23 July 2020
EMA/CHMP/458179/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Calquence

International non-proprietary name: acalabrutinib

Procedure No. EMEA/H/C/005299/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BCS	biopharmaceutics classification system
BID	twice daily
BMX	bone marrow kinase on chromosome X
BR	bendamustine+rituximab
BTK	Bruton tyrosine kinase
CEP	Certificate of suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CIRS-G	Cumulative Illness Rating Score-Geriatric
CLL	chronic lymphocytic leukaemia
Cmax	maximum concentration
CNS	central nervous system
CQA	Critical Quality Attribute
CR	complete response
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DOR	duration of response
EC	European Commission
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
ERBB	erb-b2 receptor tyrosine kinase

ESMO	European Society for Medical Oncology
EU	European Union
FCR	fludarabine+cyclophosphamide+rituximab
FDA	Food and Drug Administration
GC	Gas Chromatography
GI	gastrointestinal
HPLC	High performance liquid chromatography
HR	hazard ratio
IC50	50% inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IGHV	immunoglobulin heavy-chain variable
IPC	In-process control
IR	Infrared
IR	idelalisib+rituximab
IRC	Independent Review Committee
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
MAH	Marketing authorisation holder
MATE	multidrug and toxin extrusion transporter
MRD	minimal residual disease
MS	Mass spectrometry
NCCN	National Comprehensive Cancer Network
NF	National formulary
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
ORR	overall response rate
OS	overall survival
PDE	Permitted daily exposure
PFS	progression-free survival
Ph. Eur.	European Pharmacopoeia

PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic(s)
PLL	prolymphocytic leukaemia
PPI	proton pump inhibitor
ppm	parts per million
PR	partial response
PRL	partial response with lymphocytosis
QD	once daily
QTPP	Quality target product profile
RH	Relative humidity
R/R	relapsed/refractory
RS	Richter's syndrome
SAE	serious adverse event
SAP	Statistical Analysis Plan
SLL	small lymphocytic lymphoma
SmPC	Summary of product characteristics
TEAE	treatment-emergent adverse event
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TLS	tumour lysis syndrome
Tmax	time to maximum concentration
TSE	Transmissible spongiform encephalopathy
TTNT	time to next treatment
ULN	upper limit of normal
UV	Ultraviolet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 14 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Calquence, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 January 2019.

Calquence was designated as an orphan medicinal product EU/3/16/1624 on 21 March 2016 in the following condition: treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 10 September 2020 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website www.ema.europa.eu/en/medicines/human/EPAR/calquence.

The applicant applied for the following indication:

"CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0062/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance acalabrutinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application: on 25 June 2015 (EMEA/H/SA/3090/1/2015/III), on 15 December 2016 (EMEA/H/SA/3090/2/2016/PA/I) and on 20 September 2018 (EMEA/H/SA/3090/4/2018/III).

The Scientific Advice pertained to the following non-clinical, quality and clinical aspects of the dossier:

- The proposed starting material for the synthesis of acalabrutinib;
- The approach to qualify in-process impurities and degradants of acalabrutinib;
- The adequacy of the non-clinical, safety pharmacology and toxicology studies to support to support marketing authorisation in CLL;
- Whether the clinical pharmacology program is adequate to support the clinical development;
- The proposed design of study ACE-CL-006, including the NI margin, the choice of PFS as primary endpoint, the selection of high risk CLL (including the 17p del and 11q del CLL sub-populations), the proposed statistical analysis plan;
- The proposed design of study ACE-CL-007, mainly the proposed population and planned interim analysis;
- The proposed design of the phase 3 study ACE-CL-311, in particular, the proposed patient population, comparator arm (FCR/BR), primary (PFS per IRC assessment) and secondary endpoints, interim analysis, MRD collection and analysis plan; the proposed patient-reported outcome (PRO) measurements;

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	14 October 2019
The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	4 February 2020
The PRAC Rapporteur's first Assessment Report was circulated to all	3 February 2020

PRAC members on	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	7 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Calquence on	23 July 2020
The CHMP adopted a report on similarity of Calquence product with Gazyvaro and Imbruvica on	23 July 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in Europe and North America, and mainly, though not exclusively, affects older individuals. The World Health Organization (WHO) classification of hematopoietic neoplasias describes CLL as leukemic, lymphocytic lymphoma, being only distinguishable from SLL (small lymphocytic lymphoma) by its leukemic manifestation. In the WHO classification, CLL, by definition, is always a disease of neoplastic B-cells, while the entity formerly described as T-CLL is now called T-cell prolymphocytic leukaemia (T-PLL).

2.1.2. Epidemiology

CLL is a malignancy of B cells that predominantly affects an elderly population. It is the most prevalent form of adult leukaemia, with an age-adjusted incidence of 3.3–6.4 per 100,000 person-years and a median age at diagnosis of 70 years.

2.1.3. Biologic features

The leukaemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. Gumprecht nuclear shadows, or smudge cells, found as cellular debris, are additional morphologic features commonly associated with CLL. A small percentage of larger or atypical cells or prolymphocytes can be found admixed with morphologically typical CLL cells. Finding ≥ 55% prolymphocytes would favour a diagnosis of prolymphocytic leukaemia (B-cell PLL). However, the diagnosis of B-cell PLL remains difficult and is solely based on morphological criteria, because no reliable immunological or genetic marker has been identified. A significant proportion of circulating prolymphocytes (≥ 10%) seems to indicate a more aggressive form of CLL (with NOTCH1 or genetic TP53 aberrations).

The definition of SLL requires the presence of lymphadenopathy and the absence of cytopenias caused by a clonal marrow infiltrate. Additionally, the number of B lymphocytes in the peripheral blood should be < 5.000/µL. In SLL, the diagnosis should be confirmed by histopathological evaluation of a lymph node biopsy or biopsy of other tissues. Some patients may present with enlarged lymph nodes that are not suspicious for solid tumours and with peripheral blood B lymphocytes < 5.000/µL that carry a typical CLL immunophenotype. In these cases, a tissue or lymph node biopsy to establish the diagnosis of SLL may have limited clinical consequences and be omitted.

2.1.4. Clinical presentation, diagnosis

The diagnosis of CLL requires the presence of ≥ 5.000 B-lymphocytes/µL in the peripheral blood, sustained for at least 3 months. The clonality of these B-lymphocytes needs to be confirmed by demonstrating immunoglobulin light chain restriction using flow cytometry.

Diagnosis is established using peripheral blood and immunophenotyping and requires a minimum of 5 x 109 monoclonal B cells that co-express the surface antigens CD5, CD19, CD20, and CD23.

CLL has a variable course, with survival ranging from months to decades. Major progress has been made in identification of molecular and cellular markers that could predict disease progression in patients with CLL. In particular, the mutational profile of immunoglobulin genes and some cytogenetic abnormalities are important predictors of prognosis. Available treatments generally induce remission, although nearly all patients relapse, and CLL remains an incurable disease.

2.1.5. Management

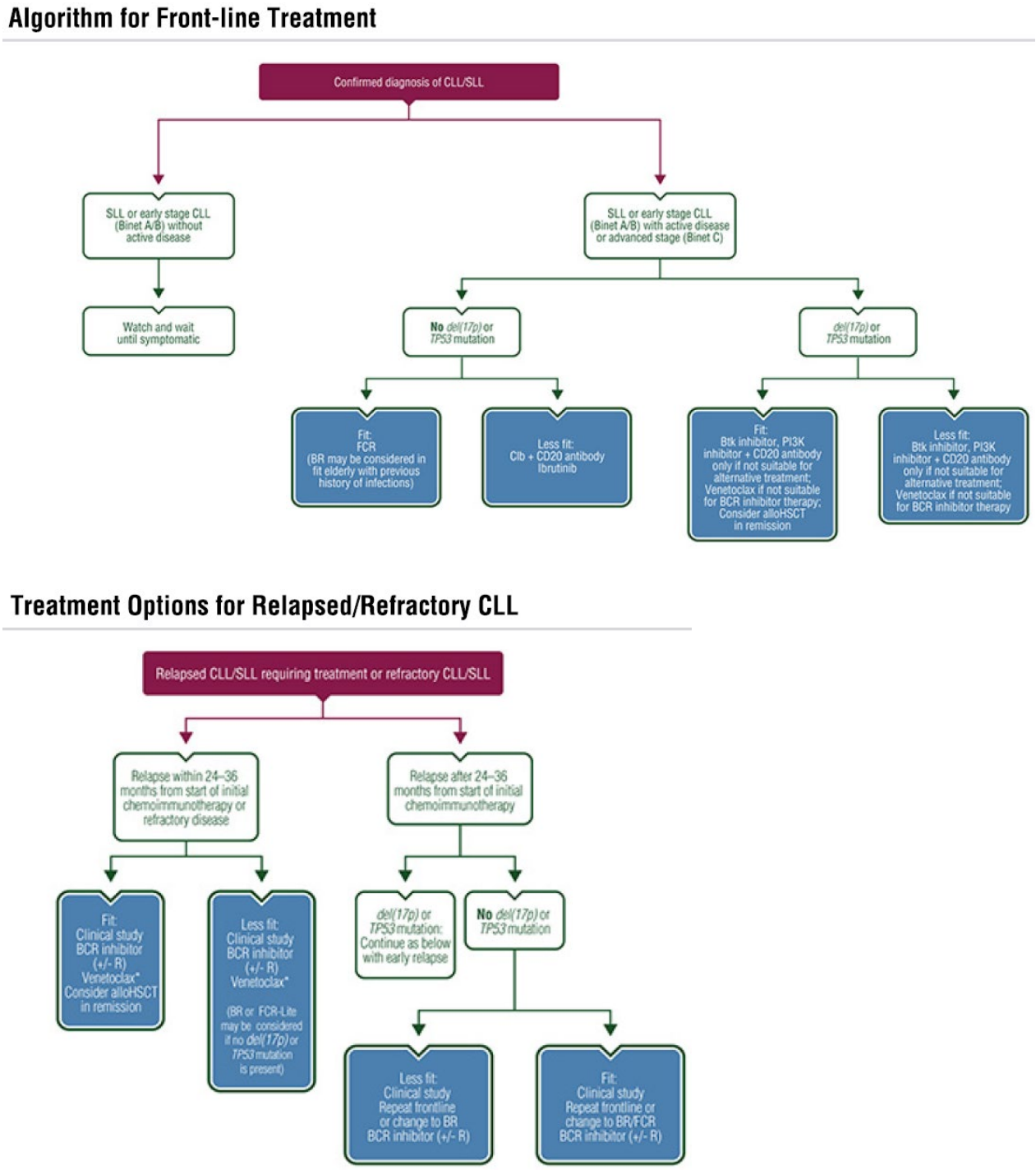
The treatment of CLL has evolved significantly over the last several decades. While alkylator therapy was used in the past (O'Brien et al. 1995), randomised trials have demonstrated a higher response rate and longer progression-free survival (PFS) with fludarabine-and cyclophosphamide-based combinations in young, fit patients with CLL (Johnson et al. 1996; Raiet al. 2000;Leporrier et al. 2001;Eichhorst et al. 2006;Catovsky et al. 2007; Flinnet al. 2007).

At the same time, the chimeric anti-CD20 monoclonal antibody rituximab was introduced for the treatment of CLL (Byrd et al. 2001, O'Brien et al. 2001). The efficacy of rituximab has been improved by combining it with traditional cytotoxic agents such as fludarabine (Byrd et al. 2003, Byrd et al. 2005) or fludarabine plus cyclophosphamide (Wierdaet al. 2005), which have produced high complete remission (CR) rates and extended PFS compared with historical controls. A large randomised clinical trial, reported by the German CLL study group, has shown the benefit of the addition of rituximab to fludarabine and cyclophosphamide (FCR) in PFS and overall survival (OS) in patients with previously untreated CLL (Hallek et al. 2010). Bendamustine in combination with rituximab (BR) has also been studied in frontline CLL and was found to be less toxic, but also less efficacious than FCR (Eichhorst et al. 2016.

Patients who have high risk cytogenetics such as deletions in the long arm of chromosome 11 (11q del) or in the short arm of chromosome 17 (17p del) have inferior outcomes and may prove to be refractory to therapy and/or experience short remission durations and rapid progression of disease when treated with standard and currently available treatment regimens (Halleket al. 2010, Hillmenet al. 2007). In addition, elderly patients and those with comorbidities are often unable to tolerate combination chemoimmunotherapy regimens, or experience inferior clinical outcomes when treated with these regimens.

Currently, CLL remains an incurable disease with relapse inevitable and most patients requiring multiple lines of therapy. Therapeutic choice after relapse requires the evaluation of the intensity of the previous therapies, the duration of response (DOR) to those therapies, and patient comorbidities. Allogeneic stem cell transplant is only recommended in eligible patients with high-risk disease failing novel targeted therapies (i.e. BTK and BCL2 inhibitors). In the last decade, anti-CD20 monoclonal antibodies (obinutuzumab, ofatumumab) were added to new and effective combination regimens. The development of targeted therapies against B cell markers/antigens or against components of the B-cell receptor (BCR) such as BTK inhibitor (ibrutinib), BCL2 inhibitor (venetoclax) or PI3Kδ inhibitor (idelalisib) have demonstrated efficacy with less toxicity (Wiestner 2015).

Figure 1 ESMO guideline on CLL 2019



About the product

Acalabrutinib (ACP-196), known chemically as (S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2- yl)-imidazo[1,5-α]pyrazin-1-yl)-N-(pyridin-2-yl)-benzamide, is a highly selective, potent, orally bioavailable, covalent inhibitor of BTK. Acalabrutinib forms a covalent bond with Cys481 in the BTK adenosine triphosphate (ATP) pocket, permanently inactivating the enzyme and resulting in the inhibition of proliferation and survival signals in malignant B cells. Acalabrutinib has an active metabolite, ACP-5862, that is also a covalent inhibitor of BTK. Biochemical profiling showed that the

pharmacological activity and kinase selectivity profile for ACP-5862 was comparable to that of acalabrutinib.

Type of Application and aspects on development

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 100 mg of acalabrutinib as active substance.

Other ingredients are:

Capsule content: microcrystalline cellulose, colloidal anhydrous silica, partially pregelatinised starch, magnesium stearate and sodium starch glycolate.

Capsule shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172) and indigo carmine (E132).

Printing ink: shellac, black iron oxide (E172) and propylene glycol (E1520).

The product is available in aluminium/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of acalabrutinib is 4-{8-amino-3-[(2*S*)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-*N*-(pyridine-2-yl)benzamide and its molecular formula and relative molecular mass are $C_{26}H_{23}N_7O_2$ and 465.51 respectively. Acalabrutinib has one chiral centre and is the (*S*)-enantiomer. Its chemical structure is presented in Figure 2.

