2 回投与時の曝露量においてほぼ完全な BTK の占有が認められたことと一貫する結果であった。
- 8 試験で得られた安全性データ（有害事象）を併合して曝露量－反応解析を実施したところ、B 細胞性腫瘍患者にアカラブルチニブを 100～400 mg/日の用量範囲で投与したとき、アカラブルチニブ又は ACP-5862 の曝露量（$AUC_{ss,(0-24)}$）と特定の有害事象との間に臨床的に意義のある関連性は認められなかった（2.7.2.3.4.3.2 項参照）。
- アカラブルチニブ及び ACP-5862 の母集団薬物動態解析及び臨床薬理試験の結果から、治療ライン（R/R あるいは未治療）、癌腫（MCL あるいは CLL）、人口統計学的特性（年齢、体重、性別、民族、人種）又は内因性要因（軽度又は中等度腎機能障害、軽度又は中等度肝機能障害、ECOG PS）に応じた用量調節は不要であると判断した（2.7.2.2.1.7.3 項及び 2.7.2.3.2.1 項～2.7.2.3.2.7 項参照）。
- Simcyp を用いたアカラブルチニブ及び ACP-5862 の PBPK モデル解析の結果及び曝露量－安全性解析において顕著な関連性が認められなかったことから、曝露量の増加が予測される場合（CYP3A4 阻害作用を有す薬剤との併用等）を考慮しても、アカラブルチニブ 100 mg の 1 日 2 回投与は忍容性が良好な用量であることが予測された（2.7.2.3.3.7.5 項参照）。
- 有効性及び安全性を評価した主要な臨床試験において、CLL 患者にアカラブルチニブ 100 mg を 1 日 2 回投与したとき許容可能な安全性プロファイル及び頑健な有効性が認められた（2.7.2.3.4.2.2 項、2.7.2.3.4.3.1 項及び 2.7.2.3.4.3.2 項参照）。

以上のように、臨床薬理試験のデータパッケージから、アカラブルチニブ及び ACP-5862 の主な薬物動態学的及び薬力学的特性が明らかになった。非臨床薬物動態試験（*in vitro* 試験）及び臨床薬理試験から、アカラブルチニブの推奨用量、特定の背景を有する患者及び他剤を併用している患者に対する適切な用量を設定することが可能であった。薬物動態及び薬力学の観点から、CLL 患者に対するアカラブルチニブの推奨用法・用量は 100 mg 1 日 2 回投与と判断した。

2.7.2.4 特別な試験

特別な試験は実施していない。

2.7.2.5 付録

表 12　アカラブルチニブの薬物動態パラメータ：健康被験者を対象とした試験（ACE-HV-001 試験、ACE-HV-005 試験、ACE-HV-007 試験、ACE-HV-008 試験、ACE-HV-009 試験及び ACE-HV-111 試験）

Study No./Location	ACE-HV-001 / Module 5.3.3.1.1
Study Design	Single-center, open-label, sequential dose-escalation study of acalabrutinib in healthy subjects to evaluate safety, pharmacokinetics, pharmacodynamics, food effects, and drug-drug interactions
Subject type, N (M/F), age: mean (range)	Healthy; N=59 (36/23); 39.7 (19-59) Part 1: Cohort 1: n=6 (1/5); 41.2 (26-57) Cohort 2: n=6 (5/1); 40.8 (23-58) Cohort 3: n=6 (1/5); 44.8 (30-59) Cohort 4: n=6 (3/3); 39.8 (27-59) Cohort 5: n=6 (6/0); 43.8 (24-56) Part 2: Cohort 6: n=12 (6/6); 40.8 (26-56); Part 3: Cohort 7: n=17 (14/3); 34.7 (19-57)
Treatments (dosage, form, route, duration)	Acalabrutinib capsules, Escalating oral doses to fasting subjects; 2nd dose ≥ 2 hours after a meal and within 12 hours (± 5 minutes) after the first dose. Cohorts 1 to 4 received 2 doses (BID); Cohort 5 received a single 100 mg dose (QD) Cohort 1: acalabrutinib 2.5 mg dose BID (1 x 2.5-mg capsule); Cohort 2: acalabrutinib 5.0 mg dose BID (2 x 2.5-mg capsules) Cohort 3: acalabrutinib 25.0 mg dose BID (1 x 25.0 capsule); Cohort 4: acalabrutinib 50.0 mg dose BID (2 x 25.0 capsule): Cohort 5: acalabrutinib 100.0 mg dose QD (4 x 25.0 capsules) Cohort 6: acalabrutinib 75.0 mg dose QD (3 x 25.0 capsules) on Days 1 and 8; fasted or fed state Cohort 7: acalabrutinib 50.0 mg dose QD (2 x 25.0 capsules) on Days 1 and 9; and itraconazole (commercially available) 200 mg BID on Days 4 to 8 given with a standard meal and Day 9 wherein a single dose was given in the morning and on a fasted state.

Arithmetic Mean Pharmacokinetic Parameters (CV%)

Dose (mg)	C_{max} (ng/mL)	t_{max}[a] (hr)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)	f_e (%)	CL_R (L/hr)
2.5 BID	3.55 (53.3)	0.500 (0.5, 13.0)	17.7 (30.3)	27.8 (10.5)	515 (38.5)	165 (8.2)	2.14 (34.8)	BLQ	ND
5 BID	5.75 (47.4)	1.00 (0.5, 1.50)	26.6 (37.9)	45.1 (28.9)	612 (67.6)	219 (26.5)	1.83 (43.3)	BLQ	ND
25 BID	125 (35.7)	0.500 (0.5, 14.0)	185 (33.6)	305 (20. 0)	287 (90.5)	169 (24.8)	1.06 (55.5)	0.378 (43.0)	0.635 (40.4)
50 BID	223 (44.1)	0.500 (0.5, 1.00)	311 (25.0)	501 (24.1)	270 (33.7)	211 (30.3)	0.884 (10.3)	0.464 (24.9)	0.983 (42.7)
100 QD	580 (25.8)	0.500 (0.5, 0.5)	632 (29.7)	633 (29.7)	233 (25.7)	170 (29.3)	0.965 (17.7)	0.596 (17.8)	1.02 (30.9)

$AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-24)}$=area under the concentration-time curve from time 0 to 24 hr postdose; BID=twice daily; BLQ=below the limit of quantification; CL/F=total body clearance after oral administration; CL_R=renal clearance; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s) ; hr=hour; M=male(s); N/n=number of subjects; ND=not determined; QD=once daily; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after administration.

[a] Presented as median (minimum, maximum)

Study No. / Location	ACE-HV-005 / Module 5.3.4.1.1
Study Design	Randomized, Double-Blind, Double-Dummy, Placebo- and Positive Controlled, 4 Way Crossover Study to Assess the Effect of Single-Dose acalabrutinib on the QTc Interval in Healthy Adult Subjects
Subject type, N (M/F), age: mean (range)	Healthy; N=48 (29/19); 45.7 (19-63) ABCD: n=12 (9/3); 41.8 (19-63) BDAC: n=12 (6/6); 48.5 (32/61) CADB: n=2 (5/7); 48.8 (35-60) DCBA: n=12 (9/3); 43.9 (26-58)
Treatments (dosage, form, route, duration)	Treatment A: oral single dose 100 mg acalabrutinib, Hour 0 after an overnight fast Treatment B: supratherapeutic oral single dose 400 mg acalabrutinib, fasted state Treatment C: oral single dose 400 mg moxifloxacin, fasted state Treatment D: placebo, fasted state

Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)

Dose	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$[b] (hr)	CL/F (L/hr)
A: 100 mg	0.7507 (0.50, 3.05)	465.87 (83.2)	677.48 (50.5)	662.53 (47.7)	2.6442 ± 2.7156	150.94 (47.7)
B: 400 mg	1.5006 (0.50, 4.00)	1672.3 (64.5)	3965.5 (60.4)	4652.9 (51.9)	3.5127 ± 2.6253	85.969 (51.9)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; CL/F=total body clearance following oral administration; C_{max}=maximum plasma concentration; F=female(s); M=male(s); N/n=number of subjects; t_{max}=time of C_{max}; $t_{½}$=terminal half-life.

[a] Presented as median (minimum, maximum)

[b] Presented as arithmetic mean ± standard deviation

Study No. / Location	ACE-HV-007 / Module 5.3.4.1.2								
Study Design	Single-center, open-label, single-treatment study to assess the Bruton Tyrosine Kinase occupancy of acalabrutinib after repeated-dose administration in healthy adult subjects under fasting conditions								
Subject type, N (M/F), age: mean (range)	Healthy: N=40 (25/15); 40.4 (20-61)								
Treatments (dosage, form, route, duration)	Acalabrutinib 15-mg capsule oral dose QD for 7 consecutive days								
Pharmacokinetic Parameters, Geometric Mean (Geom. CV%)									
Dose	Time point	C_{max}/ $C_{max,ss}$ (ng/mL)	t_{max} (hr)[b]	$AUC_{(0-4)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr /mL)	AUC (ng·hr /mL)	$t_{½}$ (hr)[a]	CL/F (L/hr)[a]	V_z/F (L)[a]
15 mg	Day 1	37.5 (81.3)	0.750 (0.499, 2.00)	52.61 (60.5)	54.90 (60.2)	57.81 (55.7)	1.033 ± 0.2915	297.6 ± 174.52	480 ± 440
	Day 7	38.33 (62.0)	0.526 (0.249, 1.50)	51.07 (43.8)	53.55 (44.0)	NC	0.981 ± 0.208	291 ± 118	NA

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-4)}$=area under the concentration-time curve from time 0 to 4 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve from time 0 to last quantifiable concentration; CL/F=total body clearance following oral administration; C_{max} ($C_{max,ss}$)=maximum plasma concentration (at steady state); F=female(s); M=male(s); N=number of subjects; NA=not applicable; NC=not calculated; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as arithmetic mean ± SD

[b] Presented as median (minimum, maximum)

Study No. / Location	ACE-HV-008 / Module 5.3.4.1.3							
Study Design	Single-center, open-label, fixed-sequence, 2-period study to evaluate the intrasubject and intersubject variability of acalabrutinib pharmacokinetics and pharmacodynamics in healthy adult subjects							
Subject type, No. (M/F), age: mean (range)	Healthy; N=40 (28/12); 48.1 (20-63)							
Treatments (dosage, form, route, duration)	Period 1: acalabrutinib 25 mg capsule, single oral dose; washout of 7 days between periods. Period 2: acalabrutinib 25 mg capsule, single oral dose:							
Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)								
Dose	Timepoint	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	t_{max} (hr)[b]	$t_{½}$ (hr)[a]	CL/F (L/hr)[a]	V_z/F (L)[a]
25 mg	Period 1	58.9 (121.5)	89.3 (70.3)	92.5 (66.7)	0.750 (0.50, 4.01)	1.26 ± 0.605	326 ± 229	608 ± 593
	Period 2	60.9 (136.3)	94.9 (66.3)	101.3 (59.3)	0.750 (0.50, 5.00)	1.29 ± 0.738	288 ± 180	593 ± 646

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-t)}$=area under the concentration-time curve from time 0 to last quantifiable concentration; CL/F=total body clearance following oral administration; C_{max}=maximum plasma concentration; F=female(s); M=male(s); N=number of subjects; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as arithmetic mean ± SD

[b] Presented as median (minimum, maximum)

Study No. / Location	ACE-HV-009 / Module 5.3.1.1.1
Study Design	Single-center, open-label, nonrandomized, 2-cohort absolute bioavailability, pharmacokinetics, excretion, and metabolism study of [^{14}C]ACP-196 (acalabrutinib) in healthy subjects
Subject type, No. (M/F), age: mean (range)	Healthy; N=14 (9/5); 41 Cohort 1: n=8 (5/3); 44; Cohort 2: n=6 (4/2); 38
Treatments (dosage, form, route, duration)	Cohort 1: single 100-mg oral capsule dose of acalabrutinib, immediately followed by 240 mL room temperature water in a fasted state. At 58 min postdose, subjects received a single microtracer (<10 µg; ≤1 µCi) IV dose of [^{14}C]acalabrutinib as a 5-mL IV push over 2 min. Cohort 2: single 100 mL dose of acalabrutinib, a 1 mg/mL oral solution containing a [^{14}C]acalabrutinib microtracer dose (<10 µg; ≤1 µCi), immediately followed by 2 x 50 mL vehicle (bottle rinse) and 40 mL room temperature water to total 240 mL in a fasted state.