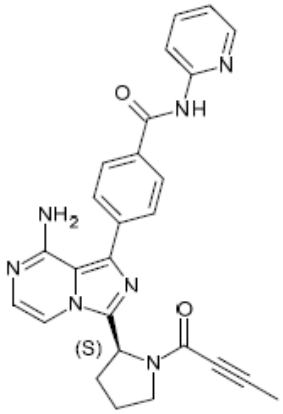


Figure 2: active substance structure

Full information on the active substance has been provided in the dossier by the MAH. The chemical structure of acalabrutinib was inferred from the route of synthesis and elucidated by a combination of mass spectrometry (MS), ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), elemental analysis, and ultraviolet spectroscopy (UV). In addition, the (*S*)-configuration of acalabrutinib was confirmed by single crystal X-ray diffraction (XRD).

The solid-state properties of the active substance were measured by gravimetric vapour sorption, differential scanning calorimetry and thermogravimetric analysis. Acalabrutinib is a non-hygroscopic white to yellow crystalline powder. It exhibits pH-dependent solubility in aqueous media. Extensive polymorph screening identified several metastable anhydrous forms as well as hydrates and solvates.

Manufacture, characterisation and process controls

Acalabrutinib is synthesised using well-defined starting materials with acceptable specifications. The applicant sought scientific advice on the choice of starting materials and CHMP recommended that they be re-defined. During this procedure, the applicant was able to able to provide data on impurity fate and purge and an updated control strategy was presented in order to justify the originally proposed starting materials. This was accepted by CHMP and they are considered to be acceptable in line with the principles of ICH Q11 and its Q&A.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials, reagents, solvents and auxiliary materials have been presented and are found acceptable. Risk management and scientific knowledge have been used to understand process parameters and unit operations that impact critical quality attributes (CQAs) of the active substance and to develop the proposed control strategy. The control strategy consists of control of process parameters, raw material quality, in-process controls (IPCs) and release testing of the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin, fate and purge and are adequately characterised.

The manufacturing process development work has been described in sufficient detail. The commercial manufacturing process for the active substance was developed in parallel with the clinical development program and changes introduced were not extensive and were designed to improve the robustness of the manufacturing process and active substance. The changes have been presented in sufficient detail and have been justified. The proposed late development process can be considered suitable and results in a reproducible active substance with high purity.

The active substance is packaged in double LDPE bags inside a rigid drum. The primary packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR), assay (HPLC), impurities (HPLC), mutagenic impurity (LCMS), enantiomeric purity (chiral HPLC), residual solvents (GC), water content (KF), particle size distribution (laser diffraction) and residue on ignition (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The limit for the mutagenic impurity has been set in line with ICH M7 and considering the 1-10 year treatment duration. The limits for particle size are set in line with the clinical batches, also considering the high aqueous solubility at gastric pH.

The absence of tests for elemental impurities, some residual solvents used early in the process, polymorphism and microbial testing has been acceptably justified by the applicant.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from several pilot to production scale batches of active substance from the proposed commercial manufacturer are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. In addition, supportive data from 3 larger scale batches from a previous manufacturer were provided as supporting information. The following parameters were tested: description, assay, impurities, enantiomeric purity, particle size, and water content. The supportive batches were also studied for polymorphic form and microbiological content. No significant changes to any of the studied attributes were observed.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. Acalabrutinib is not photosensitive.

Results under stressed conditions were also provided. No significant degradation was observed in the solid state (up to 50 °C for 3 months). Forced degradation studies were performed to elucidate degradation pathways and to conform the suitability of the analytical methods applied. Studies were performed using acalabrutinib in aqueous solutions or suspensions at pH 1, 7, and 13 and under oxidative conditions. Degradation was observed under acidic, basic, and oxidative conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months stored below 30 °C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as a size 1 hard gelatin capsule, with a blue cap and yellow body, printed with 'ACA 100 mg' in black ink and containing 100 mg of acalabrutinib. The composition of Calquence hard capsules is presented in Table 2.

Table 1: composition of finished product

Ingredient
Capsule content: Acalabrutinib
Silicified microcrystalline cellulose
Partially pregelatinized starch
Sodium starch glycolate, Type A

Ingredient
Magnesium stearate
Fill weight
Hard gelatin capsule shell[b]*:* Gelatin[c]
Iron oxide, yellow
Indigotin – FD&C Blue 2
Titanium dioxide
Hard gelatin capsule shell
Imprinting ink: Shellac glaze – 45% (20% esterified) in ethanol
Iron oxide black
Propylene glycol
Ammonium hydroxide 28%

The formulation development was performed to meet the criteria described in the Quality Target Product Profile (QTPP): an oral immediate release capsule containing acalabrutinib able to meet the clinical need and quality and pharmacopoeial requirements including purity and free from microbial contamination.

Acalabrutinib is soluble in aqueous acidic conditions. Acalabrutinib is a BCS class 2 compound with BCS class 1 like behaviour *in vivo* under normal stomach pH conditions with rapid and complete dissolution.

During the course of the development programme two different immediate release capsule formulations were produced.

The development of acalabrutinib capsules for use in pivotal clinical studies and for commercial supply, was focused on the identification of a more suitable formulation. The compatibility of acalabrutinib was evaluated with a range of commonly used excipients for the development of solid oral dosage forms, including diluents, binders, disintegrants, lubricants, glidants and surfactants. The knowledge gained through excipient compatibility studies was key in defining the composition of both clinical and commercial acalabrutinib capsule formulations. The robustness of the proposed commercial capsules formulation to changes in excipient suppliers/grades and active substance particle size has been studied. These studies demonstrate the robustness of the acalabrutinib capsules formulation to variation in input materials. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Comparison of pharmacokinetic parameters for the two formulations was conducted in healthy volunteers and indicates that exposure is similar between the formulations.

The dissolution method consists of the paddle apparatus, considered the most biorelevant pH since dissolution occurs in the stomach. The discriminatory power of the method was investigated. The method is deemed sufficiently discriminatory.

A range of development batches ranging from pilot to production scale were manufactured in order to investigate ranges of different parameters associated with the different process unit operations (blending, roller compaction, lubrication and encapsulation). These studies allowed optimisation of the various parameters although all batches manufactured complied with the release specification. Robustness was studied by deliberately varying certain parameters and material attributes from their set-points with no significant impact on product quality.

The primary packaging is aluminium/aluminium blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 4 main steps: blending of dry ingredients and lubrication; roller compaction and further lubrication; encapsulation; packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been validated at the proposed lower scale on 3 consecutive batches of finished product. A validation protocol has been provided to document prospective validation at the higher scale. The developmental robustness studies and process validation data provided to date demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. In addition, the applicant will apply a continued process verification approach to monitoring the manufacturing process and further ensure the quality of the finished product throughout its lifecycle.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (UV, HPLC), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.) and microbiological quality (Ph. Eur.).

The specified degradation products are also impurities carried over from the active substance process. The wider shelf-life limits have been justified by extrapolation from the stability studies.

No routine test for microbiological quality is deemed necessary due to the low water activity of the active substance and based on data collected during stability studies indicating that microbial growth is not supported. Enantiomeric purity and polymorphic form were both monitored during stability studies indicating that these parameters are stable and do not need to be tested at release.

The potential presence of elemental impurities in the finished product was assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities and no significant risk was identified. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was well below 30% of the respective PDE. Based on the risk assessment and the presented batch data, it was concluded that no controls for elemental impurities are needed.

The applicant submitted a risk evaluation on the potential presence of nitrosamines in Calquence. Both active substance and finished product manufacturing processes were considered, along with raw

materials and packaging. The analysis was deemed acceptable and no specific test or control measures for nitrosamine impurities are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several pilot to production batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), 36 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Calquence are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. The only differences were small changes in the extra-capsular image. In addition, more data from 3 pilot scale batches with the final commercial image was provided.

Samples were tested for appearance, assay, degradation products, dissolution, water content and microbiological quality. The analytical procedures used are stability indicating. There were small but observable increases in the specified impurities over time, more so at elevated temperature, which justify the wider shelf-life limits. No significant changes to any other measured parameters were observed.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Calquence is photostable.

An open dish study was conducted to assess the of humidity on the capsules. Samples were stored under intermediate conditions for a month without an increase in impurities. The only change was an increase in water content which had no impact on the product quality.

Finally, a study was conducted to justify bulk storage for up to 2 years in aluminium foil bags. Data from production scale batches stored for up to 2 years under long term, intermediate and accelerated conditions support the proposed bulk shelf-life.

Based on available stability data, the proposed shelf-life of 36 months in the blister pack without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture were provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The major objections

relating to the choice of starting materials and the nitrosamines risk assessment have been adequately resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacokinetics and metabolism of acalabrutinib were studied in mouse, rat, dog, monkey, and human tissues in vitro and in mouse, rat, dog, monkey and human in vivo. The species and strains used were the same as those used in pharmacology and toxicology studies except for a rat quantitative whole-body autoradiography (QWBA) study, which used a partially pigmented strain. The nonclinical toxicology profile of acalabrutinib (ACP-196) has been evaluated in mice, rats, rabbits, and dogs in agreement with relevant guidelines. A number of process intermediates/impurities have been studied. The pivotal studies were conducted in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

Potency of Acalabrutinib, Ibrutinib, Ibrutinib M37, and Spebrutinib on BTK using IMAP Assay Platform

Acalabrutinib, ibrutinib and its active major metabolite M37, and spebrutinib were evaluated using multiple platforms to assess the potency and target binding mechanism. BTK potency was evaluated for acalabrutinib and its main metabolite ACP-5862 (M27). BTK enzymatic activity was measured using an immobilized metal ion affinity-based fluorescence polarization (IMAP) assay.

Compound [a]	Experiment 1[b] IC_{50} (nM)	Experiment 2[c] IC_{50} (nM)
Acalabrutinib	5.1±1.0	3.0±0.7
ACP-5862 (M27)	ND	5.0±1.0
Ibrutinib	1.5±0.2	ND
Ibrutinib M37 R,R enantiomer (ACP-5009)	14.2±1.7	ND
Spebrutinib[d]	2.3±0.5	ND

Compound [a]	Experiment 1[b] IC_{50} (nM)	Experiment 2[c] IC_{50} (nM)

ATP=adenosine triphosphate; BTK=Bruton tyrosine kinase; IC_{50}=inhibitory concentration causing half-maximal inhibition; IMAP=ion affinity-based fluorescence polarization; ND=not done.

a Each assay included a head-to-head comparison of compounds listed. Data shown represent mean ± SD of values from 3 to 4 independent assay runs. All test compounds were preincubated for 60 minutes before starting the kinase reaction by the addition of ATP.

b Reported in Study R2013002A.

c Reported in Study R2017001.

d Also known as CC-292.

Determination of Covalent Mechanism of Action for Acalabrutinib and ACP-5862

Table 2: Characterization of BTK inhibition; IMAP assay at various preincubation times (0, 30, 60 min) and ATP concentrations (5, 25, 100 µM).

	IC_{50} (nM)					
	Acalabrutinib			ACP-5862		
ATP (µM)	0 min	30 min	60 min	0 min	30 min	60 min
5	12	4.6	3.2	27	13	6.9
25	28	7.6	3.9	72	18	9.5
100	61	9.0	4.4	101	24	10.8

ATP=adenosine triphosphate; BTK=Bruton tyrosine kinase; IC_{50}=inhibitory concentration causing half-maximal inhibition; IMAP=ion affinity-based fluorescence polarization; min=minute(s).

Note: IC_{50} values calculated from dose curves of acalabrutinib and ACP-5862 in IMAP assays where preincubation time and ATP concentrations were varied.

Table 3: Kinase Selectivity of Acalabrutinib, ACP-5862, Ibrutinib, Ibrutinib M37, and Spebrutinib.

	IC_{50} (nM)					
Kinase	Acalabrutinib (ACP-196) Exp 1	Acalabrutinib (ACP-196) Exp 2	ACP-5862 (M27) Exp 2	Ibrutinib (ACP-2001) Exp 1	Ibrutinib M37 (ACP-5009)[a] Exp 1	Spebrutinib (ACP-4006) Exp 1
BTK[b]	5.1 ± 1.0	3.0 ± 0.7	5.0 ± 1.0	1.5 ± 0.2	14 ± 2	2.3 ± 0.5
TEC	126 ± 11	139 ± 16	345 ± 34	10 ± 2	16 ± 1	16 ± 4
ITK[b]	>1,000	>10,000	>10,000	4.9 ± 1.2	1340 ± 411	24 ± 2
BMX	46 ± 12	58 ± 8	15 ± 2	0.8 ± 0.1	15 ± 4	1.6 ± 0.4
TXK	368 ± 141	352 ± 118	567 ± 174	2.0 ± 0.3	258 ± 145	9.1 ± 2.7
EGFR	>1,000	>10,000	>10,000	5.3 ± 1.3	>1000	199 ± 35
ERBB2	~1,000	413 ± 79	552 ± 166	6.4 ± 1.8	>1000	>1,000
ERBB4	16 ± 5	19 ± 1.0	343 ± 23	3.4 ± 1.4	83 ± 4	49 ± 12
BLK	>1,000	1763 ± 356	6170 ± 3348	0.1 ± 0.0	4.8 ± 0.2	131 ± 27
JAK3	>1,000	>10,000	>10,000	32 ± 15	>1000	5.4 ± 1.1

Kinase	IC_{50} (nM)					
	Acalabrutinib (ACP-196) Exp 1	**Acalabrutinib (ACP-196) Exp 2**	**ACP-5862 (M27) Exp 2**	**Ibrutinib (ACP-2001) Exp 1**	**Ibrutinib M37 (ACP-5009)[a] Exp 1**	**Spebrutinib (ACP-4006) Exp 1**

BLK=BLK proto-oncogene, Src family kinase; BMX=BMX non-receptor tyrosine kinase; BTK=Bruton tyrosine kinase; EGFR=epidermal growth factor receptor; ERBB2=erb-b2 receptor tyrosine kinase 2; ERBB4=erb-b2 receptor tyrosine kinase 4; Exp=experiment; IC_{50}=inhibitory concentration causing half-maximal inhibition; IMAP=ion affinity-based fluorescence polarization; ITK=interleukin 2 inducible T-cell kinase; JAK3=Janus kinase 3; TEC=tec protein tyrosine kinase; TXK=TXK tyrosine kinase.

Broad Kinome Selectivity of Acalabrutinib and ACP-5862

A wider kinome screen was performed for acalabrutinib, ibrutinib, and their major metabolites in commercial kinase panels at ThermoFisher (282 mammalian kinases) and DiscoveRx (384 or 392 wild-type mammalian kinases). The ThermoFisher profiling was conducted as a high-dose (10 μM) screen, using Z'-LYTE™, LanthaScreen, or Adapta assay technology.

To further investigate the kinase selectivity of acalabrutinib and ACP-5862, IC_{50} values were generated on 32 kinases identified from the initial screen, using ≥70% inhibition at 10 μM as selection criteria (and excluding the 3F-Cys kinases).

Results for all kinases with IC_{50} values of less than 1 μM for either acalabrutinib or ACP-5862 are:

Dose-Response Results from ThermoFisher Screen of 280 Kinases

Kinase	IC_{50} (nM)	
	Acalabrutinib	**ACP-5862**
CDK8 /cyclin c[a]	1280	445
FGR	1660	973
PTK5	964	2770
PTK6	626	61
RIPK2	418	732

CDK8=cyclin dependent kinase 8; FGR=FGR proto-oncogene, Src family tyrosine kinase; IC_{50}=inhibitory concentration causing half-maximal inhibition; PTK5=protein tyrosine kinase 5; PTK6=protein tyrosine kinase 6; RIPK2=receptor interacting serine/threonine kinase 2.
Note: IC_{50} values for kinases tested over a 10-point dose curve at ThermoFisher. LanthaScreen assay was used for CDK8 and RIPK2, Z'-LYTE was used for FGR, PTK5 and PTK6.
Source: Report R2017001.

Summary of DiscoveRx Kinome Profiling Hits (1 μM Screen)

Compound	Kinases Tested (WT)	Number of Hits Giving Inhibition at the Following Levels		
		>65%	**>90%**	**>99%**
Acalabrutinib*	384	7	4	1
ACP-5862	384	5	2	1
Ibrutinib	384	37	25	13
Ibrutinib M37 (ACP-5009)	384	44	26	10
Spebrutinib	384	33	14	2

BTK=Bruton tyrosine kinase; WT=wild type.
Note: Table summarizes the hit score from DiscoveRx Kinome profiling. *For acalabrutinib, the only kinase that was inhibited >99% was BTK.+
Source: Reports R2013002A, R2017001.

Nine kinases that showed >65% binding activity for acalabrutinib or ACP-5862 were considered to have significant interactions. The IC_{50} values for acalabrutinib and ACP-5862 were generated head-to-head for comparison.

Table 4 Results of the KINOMEscan Showing Hits with >65% Inhibition at 1 µM

	% Inhibition at 1 µM		IC_{50} (nM)	
Kinase	**Acalabrutinib**	**ACP-5862**	**Acalabrutinib**	**ACP-5862**
BTK*	99.95%	98.4%	15	29
BMX*	66%	76%	570	190
PTK6	21%	76%	1600	150
ERBB2*	97.9%	89%	56	120
ERBB4*	95.7%	51%	140	970
LIMK1	87%	58%	190	400
MEK5	35%	96.3%	930	69
TEC*	93.6%	93.5%	16	40
TXK*	76%	40%	540	1100

BMX=BMX non-receptor tyrosine kinase; BTK=Bruton tyrosine kinase; ERBB2=erb-b2 receptor tyrosine kinase 2; ERBB4=erb-b2 receptor tyrosine kinase 4; IC_{50}=inhibitory concentration causing half-maximal inhibition; LIMK1=LIM domain kinase 1; MEK5=mitogen-activated protein kinase kinase 5; PTK6=protein tyrosine kinase 6; TEC=tec protein tyrosine kinase; TXK=TXK tyrosine kinase.
Note: DiscoveRx scanMAX™ profiling at a single dose (1 µM) on >450 available kinases (including mutant kinases). Kinases inhibited >65% were considered to have significant interactions and were followed with IC_{50} determinations on the same platform. Kinases marked* indicate 3F-Cys kinase family members.
Source: Report R2017001.

Selectivity versus SRC Family Kinases

Some Src family of proto-oncogene nonreceptor protein tyrosine kinases showed potent inhibition with ibrutinib in both the ThermoFisher and DiscoveRx scans. As Src-family kinases are broadly expressed and important for many functions in cells of hematopoietic origin, the BTK inhibitors and ibrutinib M37 were tested in kinase inhibition assays with human members of the Src family

Table 5 Functional Assays of Src Family Kinases: Acalabrutinib, Ibrutinib, Spebrutinib and Ibrutinib Metabolite M37

	IC_{50} (nM)			
Kinase	**Acalabrutinib (ACP-196)**	**Ibrutinib (ACP-2001)**	**Spebrutinib CC-292 (ACP-4006)**	**Ibrutinib M37 R, R Enantiomer (ACP-5009)[a]**
FGR	>1000	3.3 ± 1.1	348 ± 93	2.0 ± 0.2
FYN	>1000	29 ± 0	>1000	37 ± 6
HCK	>1000	29 ± 0	>1000	32 ± 3
LCK	>1000	6.3 ± 1.3	>1000	3.9 ± 0.1
LYN	>1000	20 ± 1	>1000	19 ± 1
SRC	>1000	19 ± 1	699 ± 302	28 ± 8
YES1	>1000	4.1 ± 0.2	~1000	5.2 ± 1.3

GR=FGR proto-oncogene, Src family tyrosine kinase; FYN=FYN proto-oncogene, Src family tyrosine kinase; HCK=HCK proto-oncogene, Src family tyrosine kinase; IC50=inhibitory concentration causing half-maximal inhibition; LCK=LCK proto-oncogene, Src family tyrosine kinase; LYN=LYN proto-oncogene, Src family tyrosine kinase; SD=standard deviation; SRC=SRC proto-oncogene, non-receptor tyrosine kinase; YES1=YES proto-oncogene 1, Src family tyrosine kinase.
Note: Kinase activity was measured using the Z'-LYTE assay (ThermoFisher). Results are mean ± SD of 2 independent assay runs.
a ACP-5009 is the R, R enantiomer of ibrutinib M37. Comparable results obtained from both possible enantiomers.

Cellular Activity of BTK Inhibitors in B Cells

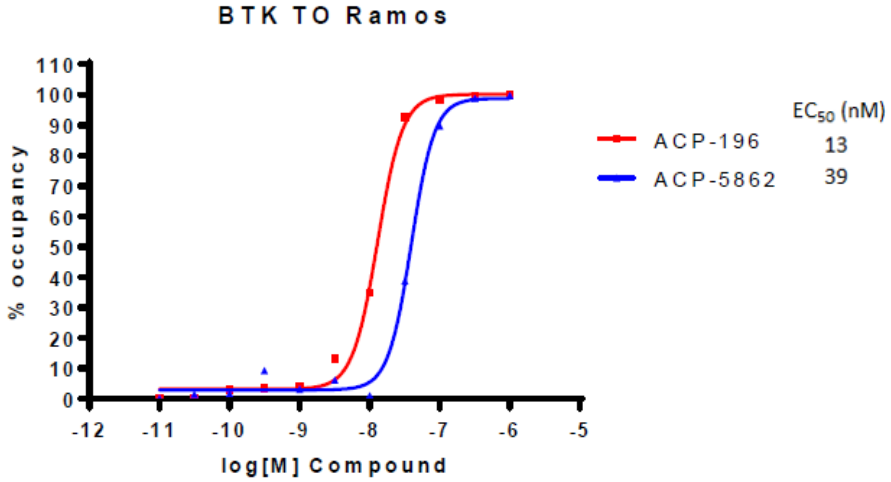
B-cell activation was measured by the up-regulation of CD69 on B cells, a cellular event downstream of BTK-mediated signals after BCR stimulation.

Test Article	EC_{50} (nM)	
	PBMC	WB
Acalabrutinib	2.9 ± 0.2	9.2 ± 4.4
Ibrutinib	0.58 ± 0.04	5.8 ± 3.0
Spebrutinib	7.4 ± 0.7	140 ± 85

BCR=B-cell receptor; EC_{50}=effective concentration causing half maximal inhibition; PBMC=peripheral blood mononuclear cells; WB=whole blood.
Note: Results are mean ± SD of at least three independent experiments.
Source: 2013003A.

Figure 3

BTK occupancy was established in the Ramos Burkitt lymphoma cell line:



BTK=Bruton tyrosine kinase; EC_{50}=effective concentration causing half maximal inhibition; ELISA=enzyme-linked immunosorbent assay.
Note: Ramos cells were incubated for 2 hours with different concentrations of acalabrutinib and ACP-5862 and then cell lysates were subjected to a BTK occupancy ELISA. Relative percentage occupancy was measured with the aid of a biotinylated acalabrutinib analogue probe.

Differential potency was also observed in inhibition of BCR-induced CD69 up-regulation.

Cellular Assay	EC_{50} (nM)	
	Acalabrutinib	ACP-5862
PBMC[a]	6.2 ± 2.3	26 ± 16
PBMC with washout[a]	13 ± 3	51 ± 19
WB[b]	8.8 ± 0.8	64 ± 6

EC_{50}=effective concentration causing half maximal inhibition; PBMC=human peripheral blood mononuclear cells; WB=whole blood.
Note: Data are from a head-to-head comparison of acalabrutinib and ACP-5862 in the same experiments.
a Data are mean ± SD for 3 independent assay runs.
b Data are mean ± SD for 4 donors.
Source: Report R2017002.

Cellular Effects of Acalabrutinib on T-Cells and Epithelial Cells

T-cell activation was evaluated by measuring anti-CD3/anti-CD28-stimulated IL-2 production in Jurkat (acute T-cell leukaemia) cells and anti-CD3-induced CD25 expression in gated primary human T cells. The phosphorylation of EGFR, upon stimulation by epidermal growth factor (EGF), was measured in A431 epidermoid carcinoma cells to assess potential EGFR inhibition.

Compound	Anti-CD3/CD28-Induced IL-2 Production Jurkat T Cells EC_{50} (nM)[a]	Anti-CD3-Induced CD25 Expression PBMCs EC_{50} (nM)[a]	EGF-Induced EGFR Phosphorylation A431 Carcinoma EC_{50} (nM)[b,c]
Acalabrutinib	>10,000	>10,000	>10,000
Ibrutinib	99 ± 17	257 ± 71	71 ± 14
Spebrutinib	150 ± 22	575 ± 60	4680 ± 720

EC_{50}=effective concentration causing half maximal inhibition; EGF=epidermal growth factor; EGFR=epidermal growth factor receptor; IL=interleukin; PBMC=peripheral blood mononuclear cells.

a Results presented are the mean ± SD of three independent experiments.

b Results presented are the mean with ± range of two independent experiments.

c Similar results were obtained using the HT-1376 cell line.

Potential effects of acalabrutinib and ibrutinib on T-cell proliferation were also assessed using primary CD8+ T cells

Compound	Human IC_{50} [nM]	Murine IC_{50} [nM]
Acalabrutinib	>10,000	>10,000
Ibrutinib	410	405

IC_{50}=inhibitory concentration causing half-maximal inhibition; PBMC=peripheral blood mononuclear cells.

Note: 72-hour proliferation assays were conducted in CD8+ T cells enriched from human PBMC preparations (n=2 replicate assays from a single donor) and from mouse spleens (n=2 replicate assays).

Source: AZ Pharmacology Report 01.

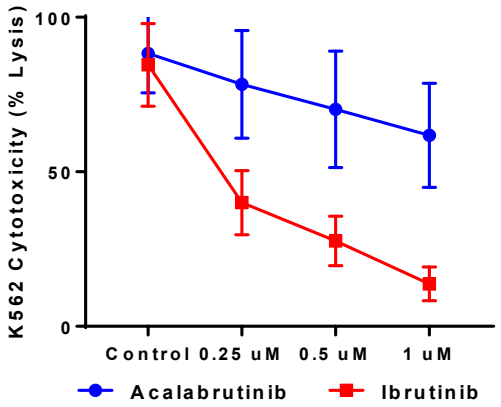
Table 6 Trastuzumab-mediated ADCC in human NK cells in the presence of acalabrutinib or ibrutinib

Donor	Acalabrutinib		Ibrutinib	
	EC_{50} (nM)	% Inhibition at 1 µM	EC_{50} (nM)	% Inhibition at 1 µM
1	5440	21%	80	87%
2	8790	15%	170	81%
3	>10,000	10%	690	63%
4	>10,000	9%	1540	5%
5	4430	3%	100	93%
6	6260	4%	290	84%

ADCC=antibody dependent cellular cytotoxicity; EC_{50}=effective concentration causing half maximal inhibition; NK=natural killer; PBMC=peripheral blood mononuclear cells.

Note: Human NK cells enriched from PBMCs in 10 concentration point assay in half-log dilutions from 10 µM [acalabrutinib] or 1µM [ibrutinib] were incubated with Eu-labelled SKBr3 target cells.

Figure 4: Natural cytotoxicity study - NK cell lysis of K562 cells



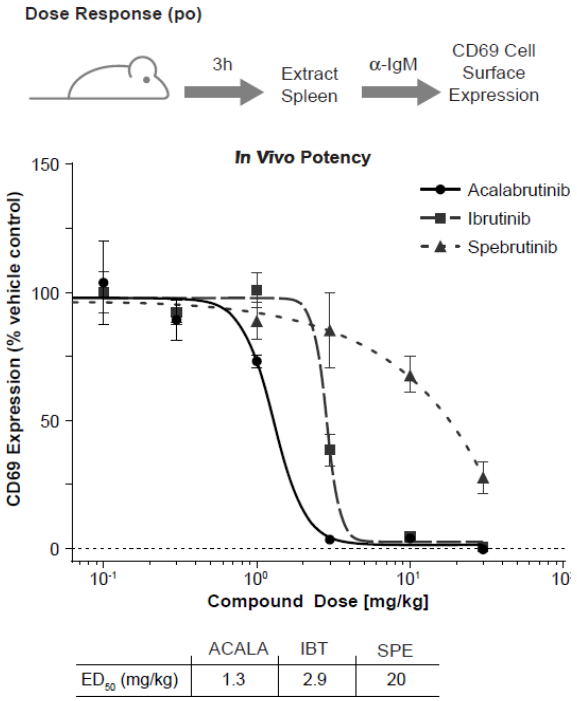
ANOVA=analysis of variance; NK=natural killer cell.
Note: Peripheral blood mononuclear cells were cultured with ^{51}Cr labelled K562 targets at an E:T ratio of 100:1 for 4 hours. Cytotoxicity was evaluated by scintillation counting of supernatants. Treatment, dose, and interaction effect were significant in 2-way ANOVA (n=5 healthy donors; ibrutinib v. acalabrutinib p <0.0001; all ibrutinib doses p <0.0001 compared with control; p=0.0117 for control versus acalabrutinib 1 µM, other acalabrutinib doses not statistically different from control condition).

In vivo studies

Single-Dose Activity in Mice: Dose-Response Comparison with Ibrutinib

In vivo potency of BTK inhibition was tested in *ex-vivo* assays of B-cell function. Mice (5 per group) were gavaged with acalabrutinib, ibrutinib, spebrutinib, or vehicle over a concentration range. After 3 hours, spleens were extracted and splenocytes stimulated with anti-IgM for 18 hours. Expression levels of the B-cell activation marker CD69 were measured in gated B cells by flow cytometry.