Dose	Pharmacokinetic Parameters Geometric Mean (Geometric Mean CV%)												
Cohort 1	C_{max} (ng/mL)	t_{max}[a] (hr)	$AUC_{(0-t)}$ (ng·hr/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-72)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	V_z (L)	V_{ss} (L)	CL/F (L/hr)	$t_{½}$[b] (hr)	CL (L/hr)	F (%)
Plasma acalabrutinib	639 (53.8)	0.500 (0.500-0.750)	643 (39.7)	642 (35.9)	612 (35.7)	612 (35.7)	344 (36.2)	---	---	163 (35.7)	1.57 (0.600)	---	0.253 (14.3)
Plasma [^{14}C] acalabrutinib	510 (56.3)	0.0750 (0.0333-0.117)	201 (32.6)	199 (30.2)	199 (30.2)	199 (30.2)	---	98.0 (42.8)	34.2 (40.2)	---	1.78 (0.461)	39.4 (30.6)	---
Cohort 2	C_{max} (ng/mL)	t_{max}[a] (hr)	$AUC_{(0-t)}$ (ng·hr/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-168)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	V_z (L)	V_{ss} (L)	CL/F (L/hr)	$t_{½}$[b] (hr)	CL (L/hr)	F (%)
Plasma acalabrutinib	305 (44.0)	0.500 (0.500-0.517)	386 (39.2)	406 (36.6)	407 (36.6)	407 (36.6)	499 (36.1)	NA	NA	246 (36.6)	1.47 (0.452)	NA	NA
Total ^{14}C in plasma	1340 (34.4)	0.875 (0.750-2.00)	5930 (29.4)	4390 (29.4)	6250 (24.9)	6410 (25.1)	---	NA	NA	---	46.5 (21.8)	NA	NA
Total ^{14}C in whole blood	1060 (31.3)	0.750 (0.750-2.00)	11500 (27.1)	3760 (29.6)	1150 (27.1)	NC	---	NA	NA	---	NC	NA	NA

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-t)}$=area under the concentration-time curve from time 0 to last quantifiable concentration; $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-72)}$=area under the concentration-time curve from time 0 to 72 hr postdose; $AUC_{(0-168)}$=area under the concentration-time curve from time 0 to 168 hr postdose; CL=total body clearance; CL/F=total body clearance following oral administration; C_{max}=maximum plasma concentration; F=absolute bioavailability (F also female(s) in 'study type'); IV=intravenous; M=male(s); min=minutes; N/n=number of subjects; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_{ss}= volume of distribution at steady state; V_z=apparent volume of distribution; V_z/F=apparent volume of distribution after oral administration; NA=not applicable; NC=not calculated.

[a] Presented as median (minimum, maximum)

[b] Presented as arithmetic mean (SD)

Study No. / Location	ACE-HV-111 / Module 5.3.4.1.4
Study Design	Single-center, randomized, double-blind, placebo-controlled repeated-dose study to assess the PD/PK of acalabrutinib after repeated-dose administration in healthy adult subjects under fasting conditions
Subject type, No. (M/F), age: mean (range)	Healthy; N=48 (28/20); 43.6 (21-62) Cohort 1/Treatment A: n=20 (11/9); 46.2 (26-59) Cohort 2/Treatment B: n=20 (12/8); 41.4 (21-56) Placebo: n=8 (5/3); 42.6 (30-62)
Treatments (dosage, form, route, duration)	Cohort 1: Acalabrutinib 30 mg dose (2 x 15-mg capsules) or placebo orally QD for 14 days, fasted state Cohort 2: Acalabrutinib 15 mg dose (1 x 15-mg capsules) or placebo orally twice daily (12 hr [± 5 minutes] apart) for 14 days, fasted state

Pharmacokinetic Parameters Geometric Mean (Geometric Mean (CV%)

Cohort 1: 30 mg QD	Day 1	C_{max} (ng/mL)	t_{max}[a] (hr)	$AUC_{(0-4)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
		160.5 (37.1)	0.502 (0.25, 3.00)	174.3 (35.7)	181.4 (36.2)	184.4 (35.7)	210.2 (40.5)	162.7 (35.7)	0.8958 (16.4)
	Day 14	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$[a] (hr)	$AUC_{(0-4)}$ (ng·hr/mL)	C_{avg} (ng/mL)	C_{min} (ng/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
		95.32 (119.7)	0.503 (0.50, 5.00)	125.8 (75.7)	8.262 (32.4)	1.679 (38.6)	NC	NC	0.997 (52.1)
Cohort 2: 15 mg BID	Day 1	C_{max} (ng/mL)	t_{max}[a] (hr)	$AUC_{(0-4)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
		49.97 (94.2)	0.502 (0.50, 4.02)	63.69 (68.0)	67.07 (58.6)	75.48 (40.0)	265.0 (47.0)	198.7 (40.0)	0.9245 11.0)
	Day 14	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$[a] (hr)	$AUC_{(0-4)}$ (ng·hr/mL)	C_{avg} (ng/mL)	C_{min} (ng/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
		38.05 (76.6)	0.750 (0.50, 2.01)	55.08 (54.6)	NC	1.555 (31.1)	NC	NC	0.968 (23.1)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-4)}$=area under the concentration-time curve from time 0 to 4 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve from time 0 to last quantifiable concentration; AUC_{τ}=area under the concentration-time curve during one dosing interval; BID=twice daily; C_{avg}=average plasma concentration over one doing interval; CL/F=total body clearance following oral administration; C_{max} ($C_{max,ss}$)=maximum plasma concentration (at steady state); C_{min}=minimum plasma concentration; F=female(s); M=male(s); N/n=number of subjects; NC=value missing or not reportable; QD=once daily; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

表 13　　アカラブルチニブの薬物動態パラメータ：B 細胞性腫瘍患者を対象とした試験（D8220C00001 試験、ACE-CL-001 試験、ACE-CL-003 試験、ACE-CL-007 試験、ACE-LY-002 試験、ACE-LY-003 試験、ACE-LY-004 試験、ACE-MY-001 試験及び ACE-WM-001 試験）

Study No. / Location		D8220C00001 / Module 5.3.5.2.9							
Study Design		A multicentre, open-label Phase 1 study to assess the safety, tolerability, pharmacokinetics and anti tumour activity of acalabrutinib in Japanese adult patients with advanced B-cell malignancies. This study was divided into 3 parts: Part 1 (dose-confirmation phase), Part 2 (dose-expansion phase) and Part 3 (dose-confirmation phase for combination therapy). This table mentions only Part 1.							
Subject type		Japanese adult patients with advanced B-cell malignancies who met all of the inclusion and none of the exclusion criteria. The study population included patients with non germinal centre B-cell-like (non-GCB) diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), MCL, CLL/SLL and Waldenström macroglobulinemia (WM).							
Treatments (dosage, form, route, duration)		Part 1: Acalabrutinib 100 mg (1 x 100 mg capsule) single dose was given to patients on Day 1, followed by a washout period of 2 days up to 7 days, and then 100 mg oral BID dosing.							
Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean) (Part 1 only)									
Acalabrutinib Dose	Timepoint (n*)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$ (hr) [b]	CL/F (L/hr) [b]	V_z/F (L) [b]
100 mg single dose	Day 1 (n = 6)	0.735 (0.520, 1.020)	601.9 (173.8)	890.7 (95.4)	961.7 (79.2)	1109 (55.1)	9.359 ± 12.46	99.54 ± 44.33	1940 ± 2903
100 mg BID dose	Day 8 (n = 6)	0.615 (0.470, 1.000)	1120 (29.7)	1208 (25.3)	1206 (25.3)	1211 (25.3)	1.795 ± 0.7404	84.89 ± 19.84	219.7 ± 107.1

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; n=number of subjects; NA=not applicable; ND=not determined; QD=once daily; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

[b] Presented as arithmetic mean ± SD

Study No. / Location	ACE-CL-001 / Module 5.3.5.2.2								
Study Design	Phase 1/2, multicenter, open-label, nonrandomized, sequential group, dose escalation study of acalabrutinib (ACP-196) in subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia								
Subject type	Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (Cohorts 7 and 11: treatment naive subjects); Cohort 8: Ibrutinib Intolerant subjects; Cohort 9: Richter's or Prolymphocytic Leukemia Transformation subjects; and Cohort 10: Ibrutinib Refractory/Relapsed subjects); NA (ongoing study)								
Treatments (dosage, form, route, duration)	Phase 1: Acalabrutinib 100 to 400 mg QD (Cohorts 1, 2a[a], 2c[b], 3[a], and 4a); acalabrutinib 100 or 200 mg BID (Cohorts 2b and 4b) Phase 2: Acalabrutinib 200 mg QD (Cohort 7[b]); acalabrutinib 100 or 200 mg BID (Cohorts 8[c], 9, 10, and 11) Administered orally in 28-day cycles until disease progression or unacceptable drug related toxicity								
Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)									
Acalabrutinib Dose	Timepoint (n*)	t_{max} (hr)[d]	C_{max} (ng/mL)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$ (hr)	CL/F (L/hr)	V_z/F (L)
Cohort 1: Acalabrutinib 100 mg QD	C1:D1 (n = 8)	1.01 (0.417, 2.00)	562 (75.4)	856 (56.0)	934 (47.4)	948 (47.1)	1.16 (70.9)	105 (47.1)	176 (110)
	C1:D8 (n = 5-7)	1.05 (0.500, 1.17)	431 (83.5)	601 (38.3)	657 (51.4)	596 (33.8)	1.08 (20.2)	168 (33.8)	261 (48.0)
Cohort 2a[a]: Acalabrutinib 175 mg QD	C1:D1 (n = 7–8)	0.917 (0.500, 3.83)	550 (119)	973 (97.3)	1070 (70.3)	1090 (76.1)	1.07 (80.9)	160 (76.1)	247 (192)
	C1:D8 (n = 6-7)	0.517 (0.467, 1.00)	582 (110)	968 (77.8)	967 (77.9)	985 (77.0)	0.936 (11.6)	178 (77.0)	240 (85.0)
Cohort 2b: Acalabrutinib 100 mg BID	C1:D1 (n = 22 – 28)	0.750 (0.500, 2.30)	485 (155)	659 (90.1)	625 (94.8)	688 (88.1)	0.853 (34.5)	145 (88.1)	179 (133)
	C1:D8 (n = 22 – 28)	0.750 (0.450, 5.75)	458 (208)	734 (73.6)	636 (104)	784 (74.8)	0.913 (36.4)	128 (74.8)	168 (117)
Cohort 2c[b]: Acalabrutinib 200 mg QD	C1:D1 (n = 11-13)	1.0 (0.250, 5.92)	1240 (216)	1630 (129)	1950 (74.6)	2170 (62.2)	0.954 (30.2)	92.1 (62.2)	127 (88.8)
	C1:D8 (n = 9 – 13)	1.03 (0.500, 2.10)	1110 (77.7)	1560 (41.3)	1680 (49.7)	1800 (49.9)	0.885 (20.8)	111 (49.9)	142 (60.7)
Cohort 3[a]: Acalabrutinib 250 mg QD	C1:D1 (n = 6-7)	1.00 (0.500, 1.83)	771 (232)	1100 (201)	1390 (137)	1440 (129)	1.85 (124)	174 (129)	463 (601)
	C1:D8 (n = 4-7)	1.00 (0.500, 1.97)	956 (146)	1680 (37.0)	1720 (72.2)	2130 (55.3)	0.878 (15.6)	117 (55.3)	149 (62.5)
Cohort 4a: Acalabrutinib 400 mg QD	C1:D1 (n = 5-6)	1.00 (0.750, 4.00)	976 (216)	2320 (119)	2920 (80.4)	2830 (71.3)	1.84 (176)	141 (71.3)	374 (396)
	C1:D8 (n = 5-6)	0.700 (0.500, 1.95)	657 (129)	1330 (88.4)	1460 (82.5)	1440 (84.4)	1.29 (43.7)	279 (84.4)	517 (113)

Study No. / Location		ACE-CL-001 / Module 5.3.5.2.2							
Cohort 4b: Acalabrutinib 200 mg BID	C1:D1 (n = 6)	0.758 (0.250, 1.08)	1580 (19.2)	1890 (27.8)	1890 (27.9)	1910 (27.9)	0.865 (9.63)	105 (27.9)	131 (22.2)
	C1:D8 (n = 4-6)	0.758 (0.500, 2.07)	826 (140)	1370 (93.1)	1290 (82.9)	1410 (105)	1.08 (38.5)	142 (105)	220 (185)
Cohort 7[b]: Acalabrutinib 200 mg QD	C1:D1 (n = 32-37)	0.783 (0.250, 2.10)	729 (243)	1020 (187)	1180 (144)	1260 (148)	1.05 (70.4)	159 (148)	241 (321)
	C1:D8 (n = 29-37)	0.642 (0.250, 2.22)	666 (183)	1050 (145)	1020 (131)	1160 (121)	0.964 (30.6)	173 (121)	240 (168)
Cohort 8[c]: Acalabrutinib 200 mg QD	C1:D1 (n = 3)	1.30 (0.750, 2.20)	128 (170)	322 (62.9)	532 (19.0)	571 (12.9)	3.27 (202)	351 (12.9)	1650 (247)
	C1:D8 (n = 1-2)	1.49 (1.08, 1.90)	376 (ND)	2080 (ND)	756 (ND)	2120 (ND)	0.914 (ND)	94.5 (ND)	125 (ND)
Cohort 8[c]: Acalabrutinib 100 mg BID	C1:D1 (n = 5-8)	0.783 (0.500, 5.83)	265 (356)	470 (157)	381 (154)	719 (56.8)	0.892 (15.0)	278 (56.8)	358 (69.6)
	C1: D8 (n = 6-8)	0.908 (0.467, 2.03)	320 (223)	617 (102)	519 (115)	757 (90.5)	1.18 (39.7)	264 (90.5)	449 (150)
Cohort 9: Acalabrutinib 200 mg BID	C1:D1 (n = 5-10)	0.992 (0.500, 4.05)	849 (119)	1500 (63.2)	1430 (84.6)	1600 (56.8)	0.793 (12.6)	125 (56.8)	143 (68.6)
	C1:D8 (n = 6-9)	1.00 (0.500, 2.08)	1220 (73.5)	1700 (51.4)	1600 (42.0)	1630 (42.4)	0.834 (28.8)	123 (42.4)	148 (68.6)
Cohort 10: Acalabrutinib 200 mg BID	C1:D1 (n = 4-5)	1.00 (0.500, 1.08)	526 (159)	898 (98.8)	897 (98.8)	1310 (27.3)	0.998 (20.8)	152 (27.3)	219 (44.0)
	C1:D8 (n = 4-5)	1.58 (0.467, 4.08)	330 (213)	935 (106)	936 (107)	1370 (68.4)	1.35 (82.4)	146 (68.4)	284 (192)
Cohort 11: Acalabrutinib 100 mg BID	C1:D1 (n = 15-17)	0.750 (0.483, 2.00)	676 (129)	662 (78.3)	702 (81.6)	837 (56.1)	0.769 (18.6)	119 (56.1)	133 (66.9)
	C1:D8 (n = 14-16)	0.533 (0.250, 1.85)	529 (65.4)	576 (52.3)	598 (50.1)	591 (49.6)	0.794 (22.3)	169 (49.6)	194 (71.0)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; C=cycle; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; D=Day; F=female(s); M=male(s); n=number of subjects; NA=not applicable; ND=not determined; QD=once daily; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_z/F=apparent volume of distribution after oral administration.

[a] Protocol amendment 4 ([redacted], 20[redacted]) stated that subjects in Cohort 2a were changed to 200 mg QD (later changed to 100 mg BID) and subjects in Cohort 3 were changed to 100 mg BID.

[b] Protocol amendment 6 ([redacted], 20[redacted]) stated that subjects in Cohorts 2c and 7 were changed to 100 mg BID.

[c] Protocol amendment 3 ([redacted], 20[redacted]) added Cohort 8: 200 mg BID; Protocol amendment 4 ([redacted], 20[redacted]) changed dose for Cohort 8 to 100 mg BID

[d] Presented as median (minimum, maximum)

* Number of subjects varied for the pharmacokinetic parameters calculated

Study No. / Location	ACE-CL-003 / Module 5.3.5.2.3								
Study Design	A Phase 1b, Single-center, Open-label Study of ACP-196 in Subjects with Relapsed/Refractory (R/R) or Untreated Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma or Prolymphocytic Leukemia								
Subject type	Relapsed/Refractory (R/R) or Untreated Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma or Prolymphocytic Leukemia; NA (ongoing study)								
Treatments (dosage, form, route, duration)	Acalabrutinib 200 mg QD or 100 mg BID administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity								
Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)									
Dose	Timepoint (n)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
R/R Acalabrutinib 100 mg BID	Day 1 (n = 3)	0.52 (0.50, 1.9)	410 (10.1)	662 (32.7)	662 (32.7)	693 (33.9)	339 (57.3)	150 (31.2)	1.49 (28.3)
R/R Acalabrutinib 200 mg QD	Day 1 (n = 5)	1.0 (0.50, 2.1)	950 (70.2)	1900 (44.0)	1950 (49.3)	1980 (47.0)	147 (62.4)	108 (38.8)	0.893 (23.5)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-4)}$=area under the concentration-time curve from time 0 to 4 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; D=Day; F=female(s); M=male(s); n=number of subjects; NA=not applicable; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

Study No. / Location	ACE-CL-007 / Module 5.3.5.1.2					
Study Design	An Open-label, Phase 3 Study of ACP-196 in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Ongoing Subject Study					
Subject type	Previously Untreated Chronic Lymphocytic Leukemia; NA (ongoing study)					
Treatments (dosage, form, route, duration)	Acalabrutinib 100 mg BID administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity					
Acalabrutinib Population Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)						
Dose	Timepoint (n)	$C_{ss,max}$ (ng/mL)	$AUC_{ss,(0-24)}$ (ng·hr/mL)	$C_{ss,min}$ (ng/mL)	V_c/F (L)	CL/F (L/hr)
Acalabrutinib 100 mg BID + Obinutuzumab	Cycle 1, Cycle 2, Day 1 (n =134)	422.4 (43.6)	1733 (20.6)	4.01 (78.1)	48.5 (153.1)	130.3 (17.2)
Acalabrutinib 100 mg BID	Cycle 1, Cycle 2, Day 1 (n = 140)	424.8 (37.1)	1732 (18.8)	3.78 (63.1)	49.8 (128.2)	131.8 (14.8)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{24h,ss}$=area under the concentration-time curve estimated over 24 hr postdose; BID=twice daily; CL/F=apparent clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; n=number of subjects; NA=not applicable; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_c/F=apparent volume of distribution after oral administration.

The PK parameters are based on population PK analysis, estimated following administration of 100 mg BID across all subjects.

Study No. / Location	ACE-LY-002 / Module 5.3.5.2.4
Study Design	An Open-label, Phase 1b Study of acalabrutinib (ACP-196) in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma
Subject type	Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma; NA (ongoing study)
Treatments (dosage, form, route, duration)	Acalabrutinib 100 mg BID administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity

Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)

Dose	Timepoint (n*)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-4)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
Refractory Acalabrutinib 100 mg BID	Day 1 (n = 2-5)	2.00 (1.00, 2.08)	372 (109)	570 (87.0)	611 (82.1)	726 (11.7)	216 (76.1)	138 (11.7)	1.09 (60.6)
	Day 8 (n = 4-5)	0.500 (0.500, 1.00)	518 (137)	702 (78.3)	756 (70.9)	917 62.2)	142 (66.3)	109 (62.2)	0.901 (10.8)
Relapsed Acalabrutinib 100 mg BID	Day 1 (n = 5-8)	1.00 (0.467, 1.00)	452 (255)	570 (266)	751 (197)	1520 (83.0)	107 (68.1)	65.7 (83.0)	1.13 (40.1)
	Day 8 (n = 5-9)	1.01 (0.467, 4.08)	381 (142)	599 (136)	727 (131)	718 (106)	222 (121)	139 (106)	1.11 (12.0)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-4)}$=area under the concentration-time curve from time 0 to 4 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; D=Day; F=female(s); M=male(s); n=number of subjects; NA=not applicable; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

* Number of subjects varied for the pharmacokinetic parameters calculated

Study No. / Location	ACE-LY-003 / Module 5.3.5.2.5
Study Design	An Open-label, Phase 1b Study of Acalabrutinib Alone or in Combination with Rituximab in Subjects with Follicular Lymphoma
Subject type	Follicular Lymphoma; NA (ongoing study)
Treatments (dosage, form, route, duration)	R/R cohort, Arm 1: Acalabrutinib 100 mg BID R/R cohort, Arm 2: Acalabrutinib 100 mg BID + rituximab 375 mg/m^2 IV (Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 to 6) TN cohort, Arm 2: Acalabrutinib 100 mg BID + rituximab 375 mg/m^2 IV (Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2 to 6) Acalabrutinib administered orally in 28-day cycles until disease progression or unacceptable drug related toxicity

Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)

Dose	Timepoint (n*)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
R/R Cohort, Arm 1: Acalabrutinib 100 mg BID	Day 1 (n = 6-8)	0.875 (0.333, 2.08)	315 (188)	580 (126)	566 (113)	675 (128)	233 (208)	148 (128)	1.09 (37.6)
	Day 8 (n = 5-9)	0.950 (0.383, 4.00)	407 (99.3)	622 (51.1)	624 (50.9)	783 (49.2)	172 (61.4)	128 (49.2)	0.933 (15.7)
R/R Cohort, Arm 2: Acalabrutinib 100 mg BID	Day 1 (n = 9-11)	0.750 (0.450, 6.00)	344 (137)	545 (78.4)	546 (78.1)	710 (50.4)	209 (72.5)	141 (50.4)	1.03 (37.0)
	Day 8 (n = 7-11)	0.833 (0.00, 3.67)	462 (105)	670 (75.8)	669 (68.8)	822 (67.1)	180 (88.5)	122 (67.1)	1.03 (21.7)
TN Cohort, Arm 2: Acalabrutinib 100 mg BID	Day 1 (n = 7-11)	1.00 (0.483, 2.08)	405 (120)	577 (45.9)	558 (48.7)	663 (30.3)	209 (54.9)	151 (30.3)	0.958 (36.6)
	Day 8 (n = 7-9)	1.00 (0.50, 3.83)	252 (152)	438 (72.0)	444 (71.9)	451 (62.0)	397 (85.1)	222 (62.0)	1.24 (42.5)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); IV=intravenous; M=male(s); n=number of subjects; NA=not applicable; R/R=relapsed/refractory; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; TN=treatment-naive; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum).

* Number of subjects varied for the pharmacokinetic parameters calculated.

Study No. / Location	ACE-LY-004 / Module 5.3.5.2.6								
Study Design	Open-label, Phase 2 Study of Acalabrutinib in Subjects with Mantle Cell Lymphoma								
Subject type	Mantle Cell Lymphoma; NA (ongoing study)								
Treatments (dosage, form, route, duration)	Cohort 1: Acalabrutinib 100 mg BID, Bortezomib naive subjects Cohort 2: Acalabrutinib 100 mg BID, Bortezomib exposed subjects Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity								
Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)									
Dose	Timepoint (n*)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
Cohort 1: Acalabrutinib 100 mg BID	Day 1 (n=19-24)	0.750 (0.500, 3.95)	574 (86.0)	840 (50.9)	765 (55.9)	885 (50.7)	156 (54.0)	113 (50.7)	0.956 (23.3)
	Day 8 (n=19-21)	0.667 (0.417, 2.00)	583 (102)	748 (54.1)	748 (54.1)	842 (45.3)	171 (80.1)	119 (45.3)	1.00 (41.3)
Cohort 2: Acalabrutinib 100 mg BID	Day 1 (n=15-20)	0.750 (0.500, 2.02)	467 (168)	823 (72.8)	734 (96.7)	974 (62.5)	171 (85.4)	103 (62.5)	1.15 (57.9)
	Day 8 (n=16-18)	0.750 (0.483, 1.08)	620 (93.4)	912 (65.2)	909 (64.9)	935 (63.6)	151 (79.0)	107 (63.6)	0.977 (23.1)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); M=male(s); n=number of subjects; NA=not applicable; $t_{½}$=terminal half-life; ; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum).