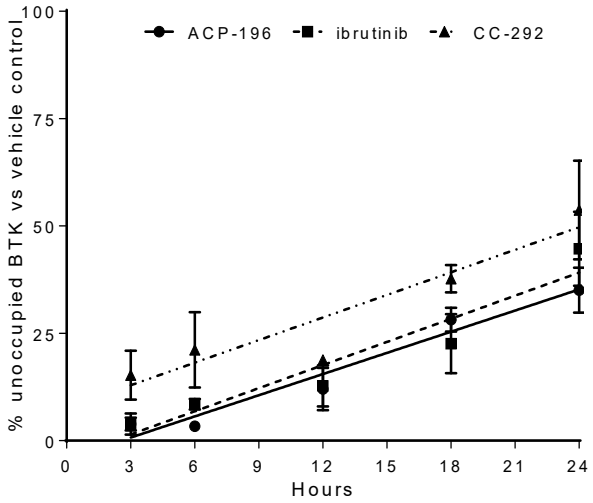
Dose Response: Inhibition of BCR-Mediated CD69 Up-Regulation



	ACALA	IBT	SPE
ED_{50} (mg/kg)	1.3	2.9	20

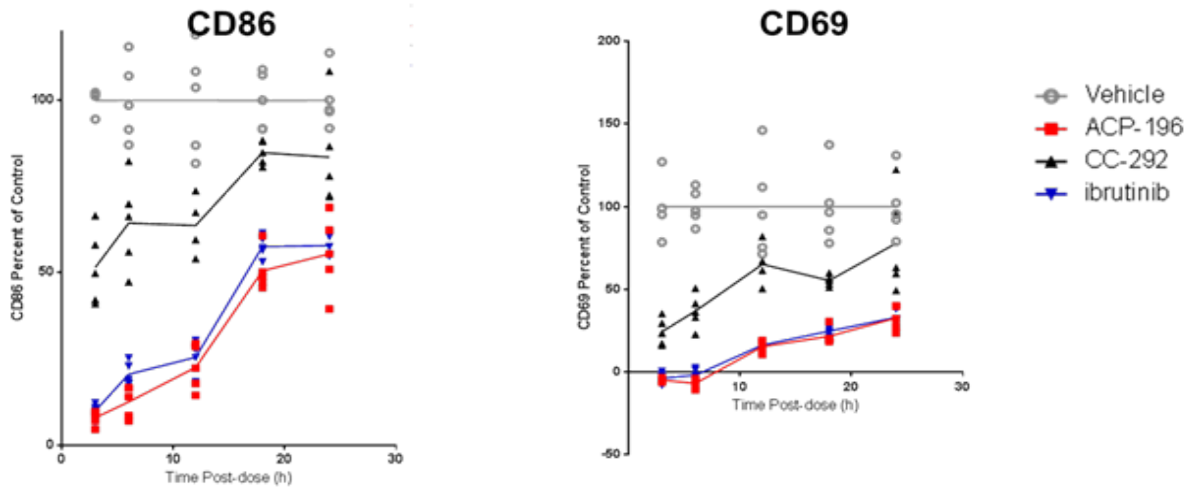
Acala=acalabrutinib; α-IgM=anti-immunoglobulin type M; BCR=B-cell receptor; ED_{50}=effective dose level causing half maximal effect; IBT=ibrutinib; SPE=spebrutinib.
Note: Expression of CD69: BCR stimulation (α-IgM) of splenocytes harvested from mice treated with a single administration of acalabrutinib, ibrutinib, or spebrutinib by oral gavage at doses up to 30 mg/kg. Data are expressed as % of control median fluorescence intensity.

Figure 5 BTK Target Occupancy over Time in Mouse Splenocytes after a Single 25 mg Dose of Acalabrutinib



BTK=Bruton tyrosine kinase; CC-292=spebrutinib.
Note: Mice (5 per group) received a single, oral, 25 mg/kg dose of acalabrutinib, ibrutinib, spebrutinib, or vehicle. Spleens were extracted at 3, 6, 12, 18, or 24 hours postdose and BTK occupancy was determined by an ELISA-based method (Module 5.3.1.4.5). Unoccupied BTK (% free BTK versus vehicle control) was calculated at various time points after dosing.

Figure 6 Inhibition Dynamics of BCR-Mediated CD86 and CD69 Up-Regulation in Splenocyte B Cells Harvested from Mice Treated with BTK Inhibitors



Mean CD86 % of Inhibition					
	3 hr	6 hr	12 hr	18 hr	24 hr
ACP-196	92.1	87.4	77.5	49.4	44.5
CC-292	48.5	35.6	36.3	15.1	16.4
Ibrutinib	90.1	79.4	74.5	42.4	42.1

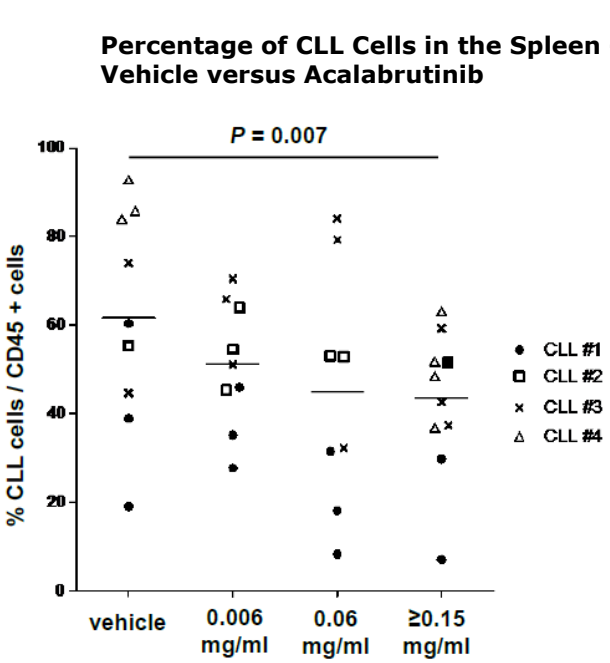
Mean CD69 % of Inhibition					
	3 hr	6 hr	12 hr	18 hr	24 hr
ACP-196	104.9	106.9	84.7	78.4	67.3
CC-292	75.6	63.2	34.8	44.7	22.1
Ibrutinib	103.7	101.9	83.7	75.3	67.0

BTK=Bruton tyrosine kinase; CC-292=spebrutinib.
Note: Mice received a single, oral, 25 mg/kg dose of acalabrutinib, ibrutinib, or spebrutinib or vehicle. Spleens were extracted at 3, 6, 12, 18, or 24 h postdose and BCR-stimulated up-regulation of CD69 in B cells was measured by

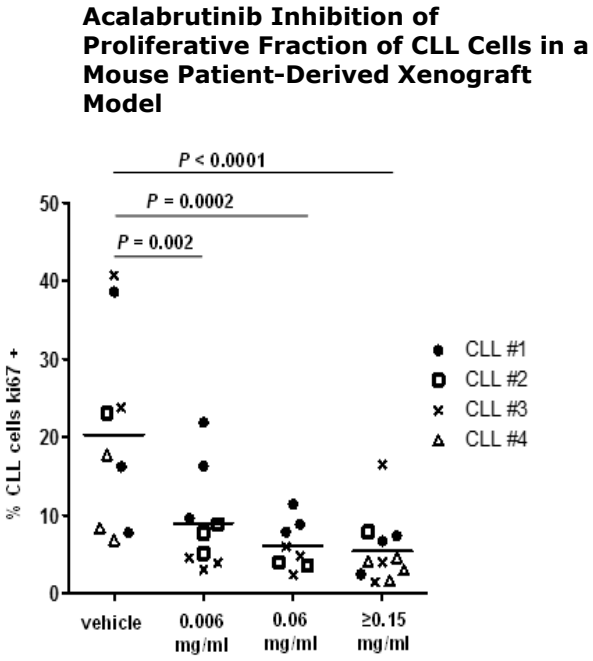
flow cytometry. Data are expressed as percentage of the BCR-stimulated up-regulation observed in splenoctyes from vehicle-treated control mice.

Human CLL Xenograft Model in Mice

Acalabrutinib was evaluated in a human primary CLL xenograft model established by engrafting primary PBMCs from patients with CLL into non-obese diabetic, severe combined immunodeficiency (SCID), interferon-$\gamma^{-/-}$ (NSG) mice.

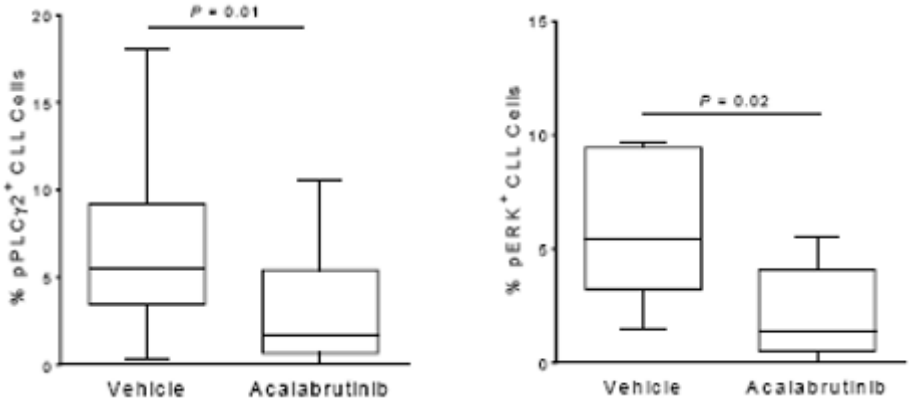


CLL=chronic lymphocytic leukemic; NSG=non-obese diabetic, severe combined immunodeficiency, interferon-$\gamma^{-/-}$.
Note: NSG mice were engrafted with primary CLL cells and treated with acalabrutinib in drinking water at the indicated concentrations. At the end of 3 weeks, spleen-resident human CD5+/CD19+ cells were evaluated by flow cytometry, as the fraction of total human CD45+ cells.



CLL=chronic lymphocytic leukemic; Ki67=proliferation antigen Ki-67.
Note: Proliferating spleen-resident CLL cells were harvested from mice and evaluated for Ki67 staining by flow cytometry at the end of the dosing period (3 weeks).

Figure 7 Acalabrutinib On-Target Effects on CLL Cells in Mouse Patient-Derived Xenograft Model - pPLCγ2 and pERK l



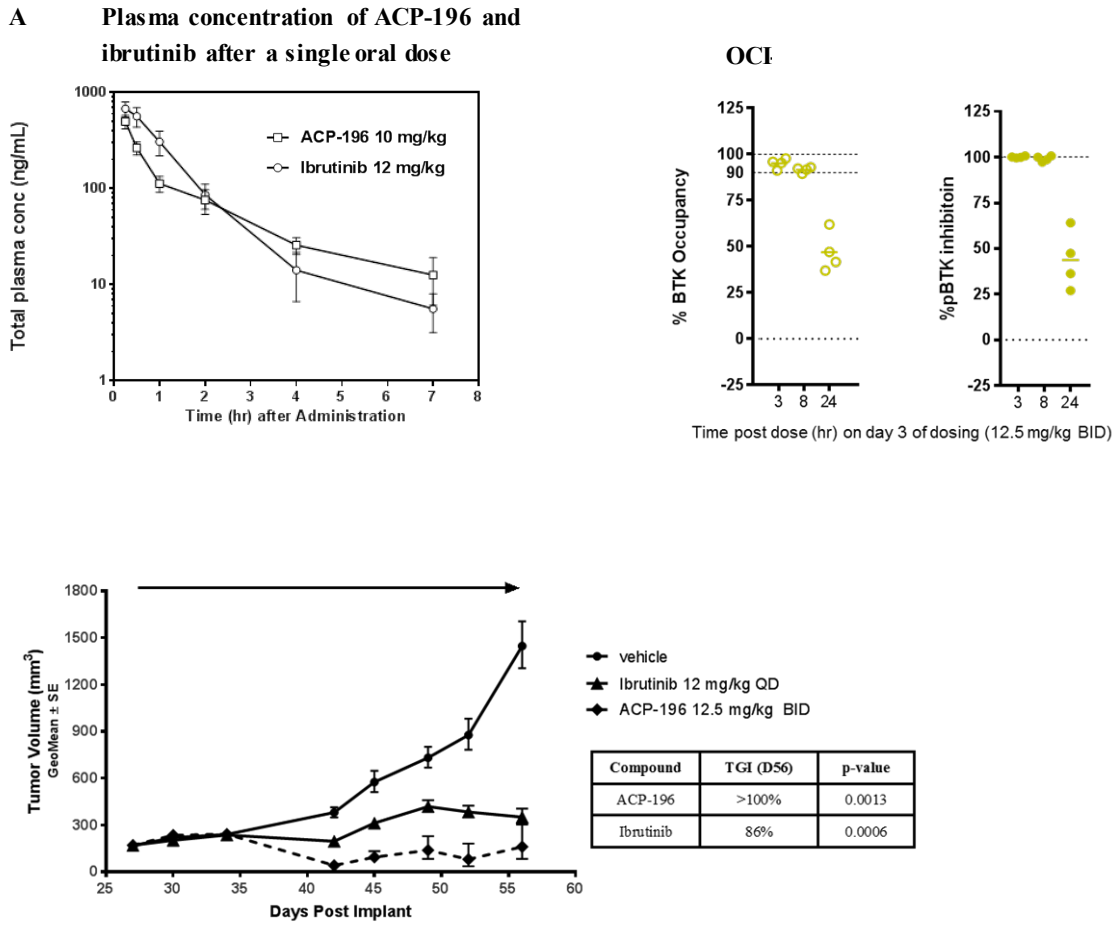
BCR=B-cell receptor; CLL=chronic lymphocytic leukaemia; NSG=non-obese diabetic, severe combined immunodeficiency, interferon-$\gamma^{-/-}$; pERK=phospho-extracellular signal regulated kinase; pPLCγ2=phosphor-phosphoinositide phospholipase C gamma 2.

Note: Phospho (p)-PLCγ2 and pERK analysis of human CLL cells from NSG mice, showing basal phosphorylation of downstream mediators of BCR signalling, after 14 days of treatment in ACE-NC-002. Results shown are median ± interquartile range.
Source: Herman et al. 2016.

In the CLL xenograft model, acalabrutinib transiently increased CLL cell counts in the peripheral blood of mice on Day 14.

Evaluation of Efficacy of Acalabrutinib and Ibrutinib in Mouse Xenograft Models of DLBCL and MCL

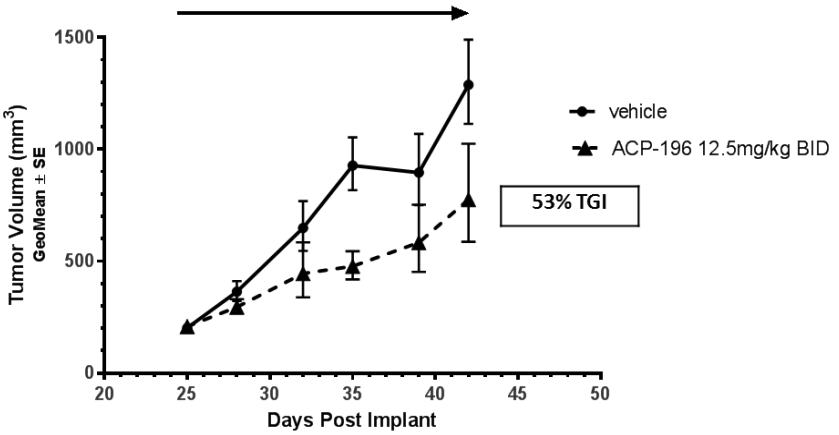
Acalabrutinib was evaluated in human xenograft models of MCL and DLBCL in mice to demonstrate antitumor activity in vivo. OCI-Ly10 human DLBCL or Jeko-1 human MCL cells (5 x 10^6/mouse) were implanted subcutaneously in female CB.17 SCID mice. Acalabrutinib was dosed at 12.5 mg/kg BID and ibrutinib was dosed at 12 mg/kg QD.