* Number of subjects varied for the pharmacokinetic parameters calculated.

Study No. / Location	ACE-MY-001 / Module 5.3.5.2.7								
Study Design	Open-label, Phase 1b Study of Acalabrutinib in Subjects with Multiple Myeloma								
Subject type	Multiple Myeloma; NA (ongoing study)								
Treatments (dosage, form, route, duration)	Cohort 1: Acalabrutinib 100 mg BID orally Cohort 2: Acalabrutinib 100 mg BID orally + dexamethasone 40 mg once weekly Treatment administered in 28-day cycles until disease progression or unacceptable drug related toxicity								
Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)									
Dose	Timepoint (n)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-4)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
Cohort 1: Acalabrutinib 100 mg BID	Day 1 (n=12)[b]	0.908 (0.483, 2.05)	524 (112)	604 (72.9)	638 (69.5)	754 (67.8)	186 (104)	133 (68.7)	0.967 (35.9)
	Day 22 (n=9)[c]	0.750 (0.250, 2.03)	271 (103)	390 (105)	423 (102)	411 (111)	404 (181)	245 (113)	1.14 (34.3)
Cohort 2: Acalabrutinib 100 mg BID + dexamethasone 40 mg	Day 1 (n=12)[b]	1.01 (0.500, 2.05)	437 (91.5)	621 (64.0)	675 (56.9)	732 (63.0)	209 (83.3)	137 (63.4)	1.05 (34.5)
	Day 22 (n=8)[d]	0.783 (0.583, 2.00)	607 (90.8)	766 (60.5)	812 (58.3)	826 (62.6)	155 (74.6)	121 (62.6)	0.887 (19.3)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-4)}$=area under the concentration-time curve from time 0 to 4 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); M=male(s); n=number of subjects; NA=not applicable; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

[b] λz could not be estimated in 3 subjects

[c] λz could not be estimated in 2 subjects

[d] λz could not be estimated in 1 subject

Study No. / Location	ACE-WM-001 / Module 5.3.5.2.8
Study Design	Open-label, Phase 1b/2 Study of Acalabrutinib in Subjects with Waldenström Macroglobulinemia
Subject type	Waldenström Macroglobulinemia; NA (ongoing study)
Treatments (dosage, form, route, duration)	Cohort 1: subjects with previously untreated Waldenström Macroglobulinemia Cohort 2: subjects with relapsed or refractory Waldenström Macroglobulinemia A small number of subjects were started on an acalabrutinib 200 mg QD treatment schedule, the dose was amended to a 100 mg BID treatment schedule Administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity

Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)

Acalabrutinib Dose	Timepoint (n*)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-4)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$ (hr)	V_z/F (L)	CL/F (L/hr)
Cohort 1: 200 mg QD	Day 1 (n = 1)	0.750	806	1280	1340	1370	0.923	195	146
	Day 8 (n = 1)	2.0	487	1090	1160	ND	ND	ND	ND
Cohort 2: 200 mg QD	Day 1 (n = 4-5)	0.750 (0.733, 1.00)	686 (58.2)	1100 (39.6)	1200 (37.3)	1250 (43.0)	0.824 (12.0)	190 (32.7)	160 (43.0)
	Day 8 (n = 4-5)	0.750 (0.417, 1.00)	344 (503)	550 (323)	587 (293)	514 (355)	1.01 (41.0)	567 (704)	389 (355)
Cohort 1: 100 mg BID	Day 1 (n = 8-12)	0.617 (0.500, 2.00)	296 (187)	423 (114)	470 (106)	545 (137)	0.985 (31.4)	261 (194)	184 (137)
	Day 8 (n = 8-10)	0.833 (0.417, 2.02)	467 (105)	586 (52.8)	625 (49.1)	683 (52.5)	0.896 (22.9)	189 (50.4)	146 (52.5)
Cohort 2: 100 mg BID	Day 1 (n = 29-33)	0.750 (0.500, 2.00)	452 (97.4)	559 (66.5)	586 (63.9)	629 (60.3)	0.872 (14.4)	200 (62.8)	159 (60.3)
	Day 8 (n = 27-31)	0.750 (0.417, 2.25)	366 (114)	463 (77.6)	495 (73.2)	517 (76.5)	0.983 (22.3)	274 (101)	193 (76.5)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-4)}$=area under the concentration-time curve from time 0 to 4 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; n=number of subjects; NA=not applicable; ND=not determined; QD=once daily; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

* Number of subjects varied for the pharmacokinetic parameters calculated

表 14　　アカラブルチニブの薬物動態パラメータ：アカラブルチニブの体内動態に及ぼす内因性の要因による影響を評価した試験（ACE-HI-001 試験、ACE-HI-102 試験及び ACE-HV-113 試験）

Study No. / Location	ACE-HI-001 / Module 5.3.3.3.1
Study Design	A 2-part, non-randomized, open label, single-dose study to investigate the influence of hepatic insufficiency on the pharmacokinetics of ACP-196. Part 1 of the study compared the pharmacokinetics of ACP-196 in subjects with mild and moderate hepatic insufficiency (based on the Child-Pugh classification) to healthy (mean) matched control subjects for age and weight. Part 2 of the study was to compare the pharmacokinetics of ACP-196 in subjects with severe hepatic insufficiency to the healthy control subjects from Part 1.
Subject type, N (M/F), age: mean (range)	Overall: N=18 (8/10); 56.2 (25-68) Group A, Mild Hepatic Insufficiency: n=6 (2/4); 50.5 (25-66) Group B, Moderate hepatic Insufficiency: n=6 (3/3); 58.8 (53-68) Group N, Normal Hepatic Function: n=6 (3/3); 59.2 (54-64)
Treatments (dosage, form, route, duration)	Single dose of acalabrutinib 50 mg (2 x 25-mg capsules) administered orally with approximately 240 mL of water on the morning of Day 1, at Hour 0, following an overnight fast.

Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)

Dose	C_{max} (ng/mL)	t_{max} (hr)[a]	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	$t_{½}$ (hr)[b]	λ_z (1/hr)[b]	CL/F (L/hr)[b]	V_z/F (L)[b]
Group A: 50 mg	292 (51.2)	0.750 (0.50, 1.50)	362 (61.6)	366 (61.2)	NA	2.25 ± 0.873	0.343 ± 0.118	157 ± 91.1	471 ± 222
Group B: 50 mg	156 (247)	1.00 (0.50, 3.00)	310 (191)	326 (178)	518 (NA)[c]	7.92 ± 12.7	0.312 ± 0.300	281 ± 373	2135 ± 2715
Group N[d]: 50 mg	159 (180)	0.50 (0.25, 1.00)	206 (102)	293 (16.7)	NA	2.24 ± 0.470	0.321 ± 0.0699	172 ± 26.5	545 ± 65.1

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-24)}$=area under the concentration-time curve from time 0 to 24 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); λ_z=elimination rate constant; M=male(s); N/n=number of subjects; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

[b] Presented as arithmetic mean ± standard deviation

[c] N = 1 for $AUC_{(0-24)}$ in Group B

[d] N = 5 for AUC, $t_{½}$, λ_z, CL/F, and V_z/F in Group N

Study No. / Location	ACE-HI-102 / Module 5.3.3.3.2
Study Design	A non-randomized, open label, single-dose study to investigate the influence of severe hepatic impairment on the pharmacokinetics of acalabrutinib and ACP-5862. The study compared the pharmacokinetics of acalabrutinib and ACP-5862 in subjects with severe hepatic insufficiency (based on the Child-Pugh classification) to healthy (mean) matched control subjects for age, gender, and weight.
Subject type, N (M/F), age: mean (range)	Overall: N=16 (14/2); 57.4 (47-69) Group A, Severe Hepatic Insufficiency: n=8 (7/1); 57.6 (47-69) Group N, Normal Hepatic Function: n=8 (7/1); 57.1 (53-65)
Treatments (dosage, form, route, duration)	Single dose of acalabrutinib 50 mg (2 x 25-mg capsules) administered orally with approximately 240 mL of water on the morning of Day 1, at Hour 0, following an overnight fast.

Acalabrutinib Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)

Dose	C_{max} (ng/mL)	t_{max} (hr)[a]	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	$t_{½}$ (hr)[b]	λ_z (1/hr)[b]	CL/F (L/hr)[b]	V_z/F (L)[b]
Group A: 50 mg	726.0 (56.2)	0.500 (0.50, 1.00)	1161 (53.9)	1169 (53.8)	1167 (53.6)	2.70 ± 1.13	0.294 ± 0.106	48.7 ± 30.7	167 ± 70.3
Group N: 50 mg	147.7 (116.8)	0.750 (0.50, 3.00)	220.0 (57.3)	226.5 (55.1)	226.1 (55.3)	2.24 ± 1.02	0.370 ± 0.168	247 ± 124	834 ± 651

ACP-5862 Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)

Dose	C_{max} (ng/mL)	t_{max} (hr)[a]	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	$t_{½}$ (hr)[b,c]	λ_z (1/hr)[b,c]	CL/F (L/hr)[b]	V_z/F (L)[b]
Group A: 50 mg	169 (30.1)	0.75 (0.50, 2.00)	638 (19.3)	782 (21.9)	638 (19.3)	11.9 ± 4.11	0.067 ± 0.033	-	-
Group N: 50 mg	167 (74.7)	1.50 (0.75, 3.00)	700 (42.8)	817 (36.8)	705 (42.5)	10.7 ± 3.88	0.078 ± 0.046	-	-

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-24)}$=area under the concentration-time curve from time 0 to 24 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); λ_z=elimination rate constant; M=male(s); N/n=number of subjects; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

[b] Presented as arithmetic mean ± standard deviation

[c] N = 6 for $t_{½}$ λz and in Group A

Study No. / Location	ACE-HV-113 / Module 5.3.1.2.1									
Study Design	Single-center, open-label, fixed-sequence, 2-period study in healthy adult subjects to evaluate the effect of gastric pH on acalabrutinib pharmacokinetics									
Subject type, No. (M/F), age: mean (range)	Healthy; N=12 (8/4); 42.0 (18-58)									
Treatments (dosage, form, route, duration)	Period 1: 100 mg acalabrutinib (1 x 100 mg capsule) and 1 [redacted] capsule administered orally with approximately 240 mL of distilled water after an overnight fast Period 2: 100 mg acalabrutinib (1 x 100 mg capsule) and 1 [redacted] capsule administered orally with approximately 240 mL of distilled water after an overnight fast.									
Pharmacokinetic Parameters, Geometric Mean (Geom. CV%)										
Dose	Time point	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	V_z/F (L)	CL/F (L/hr)	$t_{½}$ (hr)
100 mg	Period 1	601.0 (52.6)	0.751 (0.50, 2.01)	720.8 (50.6)	735.5 (49.7)	733.8 (49.8)	738.1 (49.4)	362.6 (62.0)	135.5 (49.4)	1.855 (33.0)
	Period 2	408.2 (63.5)	0.750 (0.50, 2.00)	518.6 (59.6)	533.6 (56.7)	540.9 (54.4)	587.6 (51.9)	409.5 (93.1)	170.2 (51.9)	1.668 (54.6)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose; $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); M=male(s); N=number of subjects; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after oral administration.

[a] Presented as median (minimum, maximum)

表 15　　アカラブルチニブの薬物動態パラメータ：アカラブルチニブの体内動態に及ぼす外因性の要因による影響を評価した試験（ACE-HV-001 試験、ACE-HV-004 試験及び ACE-HV-112 試験）

Study No. / Location	ACE-HV-001 / Module 5.3.3.1.1
Study Design	Single-center, open-label, sequential dose-escalation study of ACP-196 in healthy subjects to evaluate safety, pharmacokinetics, pharmacodynamics, food effects, and drug-drug interactions
Subject type, No. (M/F), age: mean (range)	Healthy; N=59 (36/23); 39.7 (19-59) Part 1: Cohort 1: n=6 (1/5); 41.2 (26-57); Cohort 2: n=6 (5/1); 40.8 (23-58); Cohort 3: n=6 (1/5); 44.8 (30-59) Cohort 4: n=6 (3/3); 39.8 (27-59); Cohort 5: n=6 (6/0); 43.8 (24-56) Part 2: Cohort 6: n=12 (6/6); 40.8 (26-56) Part 3: Cohort 7: n=17 (14/3); 34.7 (19-57)
Treatments (dosage, form, route, duration)	Acalabrutinib capsules Escalating oral doses to fasting subjects; 2nd dose ≥ 2 hr after a meal and within 12 hr (± 5 minutes) after the first dose. Cohorts 1 to 4 received 2 doses (BID); Cohort 5 received a single 100 mg dose (QD) Cohort 1: 2.5 mg dose BID (1 x 2.5-mg capsule); Cohort 2: 5 mg dose BID (2 x 2.5-mg capsules); Cohort 3: 25 mg dose BID (1 x 25 mg capsule); Cohort 4: 50 mg dose BID (2 x 25 mg capsule); Cohort 5: 100 mg dose QD (4 x 25 mg capsules) Cohort 6: Single 75 mg dose (3 x 25 mg capsules) on Days 1 & 8; fasted or fed state Cohort 7: Single 50 mg doses (2 x 25 mg capsules) on Days 1 and 9; and itraconazole (commercially available) 200 mg BID on Days 4 to 8 given with a standard meal, and on Day 9 (single doses of itraconazole+ acalabrutinib were given in the morning in a fasted state).

Summary of Least Squares Mean analyses for fed and fasted acalabrutinib (ACP-196) pharmacokinetic parameters

Dose	Parameter	Fasted (LSM ± SE)	Fasted (Geo LSM)	Fed (LSM ± SE)	Fed (Geo LSM)	Ratio	90% Lower CI	90% Upper CI
Acala-brutinib 75 mg	$AUC_{(0-t)}$	6.12 ± 0.0655	453	6.05 ± 0.0655	423	93.5	79.0	111
	$AUC_{(0-24)}$	6.11 ± 0.0667	449	6.06 ± 0.0667	427	95.1	80.2	113
	AUC	6.14 ± 0.0616	464	6.07 ± 0.0616	431	92.9	79.3	109
	C_{max}	5.9 ± 0.108	364	4.72 ± 0.108	112	30.9	23.4	40.8

Acalabrutinib Pharmacokinetic Parameters (Fed and Fasted State)

Dose	C_{max} (ng/mL)[b]	t_{max} (hr)[a]	$AUC_{(0-t)}$ (ng·hr/mL)[b]	$AUC_{(0-12)}$ (ng·hr/mL)[b]	$AUC_{(0-24)}$ (ng·hr/mL)[b]	AUC (ng·hr/mL)[b]	λ_z (1/hr)[b]	$t_{½}$ (hr)[b]	CL/F (L/hr)[b]	V_z/F (L)[b]
75 mg acalabrutinib Fasted state										
Females	503 ± 292	0.500 (0.500, 1.00)	536 ± 265	NA	538 ± 265	538 ± 265	0.746 ± 0.0419	0.931 ± 0.0506	174 ± 93.5	234 ± 123
Males	404 ± 229	0.500 (0.500, 4.00)	441 ± 121	NA	437 ± 133	455 ± 104	0.575 ± 0.300	6.94 ± 14.4	172 ± 38.5	2120 ± 4590
75 mg acalabrutinib Fed state										

Study No. / Location	ACE-HV-001 / Module 5.3.3.1.1									
Females	102 ± 30.0	2.00 (1.50, 4.00)	381 ± 96.0	NA	388 ± 94.7	388 ± 94.7	0.518 ± 0.138	1.42 ± 0.378	204 ± 55.1	412 ± 134
Males	145 ± 62.8	3.00 (1.00, 6.00)	499 ± 143	NA	502 ± 151	507 ± 145	0.584 ± 0.258	1.92 ± 2.11	158 ± 40.9	498 ± 686

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-24)}$=area under the concentration-time curve from time 0 to 24 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; AUC_{extrap}=AUC extrapolated from the last quantifiable concentration to infinity; CL/F=total body clearance after oral administration; C_{max}=maximum plasma concentration; Geo=geometric; LSM=least squares mean; CV=coefficient of variation; F=female(s); λz=elimination rate constant; M=male(s); N/n=number of subjects; NA=not available; SE=standard error; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_z/F=apparent volume of distribution after administration.

[a] Presented as median (minimum, maximum)

[b] Presented as arithmetic mean ± standard deviation

Study No. / Location	ACE-HV-001 / Module 5.3.3.1.1
Study Design	Single-center, open-label, sequential dose-escalation study of acalabrutinib (ACP-196) in healthy subjects to evaluate safety, pharmacokinetics, pharmacodynamics, food effects, and drug-drug interactions
Subject type, No. (M/F), age: mean (range)	Healthy; N=59 (36/23); 39.7 (19-59) Part 1: Cohort 1: n=6 (1/5); 41.2 (26-57); Cohort 2: n=6 (5/1); 40.8 (23-58); Cohort 3: n=6 (1/5); 44.8 (30-59) Cohort 4: n=6 (3/3); 39.8 (27-59); Cohort 5: n=6 (6/0); 43.8 (24-56); Part 2: Cohort 6: n=12 (6/6); 40.8 (26-56) Part 3: Cohort 7: n=17 (14/3); 34.7 (19-57)
Treatments (dosage, form, route, duration)	Acalabrutinib (ACP-196) capsules Escalating oral doses to fasting subjects; 2nd dose ≥2 hr after a meal and within 12 hr (± 5 minutes) after the first dose. Cohorts 1 to 4 received 2 doses (BID); Cohort 5 received a single 100 mg dose (QD) Cohort 1: 2.5 mg dose BID (1 x 2.5-mg capsule); Cohort 2: 5.0 mg dose BID (2 x 2.5-mg capsules); Cohort 3: 25 mg dose BID (1 x 25 mg capsule); Cohort 4: 50 mg dose BID (2 x 25 mg capsules); Cohort 5: 100 mg dose QD (4 x 25 mg capsules) Cohort 6: Single 75 mg doses (3 x 25 mg capsules) on Days 1 and 8; in the fasted or fed state Cohort 7: Single 50 mg doses (2 x 25 mg capsules) on Days 1 and 9; and itraconazole (SPORANOX®) 200 mg BID on Days 4 to 8 given with a standard meal, and on Day 9 (single doses of itraconazole+ acalabrutinib were given am in a fasted state).

Summary of Least Squares Mean analyses for acalabrutinib pharmacokinetic parameters in the presence and absence of itraconazole

Dose	Parameter	Acalabrutinib LSM ± SE	Acalabrutinib Geo LSM	Acalabrutinib + itraconazole LSM ± SE	itraconazole Geo LSM	Ratio	90% Lower CI	90% Upper CI
Acalabrutinib 50 mg Itraconazole 200 mg BID	$AUC_{(0-t)}$	5.48 ± 0.105	241	7.12 ± 0.106	1240	514	455	580
	$AUC_{(0-24)}$	5.48 ± 0.104	239	7.13 ± 0.106	1240	520	460	589
	AUC	5.53 ± 0.100	252	7.13 ± 0.101	1250	497	438	564
	C_{max}	5.11 ± 0.198	166	6.47 ± 0.200	648	390	320	476

Acalabrutinib pharmacokinetic parameters in the presence and absence of itraconazole

Dose	C_{max} (ng/mL)[b]	t_{max} (hr)[a]	$AUC_{(0-t)}$ (ng·hr/mL)[b]	$AUC_{(0-12)}$ (ng·hr/mL)[b]	$AUC_{(0-24)}$ (ng·hr/mL)[b]	AUC (ng·hr/mL)[b]	λ_z (1/hr)[b]	$t_{½}$ (hr)[b]	CL/F (L/hr)[b]	V_z/F (L)[b]
Acalabrutinib 50 mg	210 ± 109	0.500 (0.500, 4.00)	262 ± 97.1	NA	259 ± 96.0	271 ± 99.6	0.583 ± 0.309	3.33 ± 5.25	217 ± 100	1190 ± 2070
Itraconazole 200 mg BID	776 ± 341	0.750 0.500, 3.00	1330 ± 446	NA	1330 ± 448	1340 ± 441	0.326 ± 0.0957	2.46 ± 1.27	43.9 ± 23.2	184 ± 218

am=in the morning; AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-12)}$=area under the concentration-time curve, from time 0 to 12 hr; $AUC_{(0-24)}$=area under the concentration-time curve, from time 0 to 24 hr; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice a day; CL/F=total body clearance following oral administration; F=female(s); Geo=geometric; : λ_z=elimination rate constant; LSM=least squares mean; M=male(s); n=number of subjects; NA=not available; SE=standard error; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_z/F=apparent volume of distribution after an oral dose

[a] Presented as median (minimum, maximum);

[b] Presented as arithmetic mean ± standard deviation

Study No. / Location	ACE-HV-004 / Module 5.3.3.4.1						
Study Design	Single-center, open-label, fixed-sequence 2 period, 3-part study to evaluate the one-way interaction of calcium carbonate, omeprazole, or rifampin on acalabrutinib (ACP 196) in healthy non-tobacco using adult subjects under fasting conditions						
Subject type, No. (M/F), age: mean (range)	Healthy; N=72 (50/22); 40.8 (18-62) Part 1: n=24 (18/6); 38.5 (18-61); Part 2: n=24 (16/8); 43.9 (22-62); Part 3: n=24 (16/8); 40.0 (18-58)						
Treatments (dosage, form, route, duration)	Part 1A: 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 after an overnight fast. Part 1B: 1 g calcium carbonate (2 x 500 mg chewable tablets) and 100 mg acalabrutinib (1 x 100 mg capsule) coadministered at Hour 0 on Day 1 after an overnight fast. Part 2C: 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 after an overnight fast. Part 2D: 40 mg omeprazole (1 x 40 mg capsule) administered at Hour 0 after an overnight fast q24hr for 5 days (within ± 1 hour of dosing time on Day 1), with 100 mg acalabrutinib (1 x 100 mg capsule) coadministered on Day 5. Part 3E: 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 after an overnight fast. Part 3F: 600 mg rifampin (2 x 300 mg capsules) administered at Hour 0 after an overnight fast q24hr for 9 days (within ± 1 hour of dosing time on Day 1), with 100 mg acalabrutinib (1 x 100 mg capsule) coadministered on Day 1 and Day 9.						
Summary of Least Square Mean Analyses of Acalabrutinib Alone and in Combination with Calcium Carbonate Pharmacokinetic Parameters							
Dose	Parameter	Part 1A Geometric LSM	Part 1B Geometric LSM	Geometric Mean Ratio (%)	90% Lower CI	90% Upper CI	Intrasubject CV%
1A: Acalabrutinib 100 mg 1B: Acalabrutinib + 1 g calcium carbonate	C_{max} (ng/mL)	237.4	60.33	25.41	17.05	37.89	93.27
	$AUC_{(0\text{-}t)}$ (ng·hr/mL)	386.1	182.5	47.28	36.05	62.01	57.88
	AUC (ng·hr/mL)	483.6	229.0	47.35	32.21	69.61	60.14
Summary of Least Square Mean Analyses of Acalabrutinib Alone and in Combination with Omeprazole Pharmacokinetic Parameters							
Dose	Parameter	Part 2C Geometric LSM	Part 2D Geometric LSM	Geometric Mean Ratio (%)	90% Lower CI	90% Upper CI	Intrasubject CV%
2C: Acalabrutinib 100 mg 2D: Acalabrutinib + 40 mg omeprazole	C_{max} (ng/mL)	382.7	80.81	21.12	11.27	39.56	194.93
	$AUC_{(0\text{-}t)}$ (ng·hr/mL)	512.0	221.6	43.29	29.61	63.27	88.03
	AUC (ng·hr/mL)	548.5	451.6	82.33	61.72	109.82	45.11
Summary of Least Square Mean Analyses of Acalabrutinib Alone and in Combination with Rifampin Pharmacokinetic Parameters							
Dose	Parameter	Part 3E Geometric LSM	Part 3F (Day 1) Geometric LSM	Geometric Mean Ratio (%)	90% Lower CI	90% Upper CI	Intrasubject CV%
3E (Day 1): Acalabrutinib 100 mg	C_{max} (ng/mL)	450.2	552.2	122.7	102.92	146.16	36.60
	$AUC_{(0\text{-}t)}$ (ng·hr/mL)	641.1	874.2	136.4	121.71	152.78	23.28