Compound	TGI (D56)	p-value
ACP-196	>100%	0.0013
Ibrutinib	86%	0.0006

BID=twice daily; hr=hour; D=day; DLBCL=diffuse large B-cell lymphoma; QD=once daily; SE=standard error; TGI=tumour growth inhibition.
Note: (A) Total acalabrutinib plasma concentration ± SD; N=3 female CB-17 SCID mice per time point. Drug levels were below detectable levels at the 24 h time point. (B) BTK occupancy and pBTK was measured in OCI-LY10 tumours (4 per group) following 3 days of dosing at 12.5 mg/kg BID (second dose was administered 8 hours following first dose). BTK occupancy was determined by an ELISA-based method; pBTK (Y223) was quantified from Western Blots where 0% inhibition was the median of vehicle treated tumours at 3 hours, and 100% inhibition was 0 signal for pBTK (Y223). (C) Mice were randomized into groups of 10 based on established tumour volumes of 150 to 200 mm^3 and treated with vehicle, acalabrutinib (12.5 mg/kg BID) or ibrutinib (12 mg/kg QD) for 4 weeks. Treatment period is indicated by arrow. Tumour growth is shown as geometric mean ± SE. Data were log transformed to remove any size dependency before statistical evaluation. Statistical significance was evaluated using a one-tailed, 2-sample Student t-test.
Source: AZ Pharmacology Report 02.

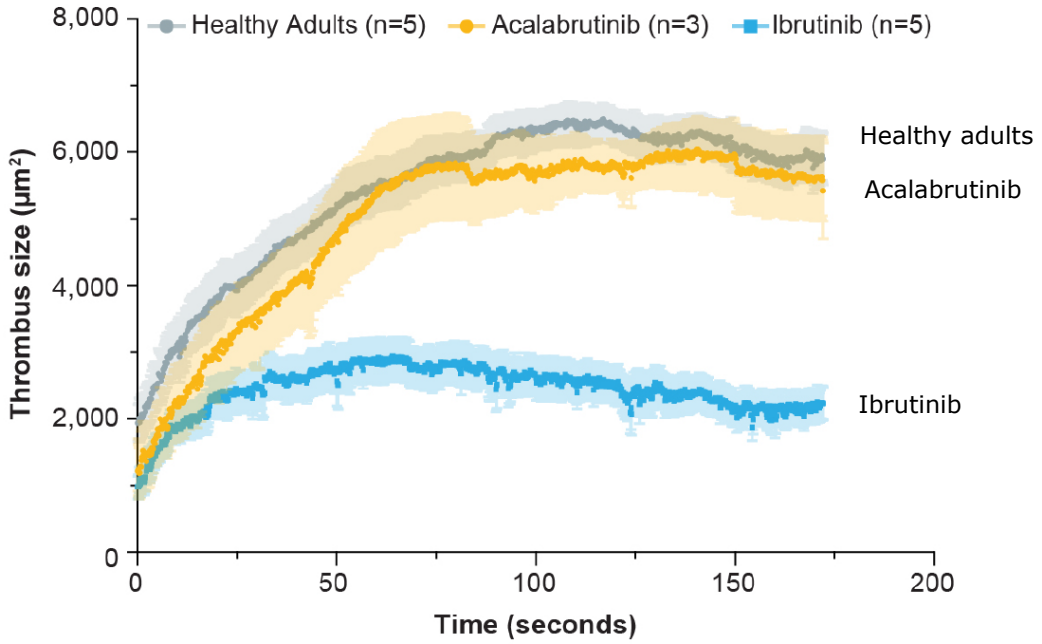
Effects of Acalabrutinib on Tumour Growth in the Jeko-1 Model of MCL



BID=twice daily; MCL=mantle cell lymphoma; SE=standard error; TGI=tumor growth inhibition.
Note: Mice were randomized based on tumor volumes using stratified sampling and enrolled into control and treatment groups. Dosing began when mean tumor size reached approximately 150 to 200 mm^3. Tumor growth is shown as geometric mean ± SE. Treatment period is indicated by arrow.
Source: AZ Pharmacology Report 02.

Effects of Acalabrutinib and Ibrutinib on Thrombus Formation

***Ex Vivo*/*In Vivo* Study of Thrombus Formation**



BID=twice daily; QD=once daily; VWF=von Willebrand factor.
Note: Platelets from patients treated with ibrutinib 420 mg QD (n=5) or acalabrutinib 100 mg BID (n=3) were evaluated for their ability to support thrombus formation in laser injured arterioles of VWF^{HA1} mice. Freshly isolated platelets from healthy volunteers (n=5) were used as non-drug treated controls. A minimum of 4 arterioles per mouse was used to assess thrombus formation for each patient/volunteer sample. The size of resulting thrombi is shown, as a function of time (shading denotes standard error of the median).
Source: Byrd et al. 2016; additional detail can be found in R2017005.

Secondary pharmacodynamic studies

Evaluation of the secondary pharmacology for acalabrutinib and ACP-5862 was performed using two radioligand binding assays across a diverse set of 80 receptors, ion channels, and transporters. No acalabrutinib activity of ≥50% was detected on 79 of the 80 tested targets. Interaction (was detected only on adenosine A3 receptor (A3), with a K_i value of 2.7 µM in the first assay and 0.91 µM in the second assay. Acalabrutinib showed some inhibition on adenosine 2A (A2A, 35.1% inhibition, K_i=17 µM).

The pharmacology interaction profile of the major metabolite ACP-5862 was comparable to that observed with acalabrutinib. No interaction was observed at 77 of the 80 receptors tested. Inhibition of specific ligand binding of ≥50% was identified for A2A, A3, and neurokinin 2 (NK2) in the 10 µM screen. The K_i values for ACP-5862 were determined to be 12 µM for A2A, 4.8 µM for A3 and 5.8 µM for NK2.

The acalabrutinib unbound C_{max} in patients at the intended therapeutic dose was 27-fold lower than the K_i for the A3 receptor. The ACP-5862 unbound C_{max} in patients at the intended therapeutic dose was 321-fold lower than the K_i for the A3 receptor.

Safety pharmacology programme

CNS

Modified Irwin test in rats, Study 503222, GLP
The potential effects of acalabrutinib on neurobehavior (modified Irwin's test) and on body temperature were assessed after a single oral administration to male Sprague-Dawley rats. Animals (8 per group) were dosed once by oral gavage with vehicle, 30, 100, or 300 mg/kg acalabrutinib or with 20 mg/kg chlorpromazine as reference substance. Animals were evaluated at predose and 1, 2, 4, 6, and 24 hours after dosing. Single oral administration of acalabrutinib at doses up to 300 mg/kg did not elicit any neurobehavioral effects, or effects on rectal temperature.

Cardiovascular

Effect on hERG channel, Study 503219, GLP
The in vitro effect of acalabrutinib on hERG channel activity was investigated in human embryonic kidney (HEK) cells stably transfected with hERG. The effect of acalabrutinib at 10 µM on the hERG tail current was measured in 5 cells. Acalabrutinib at a concentration of 10 µM showed an inhibition of 25.1±1.3% of the hERG tail current

Effect on hERG channel, Study 794950, GLP
The potential of acalabrutinib alone and in combination with ACP-319, a selective PI3Kδ inhibitor, to cause inhibition at the hERG channel was investigated using the whole-cell patch clamp electrophysiology technique in CHO-K1 (Chinese Hamster Ovary) cells stably transfected with hERG. Acalabrutinib at 1 µM and 10 µM inhibited the hERG tail current by 8.2 ± 3.7% and 24.9 ± 6.9%, respectively.

Single dose cardiovascular telemetry study in beagle dogs, Study 491868, non-GLP
This was a pilot study conducted before selection of acalabrutinib for development. The results showed that oral administration of acalabrutinib at doses of 10 and 30 mg/kg did not result in changes in the ECG parameters, heart rate, and mean arterial blood pressure up to 24 hours after administration in radiotelemetry-implanted male beagle dogs.

Cardiovascular Effects of ACP-196 after Oral Administration to Dogs, Study 594019, GLP
A single oral gavage dose of 3, 10, or 30 mg/kg acalabrutinib did not significantly affect the

cardiovascular system, body temperature, ECG intervals, or physical condition of the animals. Mean total blood concentrations of 188, 679, and 3442 ng/mL acalabrutinib were noted at 3 hours postdosing after administration of 3, 10, and 30 mg/kg, respectively.

Respiratory

Effects on Respiration by Means of Head-Out Plethysmography in male Sprague-Dawley Rats, Study 503221, GLP
There were no statistically significant changes in any respiratory parameters in acalabrutinib-treated groups at 0 (vehicle), 30, 100, and 300 mg/kg when compared with the vehicle control group at each time interval.

Pharmacodynamic drug interactions

See section Clinical Pharmacology.

2.3.3. Pharmacokinetics

Absorption

Mouse pharmacokinetics

Single dose
Acalabrutinib was administered via single oral gavage (5 mg/kg) to 12 female BALB/c mice and via single IV injection (2 mg/kg) to 12 female BALB/c mice.

Summary of Mean Pharmacokinetic Parameters of Acalabrutinib in Female BALB/c Mice Following a 2 mg/kg Intravenous or 5 mg/kg Oral Administration of Acalabrutinib

Pharmacokinetic Parameter	2 mg/kg IV Female (n=12)	5 mg/kg Oral Female (n=12)
C_0 (ng/mL)	894	ND
C_{max} (ng/mL)	488	220
$AUC_{(0\text{-}inf)}$ (ng•h/mL)	138	213
T_{max} (h)	ND	0.08
$t_{1/2}$ (h)	0.16	0.93
CL (L/h/kg)	14.5	ND
Vss (L/kg)	1.99	ND
F (%)	ND	61.8

- $AUC_{0\text{-}inf}$=area under the plasma concentration-time curve from 0 hour to infinity; C_0=plasma concentration at time zero; C_{max}=maximum observed plasma concentration; CL=total body clearance; F=bioavailability fraction of dose absorbed relative to IV dosing expressed as a percent; IV=intravenous; NA/ND=not applicable or not determined; $t_{1/2}$=terminal half-life; T_{max}=time of maximum observed plasma concentration; Vss=volume of distribution at steady state.
- **Source**: 0112-001

Rat pharmacokinetics

Single-dose
Acalabrutinib was administered via single IV injection (2 mg/kg) to 3 male Sprague-Dawley rats and via single oral gavage (5 mg/kg) to 6 male Sprague-Dawley rats (n=3 acalabrutinib free base and n=3 acalabrutinib maleate salt).

Mean (±SD) Acalabrutinib Pharmacokinetic Parameters after a Single Intravenous Injection (2 mg/kg) or Oral Gavage Administration (5 mg/kg) to Male Rats (n=3/Group)

Dose, Route, Salt form	T_{max} (h)	Co/C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{0-24h} (ng•h/mL)	AUC_{0-inf} (ng•h/mL)	Vss (L/kg)	CL (L/h/kg)	F (%)
2 mg/kg IV Free Base	NA	1550 (518)	2.74 (1.9)	298 (50.1)	300 (48.8)	3.35 (2.05)	6.78 (1.08)	NA
5 mg/kg PO Free base	0.25 (NA)	103 (22.3)	1.76 (0.34)	155 (23.9)	154 (20.9)	NA	NA	21
5 mg/kg PO Maleate salt	0.25 (NA)	125 (31.4)	2.03 (0.56)	172 (10.6)	170 (8.86)	NA	NA	23

AUC_{0-24h}=area under the plasma concentration-time curve from 0 hour to 24 hours; AUC_{0-inf}=area under the plasma concentration-time curve from 0 hour to infinity; C_0=plasma concentration at time zero; C_{max}=maximum observed plasma concentration; $t_{1/2}$=terminal half-life; CL=total body clearance; F=bioavailability, fraction of dose absorbed relative to IV dosing expressed as a percent; IV=intravenous; NA=not applicable; PO=oral; SD=standard deviation; T_{max}=time of maximum observed plasma concentration; Vss=volume of distribution at steady state.
Source: 2219-003

Repeat-dose

The repeat-dose pharmacokinetics of acalabrutinib have been evaluated in Sprague-Dawley and Wistar Han rats as part of toxicology studies from 14 days to 6 months duration. In general, exposure in Wistar Han rats was higher than in Sprague-Dawley rats.

Toxicokinetics data are presented below in the Toxicology section.

Dog pharmacokinetics

Single dose

Acalabrutinib was administered via single IV injection (1 mg/kg) to 3 fasted male Beagle dogs and via single oral gavage (2.5 mg/kg) to 3 fasted and to 3 fed male Beagle dogs

Mean (±SD) Acalabrutinib Pharmacokinetic Parameters after a Single Intravenous Injection (1 mg/kg) or Oral Gavage Administration (2.5 mg/kg) to Male Dogs (n=3/Group)

Dose Route Salt Form Diet		T_{max} (h)	Co/C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{0-24h} (ng•h/mL)	AUC_{0-inf} (ng•h/mL)	Vss (L/kg)	CL (L/h/kg)	F (%)
1 mg/kg IV Free Base Fasted	Mean (SD)[a]	NA	613 (17.7)	0.941 (0.10)	565 (26)	566 (25.3)	1.90 (0.16)	1.77 (0.08)	NA
2.5 mg/kg PO Free base Fasted	Mean (SD)	0.5 (0.25–1)[b]	388 (45.4)	1.76 (0.64)	753 (57.2)	751 (55.7)	NA	NA	53
2.5 mg/kg PO Free Base Fed	Mean (SD)	0.5 (0.25–1)[b]	377 (251)	2.59 (NA)	744 (243)	823 (NA)	NA	NA	58

AUC_{0-24h}=area under the plasma concentration-time curve from 0 to 24 hours; AUC_{0-inf}=area under the plasma concentration-time curve from 0 hour to infinity based upon the last predicted concentration; CL=total body clearance; C_{max}=maximum observed plasma concentration; C_0=plasma concentration at time zero; F=bioavailability, fraction of dose absorbed relative to IV dosing expressed as a percent; IV=intravenous; NA=not applicable; PO=oral; SD=standard deviation; T_{max}=time of maximum observed plasma concentration; $t_{1/2}$=terminal half-life; Vss=volume of distribution at steady state.
a SD is not calculated or not reported when n <3
b Median (range)

Repeat-dose

The repeat-dose pharmacokinetics of acalabrutinib have been evaluated in dogs as part of toxicology studies from 14 days to 9 months duration.

Distribution

Protein binding

The plasma protein binding characteristics of acalabrutinib were investigated in several studies using ultrafiltration, equilibrium dialysis, and ultracentrifugation methodologies. The ultracentrifugation technique was superior and used to determine plasma protein binding.

Species	Acalabrutinib Bound (%)	Unbound (%)	ACP-5862 Bound (%)	Unbound (%)
Mouse	75.4	24.6	98.6	1.4
Rat	92.0	8.0	99.8	0.2
Dog	68.4	31.6	94.3	5.7
Monkey	94.2	5.8	ND	ND
Human	97.5	2.5	98.6	1.4
HSA	93.7	6.3	ND	ND
AGP	41.1	58.9	ND	ND

AGP=acid glycoprotein; HSA=human serum albumin; ND=Not determined.
Source: XS-0850, XS-0912

Blood cell partitioning

The mean percent distribution of acalabrutinib to blood cells and the calculated blood to plasma ratio at the final concentrations of 1, 3, and 10 µM and that of ACP–5862 at 1 µM and 10 µM were predominantly independent of concentration.

Species	Acalabrutinib Distribution into Blood Cells (%)	Blood to Plasma Ratio	ACP-5862 Distribution into Blood Cells (%)	Blood to Plasma Ratio
Mouse	56.2	1.37	23.3	0.87
Rat	29.6	0.87	73.7	2.54
Dog	49.6	1.06	67.4	1.40
Monkey	27.4	0.83	ND	ND
Human	26.4	0.79	11.6	0.66

ND=Not determined.
Source: XS-0850, XS-0947

Tissue distribution

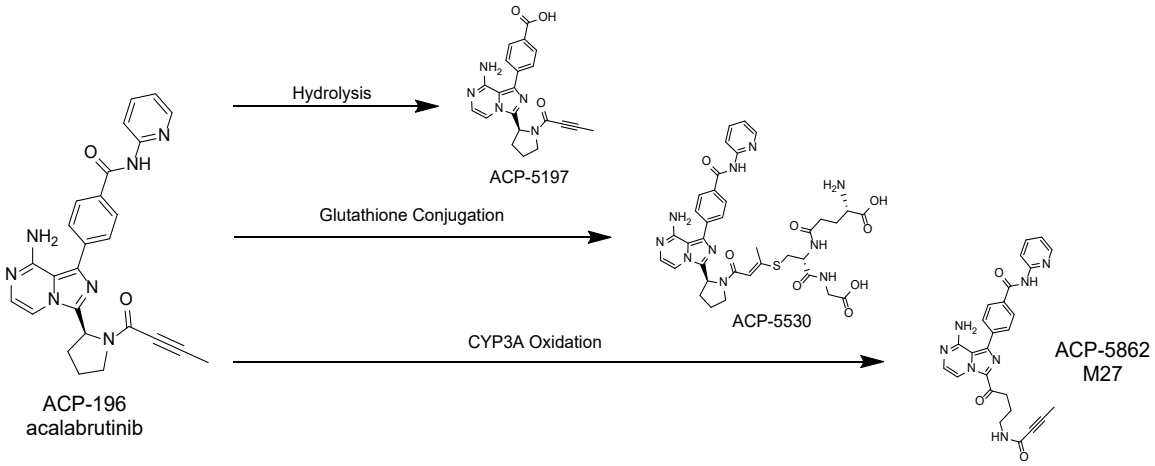
Quantitative Whole-Body Autoradiography in SD Rats, Study ESN0329
Following the administration of single oral doses of [^{14}C]acalabrutinib, radioactivity (representing acalabrutinib and/or its metabolites) was rapidly absorbed and widely distributed into tissues with maximum concentrations of radioactivity in almost all tissues being measured at 0.25 or 1 hour after dosing. During 0.25– 24 h after dosing the distribution pattern of radioactivity at each time point was similar with most tissues containing radioactivity concentrations, similar to or, less than that observed in whole blood. Greatest radioactivity concentrations were present in the small intestine wall (generally about 20-fold greater than in whole-blood), liver (approximately 6-fold greater than in whole-blood) and kidney (approximately 4-fold greater than in whole blood), adrenal gland, stomach wall, spleen, lacrimal glands and pancreas. Acalabrutinib and metabolite ACP-5862 were present in plasma of fetuses on GD 18 and were secreted into the milk of lactating rats.

Metabolism

Metabolism of [^{14}C]acalabrutinib was determined in vitro in hepatocytes from mouse, rat, dog, monkey, and human. Rat, dog, and human ADME of acalabrutinib was determined in definitive radiolabelled studies at doses of 100 mg/kg, 30 mg/kg, and 100 mg, respectively.

The primary metabolic pathways were characterized for acalabrutinib, with secondary and tertiary metabolites arising from sequential metabolism and/or combinations of the 3 major routes.

Figure 8: Metabolism of Acalabrutinib: Primary Metabolic Routes



The most abundant circulating metabolite in human was ACP–5862 (M27), which was formed by CYP3A-mediated oxidation. No other quantitatively significant acalabrutinib metabolites were observed in human plasma.

Metabolism of [^{14}C]acalabrutinib has been evaluated in vivo in rat (100 mg/kg PO), dog (30 mg/kg PO), and human (100 mg PO) with characterization of metabolites in plasma, urine and faeces. Over 3 dozen metabolites were characterized in the plasma and excreta of rat, dog, and human following an oral dose of [^{14}C]acalabrutinib.

The metabolic fate of [^{14}C]acalabrutinib was characterized in a formal mass balance study in human (ACE-HV-009).

Table 7: Quantitative Radiometric Profiling Data for Plasma, Feces, and Urine in Healthy Volunteers after a Single 100 mg Oral Dose of [^{14}C]Acalabrutinib

Component	Proposed Structure	rt (min)	% of Excreted Dose		% of AUC
			Feces	Urine	Plasma
M3	Multiple oxidation, dealkylation	17.2[a]	1.8	1.3	2.5
M5 (ACP-5530)	Glutathione adduct	24.3[b]	ND	ND	2.2
M7 (ACP-5531)	Cysteinylglycine adduct	27.6[b]	ND	2.7[e]	10.8[f]
M9	Oxidation, cysteinylglycine adduct	27.7[b]	ND		
M10 (ACP-5461)	Cysteine adduct	28.1[b]	Trace		
M11	Oxidation, cysteine adduct	28.3[a]	Trace		
M16	Reduction of M27	30.9[a]	2.9	0.6	2.2
M17	Alkyne hydration, reduced M25	31.6[a]	5.2[g]	Trace	ND
M18	Two oxidations (+O_2)	31.4[c]		ND	Trace
M22	Two oxidations (+O_2)	33.0[a]	12.1[h]	0.5	Trace
M45	Reduced ACP-5134	33.0[c]		Trace	Trace
M23 (ACP-5134)	Hydrated alkyne	33.6[a]		Trace	Trace
M24	Oxidation of reduced ACP-5134	34.2[a]	7.5	Trace	Trace
M25	Oxidation, dehydration	35.6[a]	Trace	0.2	5.9
Parent	Acalabrutinib	38.5[b]	1.2	0.5	8.6
M27 (ACP-5862)	Oxidation, ring opening	41.6[b]	3.5	0.5	34.7
Total			83.5[d]	12.0[d]	

AUC=area under the curve; rt=retention time; ND=not determined; Trace=component was observed via MS/MS, but ^{14}C was not above baseline.
Note: % of AUC=% of component in total radiometric profile from a time-averaged pool of plasma samples
a, b, c indicate retention times from urine, plasma, or feces chromatograms, respectively
d Total values are geometric means (n=6) of total ^{14}C excreted,
e components M7, M10, and M11 contribute to the % of excreted dose
f components M7, M8, M9, M10, and M11 contribute to the % of AUC
g components M17 and M18 contribute to the % of excreted dose
h components M22, M45, and M23 contribute to the % of excreted dose
Source: 8341070 and ACE-HV-009

Mass balance studies were performed in in rats and dogs and based on these data the ratio of exposure to the main human metabolite ACP-5862 was calculated.

Table 8: **Cross-Species Comparison of Total Exposure to Acalabrutinib and Major Human Metabolite ACP-5862 Following a Single Oral Dose**

Species, Sex	Dose	ACP-196 (Parent) C_{max} (ng/mL)	ACP-196 (Parent) AUC_{0-t} (ng•h/mL)	ACP-5862 (Metabolite) C_{max} (ng/mL)	ACP-5862 (Metabolite) AUC_{0-t} (ng•h/mL)	AUC Ratio (M/P)[c]
Rat, male	100 mg/kg[a]	1790	4570	3510	23300	4.93
Rat, female	100 mg/kg[a]	4110	6070	3770	22600	3.57
Dog, male	30 mg/kg[a]	6830	17800	797	2350	0.10
Dog, female	30 mg/kg[a]	8370	19300	1310	3750	0.19
Human[b]	100 mg	601	734	443	1670	2.7[d]

AUC_{0-t}=area under the concentration time curve from time zero to the last quantifiable concentration (ng equivalent hours/g); C_{max}=maximum plasma concentration; M/P=metabolite to parent; NOAEL=no observed adverse effect level.
a Male rat and male and female dog doses were at the NOAEL for each species (8340639).
b Period 1 geometric mean C_{max} and AUC_{0-t} data for parent (ACE-HV-113 CSR); period 1 and period 2 overall geometric mean C_{max} and AUC_{0-t} data for metabolite (17-RS-426CL).
c AUC ratio values were adjusted for molecular weight of parent (465.5) and metabolite (481.5).
d Human M/P based on overall geometric mean from periods 1 and 2 AUC_{INF} (17-RS-426CL).

Excretion

After oral administration of [^{14}C]acalabrutinib, mean recovery of radioactivity was >94% in rat and >87% in dog; excretion of radioactivity was essentially complete by 48 hours. In rats and dogs, mean faecal recovery was >88% of dose and >69% of dose, respectively. Excretion of radioactivity in urine accounted for approximately 3% of dose in rat and 15% of dose in dog.

2.3.4. Toxicology

Single dose toxicity

Table 9: Single dose toxicity studies

Study ID	Species/ Sex/Number/ Group	Dose/Route (mg/kg/day)	Comment on dose levels

2219-027 GLP	Rat/Sprague Dawley 16M + 16F /group +TK animals	ACP-196 i.v. Groups 1. 0 mg/kg 2. 6 mg/kg 3. 10 mg/kg Vehicle: 20% HPβCD	No ACP-196-related effects were noted in clinical observations, body weights, food consumption, haematology parameters, coagulation parameters, clinical chemistry parameters, urinalysis parameters, organ weights, or macroscopic or microscopic findings.

Repeat dose toxicity

Table 10: 28-days oral toxicity study in rats (Wistar Han)

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)
2219-049 GLP	Rat (Wistar Han) 10M/10F per group +6M/6F for recovery +9M/9F TK	ACP-196 Oral gavage Once daily Groups (mg/kg/day) 1 0 2: 2.5 3: 7.5 4: 30 5. 100 Vehicle: 0.4% hypromellose 0.2% tween 80	28 days 28 days recovery	~~100 mg/kg/day~~ 2.5 mg/kg/day

Noteworthy findings:
Mortality: No ACP-196-related mortality was noted. However, one female at 7.5 mg/kg/day was euthanized in extremis on study Day 26 due to an ophthalmoscopic observation of unilateral buphthalmia.

Clinical observations: ≥30 mg/kg: salivation, the increased incidence continued into the recovery period.

No ACP-196-related effects were noted in body weights, food consumption, ophthalmoscopic findings, or clinical pathology endpoints (haematology, clinical chemistry, coagulation, fibrinogen, or urinalysis parameters).

Post mortem:
No macroscopic findings or effects on organ weight were noted.
Microscopic: ≥7.5 mg/kg (M): **Pancreas** pancreatic islet haemorrhage, inflammation, fibrosis, and/or pigment.

Table 11: Summary of TK at Day 28

Gender	Male					Female				
Dose level (mg/kg)	0	2.5	7.5	30	100	0	2.5	7.5	30	100
Cmax (ng/mL)	NA	51.4	144	691	1160	NA	163	228	1450	3130
AUC0-24 (hrxng/mL)	NA	58.2	201	882	2630	NA	153	367	1680	6390
Human ss	AUC24h=1893 hrxng/mL, Cmax= 466 ng/mL									

Table 12: 13 weeks oral toxicity study in rats

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)
2219-029 GLP	Rat (Sprague Dawley) 16 M+F per group +4-14 M+F TK	ACP-196 Oral gavage Once daily Groups (mg/kg/day) 1 0 2: 10 3: 30 4: 100 Vehicle: 0.4% hypromellose, 0.2% Tween 80	13 weeks 28 days recovery	~~100 mg/kg/day~~ NOAEL was not established

Noteworthy findings:
Mortality: No ACP-196-related mortality was noted. One M at 10 mg/kg/day was found dead on study day 103. The cause of death was considered to be a lymphoid tumour.

No ACP-196-related effects were noted in clinical observations, body weights, food consumption, ophthalmoscopic examinations, clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis), or organ weights.

Table 13: Summary of TK at Day 90

Gender	Male				Female			
Dose level (mg/kg)	0	10	30	100	0	10	30	100
Cmax (ng/mL)	NA	113	440	820	NA	278	798	1890
AUC0-24 (hrxng/mL)	NA	155	792	2250	NA	275	1630	3700
Human ss 100 mgx2	AUC24h=1893 hrxng/mLCmax= 466 ng/mL							

Table 14: 26-week oral toxicity study in rats

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg/day)
2219-084 GLP	Rat (Wistar Han) 22 M+F per group +6 M+F for recovery +6-14 M+F TK	ACP-196 Oral gavage Once daily Groups (mg/kg/day) 1 0 2: 30 3: 100 4: 300/200 Vehicle: 0.4% hypromellose, 0.2% polysorbat	6 months 28 days recovery	~~100 mg/kg/day~~ in males Not established in males 30 mg/kg/day in females

Mortality:
First 14 days (from day 8): 6F (300 mg/kg) Clinical observations: ↓activity, rapid breathing, ataxia, hunched posture, pale skin, skin cold to touch, thin, vocalization, and/or hypersensitive to touch, slight ↓BW. Histopathology: uraemia/acute kidney failure, and/or myocardial haemorrhage/inflammation/necrosis.
After dose reduction (Day 66-132): 6F and 1M+4F TK (300/200 mg/kg/day) were found dead (10) or euthanized (1). Similar findings as for the animals that died during the first 14 days.

Clinical observations: salivation in all dose groups. Recovery: no observations

Body weight and food consumption, ophthalmoscopy, urinalysis, coagulation: no findings

Haematology
300/200 mg/kg: ↑ LYM, MON (1.1x and 1.5x at termination, relative to control; small, test item related, no microscopic correlate). After recovery period: no changes.
At week 5 red cell mass (RBC, HGB, HCT) was minimally lower in both M and F in the high dose group. Finding was considered likely related to observed general toxicity. The decrease was not observed at later time points.