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3F (Day 1 Period 2): Acalabrutinib + 600 mg rifampin	AUC (ng·hr/mL)	772.8	993.0	128.5	117.88	140.07	16.73
			Part 3F (Day 9)				
3E (Day 1): as above 3F (Day 9 Period 2): as above	C_{max} (ng/mL)	450.2	142.0	31.54	23.63	42.11	63.8
	$AUC_{(0-t)}$ (ng·hr/mL)	641.1	150.1	23.41	19.09	28.72	43.1
	AUC (ng·hr/mL)	748.6	154.4	20.62	17.51	24.29	32.5

Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)

Dose	Time Point	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	t_{max} (hr)[a]	$AUC_{\%extrap}$ (%)[b]	λ_z (1/hr)[b]	$t_{½}$ (hr)[b]	CL/F (L/hr)[b]
Part 1										
1A: Acalabrutinib 100 mg	Day 1	237.4 (199.5)	NR[c]	386.1 (98.6)	483.6 (61.4)	0.751 (0.50, 2.00)	0.7620 ± 0.64176	0.4965 ± 0.21570	1.642 ± 0.68703	243.4 ± 161.85
1B: Acalabrutinib + calcium carbonate 1 g	Day 1	57.8 (253.9)	141.1 (88.0)	178 (112.3)	221.4 (124.1)	1.502 (0.50, 4.00)	5.654 ± 12.018	0.3854 ± 0.19504	4.067 ± 7.5365	689.2 ± 737.26
Part 2										
2C: Acalabrutinib 100 mg	Day 1	382.7 (112.5)	NR[c]	512.0 (74.0)	547.6 (66.3)	0.750 (0.50, 4.02)	0.9039 ± 1.4478	0.4847 ± 0.22750	1.849 ± 1.2892	226.2 ± 214.07
2D: Acalabrutinib + omeprazole 40 mg	Day 5	81.10 (382.6)	98.63 (41.4)	222.1 (111.7)	432.8 (59.3)	1.001 (0.50, 3.01)	1.602 ± 2.5192	0.4455 ± 0.29596	2.257 ± 1.4046	281.4 ± 264.24
Part 3										
3E: Acalabrutinib 100 mg	Day 1	450.2 (148.9)	NR[c]	641.1 (86.0)	772.8 (45.4)	0.882 (0.50, 3.02)	0.4380 ± 0.18143	0.4788 ± 0.14615	1.559 ± 0.39911	143.1 ± 76.719
3F: Rifampin 600 mg	Day 1	552.2 (106.2)	NR[c]	874.2 (62.5)	993.0 (40.4)	0.751 (0.50, 4.00)	0.3725 ± 0.19035	0.4611 ± 0.13821	1.660 ± 0.60994	108.0 ± 40.627
	Day 9	142 (90.4)		150 (56.2)	154 (50.6)	0.752 (0.49, 3.00)	2.51 ± 6.53	0.976 ± 0.246	0.834 ± 0.611	724 ± 372

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-24)}$=area under the concentration-time curve from time 0 to 24 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve from time 0 to last quantifiable concentration; $AUC_{\%extrap}$=% of AUC extrapolated from the last quantifiable concentration to infinity; CL/F=total body clearance following oral administration; Cmax=maximum plasma concentration; CV=coefficient of variation; F=female(s); λ_z=elimination rate constant; LSM=least square mean; M=males(s); NR=value missing or not reportable; q24hr=every 24 hr; SD=standard deviation; tmax=time of Cmax; t½=terminal half-life.

a Presented as median (minimum, maximum)

b Presented as arithmetic mean ± SD

c AUC(0-24) values were not reportable for all subjects.

Study No. / Location	ACE-HV-112 / Module 5.3.3.4.2
Study Design	Single-center, open-label, fixed-sequence, 4-period, 3-part study in healthy adult subjects to evaluate the effect of an acidic formulation of acalabrutinib (ACP-196), acidic beverage, or grapefruit juice on the pharmacokinetics of acalabrutinib alone and coadministered with omeprazole
Subject type, No. (M/F), age: mean (range)	Healthy; N=36 (30/6); 44.5 (22-65) Part 1: n=12 (9/3); 42.6 (22-65) Part 2: n=12 (10/2); 46.8 (26-65) Part 3: n-12 (11/1); 44.3 (24-64)
Treatments (dosage, form, route, duration)	Part 1 (acidic formulation): Treatment 1A: Acalabrutinib 100 mg capsule reference formulation with 240 mL of water on Day 1 Treatment 1B: Acalabrutinib 100 mg capsule acidic formulation with 240 mL of water on Day 3 Treatment 1C: 40 mg of omeprazole plus acalabrutinib 100 mg capsule reference formulation with 240 mL of water on Day 8 Treatment 1D: 40 mg of omeprazole plus acalabrutinib 100 mg capsule acidic formulation with 240 mL of water on Day 10 Note: Omeprazole (1 x 40 mg capsule) alone was administered on Days 4 to 7 and Day 9. Part 2 (acidic beverage - orange drink): Treatment 2A: Acalabrutinib 100 mg capsule reference formulation with 240 mL of water on Day 1 Treatment 2B: Acalabrutinib 100 mg capsule reference formulation with 240 mL of acidic beverage on Day 3 Treatment 2C: 40 mg of omeprazole plus acalabrutinib 100 mg capsule reference formulation with 240 mL of water on Day 8 Treatment 2D: 40 mg of omeprazole plus acalabrutinib 100 mg capsule reference formulation with 240 mL of acidic beverage on Day 10 Note: Omeprazole (1 x 40 mg capsule) alone was administered on Days 4 to 7 and Day 9. Part 3 (grapefruit juice): Treatment 3A: Acalabrutinib 100 mg capsule reference formulation with 240 mL of water on Day 1 Treatment 3B: Acalabrutinib 100 mg capsule reference formulation with 240 mL of grapefruit juice on Day 3 Treatment 3C: 40 mg of omeprazole plus acalabrutinib 100 mg capsule reference formulation with 240 mL of water on Day 8 Treatment 3D: 40 mg of omeprazole plus acalabrutinib 100 mg capsule reference formulation with 240 mL of grapefruit juice on Day 10 Note: Omeprazole (1 x 40 mg capsule) alone was administered on Days 4 to 7 and Day 9. For all 3 parts of the study, omeprazole 40 mg QD was administered with 240 mL of water on Days 4 to 7, and according to the study schema on Days 8 to 10. Note: Subjects in Part 3 only drank 240 mL grapefruit juice on Day 2 approximately 12 hr before the Day 3 acalabrutinib dose and on Day 9 approximately 12 hr before the Day 10 acalabrutinib dose.

Summary of Least Square Mean Analyses of Acalabrutinib Pharmacokinetic Parameters

Dose	Parameter	Test Geometric LSM	Reference Geometric LSM	Geometric Mean Ratio (%)	90% Lower CI	90% Upper CI	Intrasubject CV%
Part 1							

Study No. / Location		ACE-HV-112 / Module 5.3.3.4.2					
1B vs 1A	C_{max} (ng/mL)	541.37	621.92	87.05	56.07	135.14	70.70
1C vs 1A		164.98	621.92	26.53	17.09	41.18	70.70
1D vs 1A		464.61	621.92	74.71	48.12	115.98	70.70
1D vs 1B		464.61	541.37	85.82	55.28	133.24	70.70
1D vs 1C		464.61	164.98	281.62	181.39	437.21	70.70
1B vs 1A	$AUC_{(0-t)}$ (ng·hr/mL)	593.15	750.61	79.02	67.28	92.81	23.60
1C vs 1A		434.14	750.61	57.84	49.24	67.93	23.60
1D vs 1A		569.15	750.61	75.83	64.56	89.06	23.60
1D vs 1B		569.15	593.15	95.95	81.70	112.70	23.60
1D vs 1C		569.15	434.14	131.10	111.62	153.98	23.60
1B vs 1A	AUC (ng·hr/mL)	596.75	755.73	78.96	68.01	91.68	21.87
1C vs 1A		489.32	755.73	64.75	55.76	75.18	21.87
1D vs 1A		576.11	755.73	76.23	65.66	88.51	21.87
1D vs 1B		576.11	596.75	96.54	83.15	112.09	21.87
1D vs 1C		576.11	489.32	117.74	101.40	136.71	21.87
Part 2							
2B vs 2A	C_{max} (ng/mL)	296.34	679.78	43.59	25.46	74.65	91.30
2C vs 2A		162.55	679.78	23.91	13.96	40.95	91.30
2D vs 2A		196.89	679.78	28.96	16.91	49.60	91.30
2D vs 2B		196.89	296.34	66.44	38.80	113.78	91.30
2D vs 2C		196.89	162.55	121.13	70.73	207.43	91.30
2B vs 2A	$AUC_{(0-t)}$ (ng·hr/mL)	451.96	753.80	59.56	49.69	72.34	27.69
2C vs 2A		385.10	753.80	51.09	42.34	61.64	27.69
2D vs 2A		404.22	753.80	53.62	44.44	64.70	27.69
2D vs 2B		404.22	451.96	89.44	74.13	107.91	27.69
2D vs 2C		404.22	385.10	104.96	86.99	126.65	27.69
2B vs 2A	AUC (ng·hr/mL)	467.99	758.30	61.72	52.84	72.08	22.69
2C vs 2A		444.44	758.30	58.61	49.69	69.13	22.69
2D vs 2A		433.43	758.30	57.16	48.71	67.06	22.69
2D vs 2B		433.43	467.99	92.62	78.93	108.67	22.69
2D vs 2C		433.43	444.44	97.52	82.28	115.59	22.69
Part 3							

Study No. / Location		ACE-HV-112 / Module 5.3.3.4.2					
3B vs 3A	C_{max} (ng/mL)	519.23	798.38	65.04	45.30	93.38	56.15
3C vs 3A		273.48	798.38	34.26	23.86	49.18	56.15
3D vs 3A		449.64	798.38	56.32	39.23	80.86	56.15
3D vs 3B		449.64	519.23	86.60	60.32	124.33	56.15
3D vs 3C		449.64	273.48	164.41	114.51	236.05	56.15
3B vs 3A	$AUC_{(0-t)}$ (ng·hr/mL)	676.24	809.93	83.49	71.93	96.91	21.83
3C vs 3A		508.89	809.93	62.83	51.13	72.93	21.83
3D vs 3A		684.18	809.93	84.47	72.78	98.05	21.83
3D vs 3B		684.18	676.24	101.17	87.16	117.44	21.83
3D vs 3C		684.18	508.89	134.45	115.83	156.05	21.83
3B vs 3A	AUC (ng·hr/mL)	680.60	814.28	83.58	73.28	95.33	19.20
3C vs 3A		547.66	814.28	67.26	58.74	77.01	19.20
3D vs 3A		688.97	814.28	84.61	74.18	96.50	19.20
3D vs 3B		688.97	680.60	101.23	88.75	115.46	19.20
3D vs 3C		688.97	547.66	125.80	109.87	144.05	19.20
Pooled Treatment 1C, 2C, 3C (Acalabrutinib + Omeprazole) versus Pooled Treatment 1A, 2A, 3A (Acalabrutinib Alone)							
Acalabrutinib 100 mg + Omeprazole 40 mg	C_{max} (ng/mL)	194.29	696.26	27.90	20.59	37.83	89.02
	$AUC_{(0-t)}$ (ng·hr/mL)	439.80	770.97	57.05	50.83	64.02	29.58
	AUC (ng·hr/mL)	497.59	775.64	64.15	58.01	70.94	24.59

Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)												
Dose	Time Point	C_{max} (ng/mL)	t_{max} (hr)[a]	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$AUC_{\%extrap}$ (%)	λ_z (1/hr)	$t_{½}$ (hr)	CL/F (L/hr)	V_z/F (L)
Part 1												
Acalabrutinib 100 mg RF	1A: Day 1	621.92 (94.1)	0.63 (0.50, 1.00)	735.46 (81.8)	752.71 (80.0)	750.61 (79.9)	755.73 (79.5)	0.60167 (51.7)	0.41 (32.4)	1.71 (32.4)	132.32 (79.5)	325.97 (82.6)
Acalabrutinib 100 mg AF	1B: Day 3	541.37 (48.8)	0.65 (0.50, 2.01)	586.30 (50.3)	595.47 (50.6)	593.15 (50.8)	596.75 (50.7)	0.56336 (37.8)	0.45 (37.6)	1.55 (37.6)	167.57 (50.7)	375.28 (39.0)
Acalabrutinib 100 mg RF ± 40 mg omeprazole	1C: Days 8	164.98 (237.5)	0.89 (0.50, 4.03)	338.75 (123.1)	388.69 (97.2)	434.14 (75.3)	489.32 (57.6)	2.9788 (429.9)	0.14 (140.6)	4.88 (140.6)	204.37 (57.6)	1437.7 (206.0

Acalabrutinib 100 mg AF ± 40 mg omeprazole	1D: Day 10	464.61 (54.6)	0.81 (0.47, 1.50)	559.05 (59.6)	572.21 (59.2)	569.15 (59.8)	576.11 (58.8)	0.93302 (77.2)	0.30 (46.5)	2.33 (46.5)	173.58 (58.8)	584.16 (83.4)
Part 2												
Acalabrutinib 100 mg RF	2A: Day 1	679.78 (55.0)	0.50 (0.50, 4.00)	740.28 (51.4)	755.65 (51.3)	753.80 (51.5)	758.30 (51.1)	0.47736 (65.0)	0.42 (56.1)	1.66 (56.1)	131.87 (51.1)	316.15 (96.0)
Acalabrutinib 100 mg RF	2B: Day 3	296.34 (87.0)	0.88 (0.50, 1.54)	418.37 (52.7)	441.53 (44.4)	451.96 (40.5)	467.99 (39.0)	0.84572 (170.5.)	0.45 (83.0)	1.55 (83.0)	213.68 (39.0)	476.69 (84.3)
Acalabrutinib 100 mg RF ± 40 mg omeprazole	2C: Day 8	162.55 (170.4)	1.27 (0.50, 3.02)	305.60 (87.6)	347.37 (73.4)	385.10 (59.6)	452.38 (49.6)	2.9933 (235.3)	0.14 (135.4)	4.94 (135.4)	221.05 (49.6)	1574.7 (204.2)
Acalabrutinib 100 mg RF ± 40 omeprazole	2D: Day 10	196.89 (117.9)	1.29 (0.76, 2.02)	363.86 (77.8)	389.33 (67.3)	404.22 (57.9)	459.47 (42.3)	1.1119 (165.4)	0.31 (78.9)	2.27 (78.9)	217.64 (42.3)	711.38 (115.1)
Part 3												
Acalabrutinib 100 mg RF	3A: Day 1	798.38 (41.5)	0.63 (0.50, 1.01)	802.22 (39.9)	813.15 (39.9)	809.93 (40.1)	814.28 (39.9)	0.48972 (46.9)	0.42 (23.4)	1.66 (23.4)	122.81 (39.9)	293.64 (36.6)
Acalabrutinib 100 mg RF	3B: Day 3	519.23 (51.7)	1.00 (0.75, 1.52)	662.50 (45.2)	677.92 (45.1)	676.24 (45.3)	680.60 (45.1)	0.56800 (58.3)	0.37 (37.3)	1.87 (37.3)	146.93 (45.1)	397.44 (52.1)
Acalabrutinib 100 mg RF ± 40 mg omeprazole	3C: Day 8	273.48 (165.9)	0.78 (0.50, 3.01)	434.57 (96.3)	475.83 (79.7)	508.89 (68.1)	546.47 (64.8)	1.3656 (347.9)	0.22 (111.6)	3.22 (111.6)	182.99 (64.8)	850.36 (191.3)
Acalabrutinib 100 mg RF ± 40 mg omeprazole	3D: Day 10	449.64 (62.1)	1.50 (0.75, 2.01)	666.00 (47.4)	685.94 (46.9)	684.18 (47.1)	688.97 (46.8)	0.60500 (63.7)	0.35 (20.2)	1.98 (20.2)	145.14 (46.8)	414.03 (53.2)

AF=Acidic Formulation; AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve from time 0 to last quantifiable concentration; $AUC_{\%extrap}$= percent of AUC which is extrapolated; CL/F=total body clearance following oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation: F=female(s); λ_z = elimination rate constant; LSM=least square mean; M=male(s); RF=Reference Formulation; t_{max}=time of C_{max}; $t_{½}$=terminal half-life; V_z/F=volume of distribution.

[a] Presented as median (minimum, maximum)

表 16　　ACP-5862 の薬物動態パラメータ：健康被験者を対象とした試験（ACE-HV-005 試験及び ACE-HV-113 試験）並びに CLL 患者を対象とした試験（D8220C00001 試験、ACE-CL-001 試験及び ACE-CL-007 試験）

Study No. / Location	ACE-HV-005 / Module 5.3.4.1.1
Study Design	Randomized, Double-Blind, Double-Dummy, Placebo- and Positive Controlled, 4 Way Crossover Study to Assess the Effect of Single-Dose acalabrutinib on the QTc Interval in Healthy Adult Subjects
Subject type, N (M/F), age: mean (range)	Healthy; N=48 (29/19); 45.7 (19-63) ABCD: n=12 (9/3); 41.8 (19-63) BDAC: n=12 (6/6); 48.5 (32/61) CADB: n=2 (5/7); 48.8 (35-60) DCBA: n=12 (9/3); 43.9 (26-58)
Treatments (dosage, form, route, duration)	Treatment A: oral single dose 100 mg acalabrutinib, Hour 0 after an overnight fast Treatment B: supratherapeutic oral single dose 400 mg acalabrutinib, fasted state; Hour 0 after an overnight fast Treatment C: oral single dose 400 mg moxifloxacin, fasted state; Hour 0 after an overnight fast Treatment D: placebo, fasted state; Hour 0 after an overnight fast ACP-5862 PK analysis: Subjects were selected from treatment groups A (100 mg acalabrutinib) and B (400 mg acalabrutinib) for PK analysis of the metabolite ACP-5862. The acalabrutinib (parent) PK parameters were reviewed before selection of subjects for metabolite PK analysis. The 6 highest AUCs, 6 lowest AUCs, and 6 medium AUCs subjects were selected that had full pharmacokinetic profiles for parent molecule exposure in both treatment groups. The metabolite PK analysis for these subjects is reported.

ACP-5862 Pharmacokinetic Parameters, Geometric Mean (Geometric Mean CV%)

Dose	No of subjects	t_{max}[a] (hr)	C_{max} (ng/mL)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$ (hr)	MR
A: 100 mg	18	1.00 (0.75, 2.00)	444 (57.7)	1220 (54.0)	1480 (49.1)	1670 (46.1)	1720 (44.7)	2.54 (22.7)	2.36* (27.9)
B: 400 mg	18	2.00 (0.50, 4.00)	2040 (43.7)	6640 (49.7)	7730 (49.8)	8230 (49.1)	8280 (48.9)	1.91 (10.8)	1.70 (26.8)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose; $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); M=male(s); MR=Metabolite ratio calculated as ACP-5862 AUC/acalabrutinib AUC using molar conversions; N=number of subjects; No=number; $t_{½}$=terminal half-life; t_{max}=time of C_{max}.

[a] Presented as median (minimum, maximum)

* n=16

Study No. / Location		ACE-HV-113 / Module 5.3.1.2.1							
Study Design		Single-center, open-label, fixed-sequence, 2-period study in healthy adult subjects to evaluate the effect of gastric pH on acalabrutinib pharmacokinetics							
Subject type, No. (M/F), age: mean (range)		Healthy; N=12 (8/4); 42.0 (18-58)							
Treatments (dosage, form, route, duration)		Period 1: 100 mg acalabrutinib (1 x 100 mg capsule) and 1 [redacted] capsule administered orally with approximately 240 mL of distilled water after an overnight fast Period 2: 100 mg acalabrutinib (1 x 100 mg capsule) and 1 [redacted] capsule administered orally with approximately 240 mL of distilled water after an overnight fast. ACP-5862 PK analysis: Samples from all subjects within the PK population were evaluated (data from Periods 1 and 2 were combined).							
		ACP-5862 Pharmacokinetic Parameters, Geometric Mean (Geom. CV%)							
Dose	Time point (no of subjects)	C_{max} (ng/mL)	t_{max}[a] (hr)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$ (hr)	MR
Acala-brutinib 100 mg	Period 1 + 2 (24)	443 (52.4)	1.00 (0.751, 3.00)	1220 (47.2)	1480 (42.4)	1670 (38.5)	1770 (36.1)	6.53 (32.3)	2.69* (23.9)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose; $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); M=male(s); MR=Metabolite ratio calculated as ACP-5862 AUC/acalabrutinib AUC using molar conversions; N=number of subjects; $t_{½}$=terminal half-life; t_{max}=time of C_{max}.

[a] Presented as median (minimum, maximum)

* n=21

Study No. / Location	D8220C00001 / Module 5.3.5.2.9
Study Design	A multicentre, open-label Phase 1 study to assess the safety, tolerability, pharmacokinetics and anti tumour activity of acalabrutinib in Japanese adult patients with advanced B-cell malignancies. This study was divided into 3 parts: Part 1 (dose-confirmation phase), Part 2 (dose-expansion phase) and Part 3 (dose-confirmation phase for combination therapy). This table mentions only Part 1.
Subject type	Japanese adult patients with advanced B-cell malignancies who met all of the inclusion and none of the exclusion criteria. The study population included patients with non germinal centre B-cell-like (non-GCB) diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), MCL, CLL/SLL and Waldenström macroglobulinemia (WM).
Treatments (dosage, form, route, duration)	Part 1: Acalabrutinib 100 mg (1 x 100 mg capsule) single dose was given to patients on Day 1, followed by a washout period of 2 days up to 7 days, and then 100 mg oral BID dosing. ACP-5862 PK analysis: Samples from all subjects within the PK population were evaluated.

Pharmacokinetic Parameters, Geometric Mean (Geom. CV%) (Part 1 only)

Acalabrutinib Dose	Timepoint (n*)	t_{max} (hr)[a]	C_{max} (ng/mL)	$AUC_{(0-12)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$ (hr) [b]	MR [b]
100 mg single dose	Day 1 (n = 6)	0.965 (0.900, 4.000)	316.5 (260.1%)	1092 (123.8%)	1306 (93.9%)	1557 (60.4%)	10.18 ± 7.986	1.36
100 mg BID dose	Day 8 (n = 6)	0.940 (0.750, 1.080)	629.7 (26.9%)	1987 (7.7%)	1985 (7.7%)	2099 (6.6%)	3.216 ± 0.3938	1.65

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-12)}$=area under the concentration-time curve from time 0 to 12 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; BID=twice daily; C_{max}=maximum plasma concentration; CV=coefficient of variation; MR=Metabolite ratio calculated as ACP-5862 geometric mean $AUC_{(0-t)}$/acalabrutinib geometric mean $AUC_{(0-t)}$; n=number of subjects; t_{max}=time of C_{max}; $t_{½}$=terminal half-life.

[a] Presented as median (minimum, maximum)

[b] Geometric CV% was not calculated.