Clinical chemistry
≥100 mg/kg: ↓triglyceride (-51% at week 2, resolved by week 5)
300 mg/kg (F): ↑hepatobiliary endpoints (totBIL (1.9x), GGT (1.7x), AST (1.9x), ALT (2.3x); observed at week 2 but not at later time points)
↑BUN, CREA in 2 F at week 2. Not observed at later time points.
And multiple statistically significant differences in K, CA, ALP, AST, ALT that were not considered relevant based on sporadic nature, lack of a dose response, small magnitude, lack of findings among other correlative endpoints.

Primary T-cell Dependent Antibody Response (TDAR):
Secondary (recall) TDAR: mild to moderate ↓anti-keyhole limpet hemocyanin (KLH) immunoglobulin type M (IgM) and/or immunoglobulin type G (IgG) in M (100 and 300/200 mg/kg) and in F (30 and 300/200 mg/kg)

Post mortem
Macroscopic
Kidney: white/tan foci, correlated with areas of tubular mineralization (300/200 mg/kg F, unscheduled death, after reduction of the dose
Lungs: 300/200 mg/kg (2M+1F) white foci (micro: bronchus-associated lymphoid tissue BALT)

Organ weights
≥100 mg/kg (F): ↑kidney (+14% vs control, related to the microscopic findings). Recovery: 300/200 (F): ↑
100 mg/kg (F): ↓ovaries
300/200 mg/kg (F) notable but not statistically significant increase in weights of ovaries, uterus and cervix. Recovery: ↓ovaries and ↑uterus and cervix in 30 mg/kg and 300/200 mg/kg groups. No microscopic correlate.
≥100 mg/kg (M): ↓spleen (no microscopic correlate)
300/200 mg/kg (M):↓adrenal glands (no microscopic correlate)

Microscopic
Pancreas: ≥30 mg/kg (M): haemorrhage/pigment/inflammation/fibrosis; varying presence and severity of lymphocytes and plasma cells that invaded the islets. Shrunken exocrine pancreatic cells with decreased secretory and apoptotic bodies (acinar atrophy)
Kidney: ≥100 mg/kg (F) tubular degeneration/necrosis. Findings in the kidneys were most severe in in the animals that died preterm.
Liver: DOS (F): individual hepatocyte degeneration/necrosis. Increased mitotic figures were present in 4 of the 6 DOS females. Similar findings were noted in females at 100 mg/kg and in both sexes at 300/200 mg/kg.
Heart: In the heart of 10 out of 11 DOS females, there were multiple areas of myocardial loss of varying degrees, with replacement by a mixed inflammatory cell population and extravasated red blood cells.
Mesenteric lymph node: erythrocytosis/erythrophagocytosis. Increased in incidence as the dose increased in males. Similar incidence and severity in F
Lymphoid organ: 300/200 mg/kg (F): generalized lymphoid depletion in the thymus and/or spleen. Considered related to stress and the other related systemic findings

Recovery: Findings were present in the pancreas of M and kidneys of F, but at lower incidence and lesser severity than in terminal animals.

The microscopic lesions in the liver (individual hepatocyte degeneration/necrosis) in females at 100 mg/kg/day and both sexes at 300/200 mg/kg/day and in the kidney (tubular degeneration/necrosis) at 100 and 300/200 mg/kg/day (females only) were considered adverse. Therefore, the NOAEL is 100 mg/kg/day ACP-196 in males and 30 mg/kg/day in females.

Table 15: Summary of TK values (Day 182)

Gender	Male				Female			
Dose level (mg/kg)	0	30	100	300/200	0	30	100	300/200
Cmax (ng/mL)	NA	763	2510	3110	NA	1640	3820	6920
AUC0-24 (hrxng/mL)	NA	1150	4760	7930	NA	2010	8130	13100
Human ss	AUC24h=1893 hrxng/mL, Cmax= 466 ng/mL							

Genotoxicity

A standard program of genotoxicity studies was performed with acalabrutinib. The results are summarised in the table below.

Table 16: Genotoxicity studies conducted with acalabrutinib.

Type of test/study ID/GLP	**Test system**	**Concentrations**	**Results**
Gene mutations in bacteria Evaluation of the mutagenic activity of ACP-196 in the Salmonella typhimuriom reverse mutation assay and the Escherichia coli reverse mutation assay. #503223 GLP	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *E.coli* WP2 *uvrA* +/- induced rat liver S9-mix Positive controls: sodium azide, ICR-191, 2-nitrofluorene, methyl methanesulfonate, 4.nitroquinolone N-oxide, 2-amino-anthracene, Triplicate testing	3-5000 µg/plate Solvent: DMSO	Precipitate of ACP-196 was observed at 5000 µg per plate. Toxicity was observed in TA100 at 5000 µg +S9. In strain TA98 an increase of revertant colonies was observed +/- S9 in two independent experiments. The increase was above the historical control data but less than three times the concurrent control (x1.8-1.9) *Outcome:* **Negative**
Chromosomal aberrations in vitro Evaluation of the ability of ACP-196 to induce chromosome aberrations in cultured peripheral human lymphocytes #503225 GLP	Cultured peripheral human lymphocytes +/- rat liver S9 Tested in duplicate in two independent experiments. Positive controls: MMS and cyclophosohamide 3 h exposure +/- S9, 24, 48 h exposure –S9	3-333 µg/plate Solvent: DMSO	No statistically significant or biologically relevant increase in the number of cells with chromosome aberrations +/- S9 No biologically relevant effects on the number of polyploid cells and cells with endoreduplicated chromosomes +/-S9-mix Positive control produced expected effects. *Outcome:* **Negative**
Chromosomal aberrations in vivo In vivo micronucleus assay in rats AD92XN.125M012I CH.BTL	Sprague Dawley rat Micronuclei in bone marrow 5 M/group Prior to the definitive study a DRF study was conducted with 3 rats/sex/group	500, 1000, 2000 mg/kg Oral gavage, single dose Negative control: vehicle Positive control: cyclophosphamide. Vehicle: 0.4% hydroxypropyl methylcellulose with 0.2% tween 80	*Mortality:* no mortality occurred. *Clinical signs:* All rats appeared normal throughout the observation period. *Results* Dose (mg/kg) | Number of MPCE/10000 PCE scored Vehicle (neg) 24 h | 2

Type of test/study ID/GLP	Test system	Concentrations	Results
GLP		Sampling 24 and 48 h post dose	<table><tr><td>Vehicle (neg) 48h</td><td>3</td></tr><tr><td>500 24h</td><td>2</td></tr><tr><td>1000 24h</td><td>2</td></tr><tr><td>2000 24h</td><td>3</td></tr><tr><td>2000 48h</td><td>4</td></tr><tr><td>Positive 24h</td><td>217</td></tr></table> PCE- polychromatic erythtrocytes MPCE- micronucleated PCE *Exposure* Exposure was not measured in the study. Acalabrutinib was not cytotoxic to the bone marrow and did not induce any increases in micronucleated PCEs at any dose level examined *Outcome:* **Negative**

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib (see discussion on non-clinical aspects).

Reproduction Toxicity

Studies were conducted to evaluate the standard reproductive and developmental toxicity profile of acalabrutinib: one combined segment I 'fertility' and segment II 'EFD' study (Sprague-Dawley rats), one segment II 'EFD' study (New Zealand white rabbits), and one segment III 'prenatal/postnatal study (Sprague Dawley rats).

Male and female fertility

Male and female fertility and early embryonic development were evaluated in rats after administration of acalabrutinib at 0, 30, 100, 300 (M)/200 (F) mg/kg/day.

In males, the highest tested dose (300 mg/kg) was not tolerated. The findings in the animals that were found dead were similar as observed in the repeat dose toxicity studies and are considered related to acalabrutinib and adverse. However, no influence was noted on the fertility index and sperm parameters in the surviving animals or in the animals administered lower doses. The NOAEL for fertility suggested by the applicant, 300 mg/kg, is accepted. This corresponds to an exposure margin of 19900/1893 = 10.5 times (based on AUC) when compared with the exposure observed in patients.

In the female rats, acalabrutinib was administered at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day 17. No acalabrutinib related changes were noted on mating, fertility, and fecundity indices, mean number of implantation sites, viable foetuses, nonviable foetuses, litter size or resorption sites. A decreased cycle count (2.1 cycles vs 2.6 in controls) during the premating period in animals administered 100 and 200 mg/kg, and increased cycle length (5.0 days vs 4.1 days in controls) in animals administered 100 mg/kg were observed. However, since these values were within historical control range and since no effects on fertility were observed, the findings were not considered test article related or adverse. The NOAEL for fertility parameters was 200 mg/kg. This dose level corresponds to 17500/1893 = 9.2 times the exposure observed in patients, based on AUC.

Embryo-foetal development

Embryo-foetal development was investigated in rats and rabbits. Dose range finding studies were conducted in both species. The investigation in rats was conducted as a combination study including investigation of fertility parameters.

In the female rats, acalabrutinib was administered at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day 17. A higher top dose (200 mg/kg/day) was selected for the pivotal fertility and embryo-foetal study than in the DRF study (100 mg/kg/day) since no test article related effects were observed in the DRF study. The NOAEL for maternal toxicity and embryo-foetal development was considered by the applicant to be 200 mg/kg. One female in the 200 mg/kg group was euthanised *in extremis* on GD19. The death was considered to be related to dystocia, and not considered by the applicant to be test article related. However, dystocia was also observed in the PPND study (see below) and should be considered related to the test article and adverse. The maternal NOAEL and NOAEL for embryo-foetal development and survival was thus lowered to 100 mg/kg. This dose level corresponds to 6830/1893 = 3.6 times the exposure observed in patients, based on AUC.

In the embryo-foetal study in rabbits, pregnant animals were administered acalabrutinib at doses up to 200 mg/kg/day during the period of organogenesis (GD6-18). The highest dose was not tolerated and several animals were found dead, which lead to the decision to terminate the whole group earlier. Maternal toxicity was also observed at 100 mg/kg/day, a dose that resulted in decreased foetal body weights and delayed skeletal ossification. The maternal and developmental NOAEL was set at 50 mg/kg/day which corresponds to an exposure similar to what is seen in patients based on AUC (2030 in animals vs 1893 in humans).

Prenatal and postnatal development

The potential effects of acalabrutinib on development, growth, behaviour, reproductive performance and fertility of F1 generation were evaluated in rats after administration of 0, 50, 100 and 150 mg/kg/day to F0 females from gestation day 6 through day 20 post-partum. In the study, only F0 dams were administered acalabrutinib. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥100 mg/kg/day. At the highest dose decreased liver weights were observed in the offspring.

Dystocia and mortality of offspring were observed at exposures corresponding to 4470/1893 = 2.4 times the exposure observed in patients. The exposure at NOAEL is at exposures lower than what is observed in patients (1420/1893 = 0.75).

In a preceding pilot study, the concentrations of ACP-196 and the human metabolite ACP-5862 were measured in maternal milk and plasma and fetal and pup plasma. Both acalabrutinib and the active metabolite were measured in foetal plasma. Furthermore, both substances were observed in milk with higher concentrations in milk than plasma 3 h post dose, indicating that the pups were exposed also during lactation although the mean plasma concentrations in the pups 1 hour after the dose was less than 1% of what was observed in the dams.

Toxicokinetic data

See under repeat dose toxicity above.

Local Tolerance

No local tolerance studies have been submitted (See discussion on non-clinical aspects).

Other toxicity studies

Metabolites

No specific studies were conducted with the acalabrutinib metabolite (ACP-5862). The exposure of the metabolite ACP-5862 was not measured in any of the pivotal toxicity studies.

Impurities

Several GLP nonclinical studies have been performed to qualify acalabrutinib process-related substances, impurities and degradation products.

Process impurities/degradants ACP-5134, ACP-1049, ACP-5541, and ACP-2009 did not induce a mutagenic response in the bacterial reverse mutation assay.

One process impurity of ACP-196, ACP-5187, induced a positive mutagenic response in the bacterial reverse mutation assay. ACP-5187 is controlled at a level of no more than 50 ppm, which corresponds to the Threshold of Toxicological Concern of 10 µg/day for drugs where the total expected duration of use is between 1 and 10 years.

The process impurity ACP-2009 was investigated in the bacterial reverse mutation assay, in vitro mammalian chromosomal aberration test, and a 14-days repeat dose toxicity study in rats. ACP-2009 was not tested as a pure substance but was present in ACP-196 (6.49% w/w) in all three studies. ACP-2009 was found to be non-genotoxic. In the in vivo study in rat, the total daily intake of ACP-2009 was 0.0649x25 mg/kg= 1.6 mg/kg. The conversion factor 0.16 could be used to convert the dose to a human equivalent dose based on body surface area: 1.6 mg/kgx0.16= 0.256 mg/kg, assuming a 60 kg human the daily intake of ACP-2009 would thus be 15.4 mg/day. ACP-2009 is controlled at a level of no more than 0.3%, with the maximum daily dose of 200 mg a human daily intake of ACP-2009 would be 0.3%x200 mg/day= 0.6 mg/day. The specification limit of 0.3% w/w could thus be considered supported by toxicological qualification.

Phototoxicity

The chemical structure of acalabrutinib contains a conjugated aromatic system with Molar extinction coefficient >1000 $cm^{-1}M^{-1}$ between 290 and 700 nM. Peak maxima were observed at approximately 197, 230, and 283 nm. In vitro phototoxicity screens were performed with mouse fibroblasts (3T3 cells) to determine the relative cytotoxicity of acalabrutinib with or without of UVA radiation. In addition, an Ames test was conducted with UV activation of acalabrutinib to evaluate photo-activation of mutagenic potential.

Acalabrutinib absorbs light within the range of natural sunlight, with molar extinction coefficient >1000 $cm^{-1}M^{-1}$ between 290 and 700 nM. In other words, acalabrutinib has a photoreactive potential.

Testing for photogenotoxicity is not recommended as a part of the standard photosafety testing program. Acalabrutinib was however investigated for photogenotoxicity in a bacterial reverse mutation assay and found not mutagenic in the *S. typhimurium* reverse mutation assay under the influence of UV irradiation (315-690 nm).

Acalabrutinib was positive in the 3T3 neutral red uptake assay. The EC50 was 32.7 µg/mL which is higher than the observed clinical Cmax= 466 ng/mL.

2.3.5. Ecotoxicity/environmental risk assessment

In the Phase I exposure assessment, the $PEC_{SURFACEWATER}$ for acalabrutinib 0.048 µg/L exceeded the action limit of 0.01 µg/L. Therefore, a Phase II Tier A assessment was triggered.

The Log Dow was <2 at relevant pH values and acalabrutinib was thus not considered a PBT substance in the screening for persistence, bioaccumulation, and toxicity (PBT). Acalabrutinib is however very persistent in sediment according to the OECD 308 study.