Study No. / Location		ACE-CL-001 / Module 5.3.5.2.2						
Study Design		Phase 1/2, multicenter, open-label, nonrandomized, sequential group, dose escalation study of acalabrutinib (ACP-196) in subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia						
Subject type		Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (Cohorts 7 and 11: treatment naive subjects); Cohort 8: Ibrutinib Intolerant subjects; Cohort 9: Richter's or Prolymphocytic Leukemia Transformation subjects; and Cohort 10: Ibrutinib Refractory/Relapsed subjects); NA (ongoing study)						
Treatments (dosage, form, route, duration)		Phase 1: Acalabrutinib 100 to 400 mg QD (Cohorts 1, 2a, 2c, 3, and 4a); acalabrutinib 100 or 200 mg BID (Cohorts 2b and 4b) Phase 2: Acalabrutinib 200 mg QD (Cohort 7); acalabrutinib 100 or 200 mg BID (Cohorts 8, 9, 10, and 11) Administered orally in 28-day cycles until disease progression or unacceptable drug related toxicity ACP-5862 PK analysis: For the analysis of ACP-5862 concentrations, only select subset of subjects from Cohorts 2b and 11 were selected to represent low, medium or high acalabrutinib exposure (6 subjects each). Data from all subjects were pooled and used for the summary statistics. Doses used in Cohort 2b: 100 mg/day BID for 28 days; Cohort 11: 100 mg BID treatment naive subjects (expansion cohort) Day 1: $AUC_{(0-t)}$, C_{max}, t_{max}, & MR were calculated for 17 subjects; $AUC_{(0-6)}$ was calculated for 14 subjects; AUC and $t_{½}$ were calculated for 11 subjects. Day 8: $AUC_{(0-t)}$, C_{max}, t_{max}, & MR were calculated for 17 subjects; $AUC_{(0-6)}$ was calculated for 11 subjects; AUC and $t_{½}$ were calculated for 9 subjects.						
Acalabrutinib Dose	Timepoint	ACP-5862 Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)						
		t_{max}[a] (hr)	C_{max} (ng/mL)	$AUC_{(0-6)}$ (ng·hr/mL)	$AUC_{(0-t)}$ (ng·hr/mL)	AUC (ng·hr/mL)	$t_{½}$ (hr)	MR
100 mg BID	Day 1	1.00 (0.683, 4.00)	310 (168)	879 (113)	801 (135)	1310 (46.8)	1.77 (17.9)	1.01 (53.2)
100 mg BID	Day 8	1.90 (0.500, 2.10)	403 (75.7)	1410 (50.0)	1150 (57.7)	1540 (45.7)	1.84 (16.2)	1.76 (33.6)

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-6)}$=area under the concentration-time curve from time 0 to 6 hr postdose; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; C_{max}=maximum plasma concentration; CV=coefficient of variation; F=female(s); M=male(s); MR=Metabolite ratio calculated as ACP-5862 $AUC_{(0-t)}$/acalabrutinib $AUC_{(0-t)}$ using molar conversions; N=number of subjects; NA=not applicable; $t_{½}$=terminal half-life; t_{max}=time of C_{max}.

[a] Presented as median (minimum, maximum)

Study No. / Location	ACE-CL-007 / Module 5.3.5.1.2					
Study Design	An Open-label, Phase 3 Study of ACP-196 in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Ongoing Subject Study					
Subject type	Previously Untreated Chronic Lymphocytic Leukemia; NA (ongoing study)					
Treatments (dosage, form, route, duration)	Acalabrutinib 100 mg BID administered orally in 28-day cycles until disease progression or unacceptable drug-related toxicity					
ACP-5862 Population Pharmacokinetic Parameters, Geometric Mean (CV% Geometric Mean)						
Dose	Timepoint (n)	$C_{ss,max}$ (ng/mL)	$AUC_{ss,(0-24)}$ (ng·hr/mL)	$C_{ss,min}$ (ng/mL)	V_c/F (L)	CL/F (L/hr)
Acalabrutinib 100 mg BID + Obinutuzumab	Cycle 1, Cycle 2, Day 1 (n = 134)	430.9 (29.3)	4193 (11.5)	58.9 (22.9)	23.2 (17.4)	21.6 (5.4)
Acalabrutinib 100 mg BID	Cycle 1, Cycle 2, Day 1 (n = 140)	441.6 (25.4)	4230 (10.7)	58.1 (20.5)	23.4 (21.7)	21.6 (4.6)

The PK parameters are based on population PK analysis, estimated following administration of 100 mg BID across all subjects.

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{24h,ss}$=area under the concentration-time curve estimated over 24 hours postdose; BID=twice daily; CL/F=apparent clearance after oral administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; n=number of subjects; NA=not applicable; $t_{½}$=terminal half-life; t_{max}=time of C_{max}; V_c/F=apparent volume of distribution after oral administration.

表 17　　ACE-HV-113 試験において、第 1 期及び第 2 期にアカラブルチニブ 100 mg を単回経口投与したときの ACP-5862 の薬物動態パラメータの統計解析結果（被験者分散、残差分散、個体内変動及び個体間変動の評価）

	Period 1[a]		Period 2[b]					
PK Parameter	Geometric LSM	n	Geometric LSM	n	Subject Variance	Residual Variance	Intersubject CV%	Intrasubject CV%
C_{max} (ng/mL)	479.07	12	409.38	12	0.0622	0.1848	25.33	45.05
$AUC_{(0-t)}$ (ng·hr/mL)	1772.77	12	1583.04	12	0.0929	0.0483	31.21	22.24
AUC (ng·hr/mL)	1864.19	12	1677. 48	12	0.0852	0.0395	29.82	20.06

AUC=area under the concentration-time curve from time 0 to infinity; $AUC_{(0-t)}$=area under the concentration-time curve, from time 0 to last quantifiable concentration; C_{max}=maximum plasma concentration; CV=coefficient of variation; LSM=least squares mean.

Notes:　Geometric LSMs are calculated by exponentiating the LSMs derived from the MIXED model.

Intrasubject CV% = 100 x sqrt[exp(residual variance)-1]

Intersubject CV% = 100 x sqrt[exp(between subject variance)-1]

[a] Period 1: A single oral dose of 100 mg acalabrutinib and 1 [redacted] capsule

[b] Period 2: A single oral dose of 100 mg acalabrutinib and 1 [redacted] capsule

Source: ACP-196/ACE-HV-113/Variability/Programs/t_ACP5862.sas

表 18　　アカラブルチニブの主な臨床薬理学的特性及び心血管系への影響

Therapeutic dose	100 mg twice daily (BID) acalabrutinib (oral capsules) for the treatment of subjects with mantle cell lymphoma (MCL) who have received at least one prior therapy.	
Maximum tolerated dose (MTD)	30 mg/kg/day in dogs 100 mg/kg/day in rats (6 months) Not determined in human subjects (doses in clinical trials did not reach MTD)	
Principal adverse events	See Module 2.7.4	
Maximum dose tested	Single Dose	400 mg
	Multiple Dose	400 mg QD
Exposures Achieved at Maximum Tested Dose	Single Dose	C_{max}: 1672.3 ng/mL (64.5%)[a]; AUC: 4652.9 ng·hr/mL (51.9%)[a]
	Multiple Dose	400 mg QD (n=5-6): $C_{ss,max}$: 657 ng/mL (129%)[b]; $AUC_{(0-t)}$: 1460 ng·hr/mL (82.5%)[b]
Range of linear PK	75–250 mg after single and multiple doses in healthy subjects and subjects based on a population PK analysis (D8223C00002)	
Accumulation at steady state	None	
Metabolites	One pharmacologically active metabolite, ACP-5862 (M27) has been assessed in healthy subjects and subjects with B-cell malignancies. Acalabrutinib and ACP-5862 accounted for 8.63% and 34.7%, respectively, of total acalabrutinib-related radioactivity in human plasma. ACP-5862 had approximately 0.5-fold potency for BTK inactivation relative to acalabrutinib with generally similar kinase specificity.	
Absorption	Absolute Bioavailability	25% (range 20% to 30%)
	t_{max} @ 100 mg median (min-max)	• Acalabrutinib: Single dose: 0.750 hr (0.50, 2.30 hr)[c] Multiple dose: 0.750 hr (0.450, 5.75 hr)[c] • ACP-5862: Single dose: 1.00 hr (0.683, 4.00 hr)[c] Multiple dose: 1.90 hr (0.50, 2.10 hr)[c]
Distribution	Vd/F or Vd	V_z = 98.0 L[e] V_{ss} = 34.2 L[e] ([^{14}C]acalabrutinib IV microtracer dose)
	% bound	In vitro protein binding of acalabrutinib was 97.5% in human plasma, 93.7% to human serum albumin, and 41.1% to α1-acid glycoprotein. In vitro human plasma protein binding of the active metabolite, ACP-5862 was 98.6%.
Elimination	Route	Fecal elimination accounts for 83% of an oral [^{14}C]acalabrutinib dose with urinary elimination accounting for 12% of the dose. Unchanged acalabrutinib accounts for <1% of the dose in urine after both oral and IV administration in healthy subjects.[e]
	Terminal $t_{½}$	Acalabrutinib: 1 – 2 hr ACP-5862: 6.53 hr (32.5%)[d]
	CL/F or CL	CL = 39.4 L/h (30.6%)[e] ([^{14}C]acalabrutinib IV microtracer dose)
Intrinsic Factors	Age	Based on a population PK analysis, no dose adjustment of acalabrutinib is required based on age.
	Sex	Based on a population PK analysis, no dose adjustment of acalabrutinib is required based on sex.
	Race	Based on a population PK analysis, no dose adjustment of acalabrutinib is required based race (white vs black) or ethnicity.

Therapeutic dose	100 mg twice daily (BID) acalabrutinib (oral capsules) for the treatment of subjects with mantle cell lymphoma (MCL) who have received at least one prior therapy.	
	Hepatic & Renal Impairment	$AUC_{(0-t)}$ of acalabrutinib increased <2-fold in subjects with mild/moderate hepatic impairment compared to healthy subjects. Together with a population PK assessment, no dose adjustment of acalabrutinib is required for subjects with mild or moderate hepatic impairment. It is not recommended to administer acalabrutinib in subjects with severe hepatic impairment. Based on a population PK analysis, no dose adjustment of acalabrutinib is required for subjects with mild or moderate renal impairment. The effects of severe renal impairment or hemodialysis on the pharmacokinetics of acalabrutinib have not been studied.
Extrinsic Factors	Drug interactions	Victim: CYP3A inhibitors and inducers; pH modulators Perpetrator: May increase exposure to orally coadministered BCRP substrates (e.g. methotrexate)
	Food Effects	C_{max} decreased to 31% and AUC was similar (93%) in the fed compared to the fasting state. Acalabrutinib can be taken with or without food.
Expected High Clinical Exposure Scenario	Coadministration with strong CYP3A4 inhibitors led to increased exposure (5-fold increase in AUC). A PBPK model also predicted mean C_{max} and AUC ratio of ACP-5862 after repeated doses of itraconazole were 0.11 and 0.16 respectively, suggesting itraconazole significantly blocked the metabolism of acalabrutinib to ACP-5862. The predicted mean AUC ratio for total moiety (acalabrutinib plus ACP-5862) was 1.35 (表 10 参照). No dose adjustment is necessary with concomitant use of acalabrutinib with strong, moderate, or weak CYP3A inhibitors	
Preclinical Cardiac Safety	Safety Pharmacology: No acalabrutinib-related effects were observed in the dog CV safety study at 30 mg/kg, the highest dose administered. At a concentration of 10 μM (588 times the clinical unbound C_{max}), acalabrutinib showed approximately 25% inhibition of hERG in stably transfected HEK-293 cells. Toxicology: In repeat-dose studies of acalabrutinib at doses exceeding MTD, heart findings have been observed in animals that died ahead of the scheduled necropsy (DOS animals). In DOS rats, microscopic changes in the heart were noted, consisting of minimal to moderate hemorrhage/inflammation/necrosis and vascular mineralization. These changes and microscopic changes in the kidneys were considered the cause of moribundity/mortality. In DOS dogs, microscopic findings in the heart were noted in 2 non-naive dogs whose deaths were attributed to severe kidney toxicity and associated uremia. Heart findings in these dogs were consistent with the spectrum of pathological abnormalities commonly reported in acute renal failure in the dog. Because heart findings were only observed in animals with unscheduled deaths, no information is available regarding reversibility.	
Clinical Cardiac Safety	A thorough QT study (ACE-HV-005) demonstrated that there is no significant prolongation of QTc interval by acalabrutinib at either the therapeutic (100 mg) or a supratherapeutic (400 mg) dose. These results were consistent with previous ECG results obtained from healthy subjects (ACE-HV-001) as well as from subjects with CLL, SLL, RS, or PLL (ACE-CL-001). See Module 2.7.4	

hERG=human ether-a-go-go-related gene; MTD=maximum tolerated dose.

[a] ACE-HV-005 (n=43): Geometric mean (CV%)

[b] ACE-CL-001 Cohort 4a (Day 8): Geometric mean (CV%)

[c] ACE-CL-001: acalabrutinib: Cohort 2b (Day 1: n = 28; Day 8: n = 27); ACP-5862: ACE-CL-001 Cohorts 2b and 11 (Days 1 & 8: n = 17)

[d] ACE-HV-113 (Period 1+2; n=24): Geometric mean (CV%)

[e] ACE-HV-009