The organic content solid adsorption coefficient for acalabrutinib was below 10000 L/kg for sludge, not triggering the Tier B for the terrestrial compartment. Acalabrutinib was primarily partitioned to the sediment layers. A Phase II Tier B extended effects on the sediment compartment was therefore triggered.

Based on the Phase I PECSW, the applicant has provided a set risk quotients/ratios that are below 0.1 for sludge micro-organisms and below 1 for other compartments.

Acalabrutinib is not expected to pose a risk to the environment.

Table 17: Summary of main study results

Substance (INN/Invented Name): Acalabrutinib			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD107	1.29 at pH 5 1.96 at pH 7 1.99 at pH 9	Not Potential PBT
PBT-statement :	The compound is very persistent in sediment according to the OECD 308 study but is not considered a PBT substance.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.048	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Activated sludge 1. $K_{oc} = 4.21x10^2$ 2. $K_{oc} = 5.89x10^2$ Soil 3. $K_{oc} = 8.79x10^5$ 4. $K_{oc} = 1.84x10^6$ Sediment 5. $K_{oc} = 1.37x10^5$ 6. $K_{oc} = 1.20x10^5$	3 and 5: High organic matter 4 and 6: Low organic matter No trigger for terrestrial studies as K_{oc} sludge <10000 L/kg
Ready Biodegradability Test	OECD 301		Not available, but can be waived since OECD308 is submitted.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Brandywine creek/Choptank river $DT_{50, water}$ = 3.5/5.8 days $DT_{50, sediment}$ =95/53 days $DT_{50, whole\ system}$ =14/28 days Corrected to 12◦C: $DT_{50, water}$ = 7.4/12 days $DT_{50, sediment}$ =203/114 days	Results obtained in two river systems; sediment risk assessment triggered Acalabrutinib is very persistent in sediment.

		$DT_{50, whole system}$ =29/59 days % shifting to sediment = 89.6/51.9 at Day 14 and increasing			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	2.7	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	1.2	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	3.8	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD218	NOEC	244	mg/kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

Acalabrutinib is a highly selective inhibitor of BTK. The pharmacological relevance of the toxicology species was established in animal models where BTK inhibition is at play.

In the rat, acalabrutinib showed activity in the adjuvant arthritis model. In this study it was demonstrated that therapeutic doses were associated with complete BTK occupancy. In the dog, a veterinary study showed anti-tumour effect in dogs with spontaneous B-cell lymphoma. Complete BTK occupancy was demonstrated in both species.

No effects were reported on CNS and respiratory system. For the cardiovascular system, an inhibition of the hERG current tail has been described and significant findings have been reported in *in vivo* studies (QTc changes in *in vivo* study 2219-015; changes in relevant parameters in cardiovascular study 594019; and heart findings in repeat dose toxicity studies and atrial fibrillation/flutter in humans; actions of other BTK inhibitors on PI3K/Akt pathway and its role as a critical regulator of cardiac tissues) (see SmPC section 4.4).

The non-clinical pharmacokinetics for acalabrutinib was adequately evaluated. Of importance for the safety assessment, a distribution study in the pigmented rat demonstrated binding to melanin leading to retention in skin and eye, which led to a need for investigation of the phototoxic potential.

In a human mass balance study, ACP-5862 was identified as the only metabolite that accounted for >10% of total acalabrutinib-related radioactivity in human plasma. Due to late identification of this main metabolite, exposure to the metabolite was not addressed in pivotal toxicity studies. Based on data from mass balance studies it is concluded that the metabolite is present in both species. In rat, exposure ratio metabolite / parent is higher than in humans. In dogs the ratio is lower than in humans, resulting in approximately the same exposure at the high dose in the repeat dose toxicity studies and clinical exposure. It is considered that the main metabolite is adequately qualified in the toxicology program with rat and dog. No information is provided on *in vivo* metabolism in rabbit, a species used for the evaluation of embryofetal toxicity. However, the main metabolite ACP-5862 was formed in vitro with rabbit hepatocytes, and it is likely that it is present *in vivo*.

Acalabrutinib was not tolerated in rats and dogs at high doses. Acute kidney failure and/or myocardial haemorrhage/inflammation/necrosis were considered the cause of death. The mechanism that would lead to these conditions is not understood.

In rats, microscopic findings of minimal to mild severity were observed in the pancreas (haemorrhage/pigment/inflammation/ fibrosis in islets) at all dose levels. Non-adverse findings of minimal to mild severity in the kidneys (tubular basophilia, tubular regeneration, and inflammation) were observed in studies of up to 6-month duration with a No Observed Adverse Effect level (NOAEL) of 30 mg/kg/day in rats. The mean exposures (AUC) at the NOAEL in male and female rats correspond to 0.6x and 1x, respectively, the clinical exposure at the recommended dose of 100 mg twice daily, respectively. The Lowest Adverse Observed Effect Level (LOAEL) at which reversible renal (moderate tubular degeneration) and liver (individual hepatocyte necrosis) findings were observed in the chronic rat study was 100 mg/kg/day and provided an exposure margin 4.2 times greater than the clinical exposure at the recommended dose of 100 mg twice daily. In studies of 9 months duration in dogs, the NOAEL was 10 mg/kg/day corresponding to an exposure 3x the clinical AUC at the recommended clinical dose. Minimal tubular degeneration in kidney, slight decreases in spleen weights and transient minimal to mild decreases in red cell mass and increases in ALT and ALP were observed at 30 mg/kg/day (9x the clinical AUC) in dogs.

Although the pancreatic findings are considered of low clinical relevance to humans, the findings are considered adverse and are included in the SmPC section 5.3.

Cardiac toxicities in rats (myocardial haemorrhage, inflammation, necrosis) and dogs (perivascular/vascular inflammation) were observed only in animals that died during studies at doses above the maximum tolerated dose (MTD). The exposures in rats and dogs with cardiac findings was at least 6.8 times and 25 times the clinical AUC, respectively. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the MTD (see SmPC section 5.3). Cardiac function was also monitored in the clinical studies (see discussion on Clinical Safety).

In the repeated dose toxicity studies in dog, findings such as haematology findings, increased ALT and ALP, and lower spleen weights were observed in acalabrutinib-treated animals. (See also Clinical safety discussion and the RMP).

No effects on fertility were observed in male or female rats at exposures 10 or 9 times the clinical AUC at the recommended dose, respectively. No effects on embryofoetal development and survival were observed in pregnant rats, at exposures approximately 9 times the AUC in patients at the recommended dose of 100 mg twice daily. In two rat reproductive studies, dystocia (prolonged/difficult labour) was observed at exposures >2.3 times the clinical exposure at 100mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Recommendation to not breast-feed during treatment and for 2 days after the last dose is included under SmPC section 4.6.

In an embryofoetal study in pregnant rabbits, decreased foetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity which were 2.4 times greater than the human AUC at the recommended dose.

Acalabrutinib was not genotoxic in the conducted genotoxicity studies. The genotoxic potential of the human major metabolite ACP-5862 was not specifically addressed. However, the *in vitro* genotoxicity studies contained rat S9 mix, and the *in vivo* genotoxicity study was conducted in rat. It is not known at what levels the metabolite ACP-5862 could be found in the in vitro set up with S9. However, in *in vitro* studies with human microsomes ACP-5862 is formed. Furthermore the metabolite is found *in vivo* in rats and presumably also formed by rat S9 in vitro. The metabolite ACP-5862 can be considered non-genotoxic.

Carcinogenicity studies have not been conducted with acalabrutinib. Second primary malignancies (SPM) have been detected in acalabrutinb patients (see discussion on clinical safety) and can be considered treatment related. It is agreed that rodent carcinogenicity studies investigating acalabrutinib would be of limited value and is not required. The existing literature indicates that both the inherent risk in the disease itself and the B-cell role in both promoting and inhibiting cancer progression could be involved in the mechanism.

Acalabrutinib is not recommended to be used during pregnancy (see SmPC section 4.6). In the most sensitive species, the rabbit, decreased foetal body weights and delayed skeletal ossification were observed at similar exposure levels as in human patients. Due to maternal toxicity, it was not possible to increase the exposure in the rabbits further. In the rat PPND study, dystocia and mortality of the offspring was noted at doses corresponding to 2.4 times the exposure observed in patients. No further discussions on the mechanistic aspects were provided.

No local tolerance studies have been conducted. Acalabrutinib will be administered via the oral route. There are no findings from the repeat-dose toxicity studies that are indicative of low local tolerance. The lack of separate local tolerance studies is acceptable.

Immunotoxicity of acalabrutinib has not been assessed although BTK is known to play a relevant role in B-cell activation and immunological endpoints were reported in repeated dose toxicity studies. The observed effects are described to be partially or completely reversed during the recovery period. In the clinical trials, no changes in serum IgM and IgG were reported.

No specific studies were conducted with the human major metabolite (ACP-5862). Characterization of ACP-5862 following a single oral dose has been conducted. The applicant refers to data suggesting that the main human metabolite is formed by rabbit hepatocytes *in vitro*. It is agreed that rabbits were most likely exposed to ACP-5862 in the embryo foetal toxicity study; data indicates adequate exposure of the metabolite in the toxicological studies.

Both degradation impurities in the final product: ACP-1049 and ACP-5134 were found negative in the bacterial reverse mutation assay. ACP-1049 and ACP-5134 were present in the 13 weeks repeat dose toxicity study in rats. NOAEL was not established in the study, but the highest tested dose was 100 mg/kg/day. The level of the impurities was 0.21 and 0.12 %, and thus administered at 0.21 and 0.12 mg/kg/day. These levels would represent 5.3 and 3.0%, if transformed to a 200 mg dose per day in a 50 kg person. Levels which are 8 and 5 times the proposed specification limit (0.6 %), which were margins that were previously unclear. ACP-5541 was present in the 26 weeks repeat dose toxicity study in rats. The NOAEL was not established in male rats. The qualification level was calculated at 100 mg/kg, which is accepted. ACP- 5812 was present in the designated impurity repeat dose study in rats.

The applicant justified the proposed dose-free period by claiming at least 5 half-lives for acalabrutinib and the metabolite ACP-5862. The recommendation of 2 days is endorsed.

Acalabrutinib was positive in the 3T3 neutral red uptake assay. The applicant claims that the concentration that caused the positive reaction (32.7 µg/mL) is well above the clinical Cmax (0.47 µg/mL). Currently, a phototoxic potential of acalabrutinib is possible, but due to lack of further phototoxicity testing, the clinical relevance of the 3T3 data is not possible to adequately assess. It is agreed that UVB -induced phototoxicity rarely is a problem for pharmaceuticals with systemic exposure due to the limited penetration beyond epidermis. However, acalabrutinib is shown to bind to melanin which is formed in the basal layer of the epidermis, there is a concern for a possible potential phototoxicity of acalabrutinib. In SmPC section 4.4 advice on protection from sun exposure is included. The applicant was also asked to complete the information about potential phototoxicity by performing an in vitro GLP 3T3 phototoxicity study. The results will be reported post authorization, by Q2 2021 as recommended by the CHMP.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical aspects of the MAA of acalabrutinib have been adequately studied.

The applicant is recommended to submit results from a modified 3T3 NRU phototoxicity study with adjusted wavelengths, the results should be submitted by Q2 2021.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 18: Clinical efficacy studies

Study No. of Sites Location	Study Dates Enrollment Total/Planned	Study Design Study Objective	Diagnosis	Study Treatments	Duration of Acalabrutinib Treatment, Median (Range)	Subjects Treated/Continuing Treatment Sex (M/F) Median Age (Range)	Efficacy Endpoints
Pivotal Studies							
ACE-CL-007 142 sites 18 countries	14 Sep 2015 to 08 Feb 2019 (data cutoff) 535/510	Phase 3, multicenter, open-label, randomized, active comparator-controlled Efficacy and safety	Previously untreated CLL	Arm A: Obinutuzumab + chlorambucil Arm B: Acalabrutinib 100 mg BID + obinutuzumab Arm C: Acalabrutinib 100 mg BID	Arm B: 27.7 months (0.7-40.3 months) Arm C: 27.7 months (0.3-40.2 months)	Arm A: 169/0 106M/71F 71 years (46-91 years) Arm B: 179/146 111M/68F 70 years (41-88 years) Arm C: 178/142 111M/68F 70 years (44-87 years)	Primary: • IRC-assessed PFS in Arm A vs. Arm B Secondary: • IRC-assessed PFS in Arm A vs. Arm C • IRC-assessed ORR (Arm A vs. Arm B and Arm A vs. Arm C) • OS (Arm A vs. Arm B and Arm A vs. Arm C) • TTNT (Arm A vs. Arm B and Arm A vs. Arm C)
ACE-CL-309 102 sites 25 countries	01 Dec 2016 to 15 Jan 2019 (data cutoff) 310/306	Phase 3, multicenter, open-label, randomized, active comparator-controlled Efficacy and safety	R/R CLL Must have received ≥1 prior systemic therapy for CLL	Arm A: Acalabrutinib 100 mg BID Arm B: Investigator's choice of IR or BR	Arm A: 15.7 months (1.1-22.4 months)	Arm A: 154/124 108M/47F 68 years (32-89 years) Arm B: 153/0 100M/55F 67 years (34-90 years)	Primary: • IRC-assessed PFS in Arm A vs. Arm B Secondary: To compare the following in Arm A vs. Arm B: • INV-assessed PFS • IRC- and INV-assessed ORR • OS • PROs (data not included in this SCE) • IRC- and INV-assessed DOR • TTNT

Study No. of Sites Location	Study Dates Enrollment Total/Planned	Study Design Study Objective	Diagnosis	Study Treatments	Duration of Acalabrutinib Treatment, Median (Range)	Subjects Treated/Continuing Treatment Sex (M/F) Median Age (Range)	Efficacy Endpoints
Supportive Studies							
ACE-CL-001 12 sites US, UK, and Italy	30 Jan 2014 to 04 Jan 2019 (data cutoff) All cohorts: 306/286	Phase 1/2, open-label, multicenter, sequential group, dose escalation Efficacy, safety, PK, and pharmacodynamics	Cohorts 1, 2a, 2b, 2c, 3, 4a, and 4b): R/R CLL/SLL Cohorts 7 and 11: Previously untreated CLL/SLL	Acalabrutinib 100 mg BID or 200 mg QD	R/R CLL/SLL subgroup: 40.8 months (0.2-58.5 months) Previously untreated CLL/SLL subgroup: 44.2 months (0.2-52.1 months)	R/R CLL/SLL subgroup: 134/75 99M/35F 66 years (42-85 years) Previously untreated CLL/SLL subgroup: 99/88 66M/33F 64 years (33-85 years)	Secondary: • INV-assessed ORR, DOR, and PFS
ACE-CL-003 1 site US	12 Jan 2015 to 01 Nov 2018 (data cutoff) Cohorts 1 and 2: 45/45	Phase 1b, open-label, single-center, sequential group, dose-escalation/expansion (data included in this submission are for Cohorts 1 and 2 only) Efficacy, safety, PK, and pharmacodynamics	Cohort 1: R/R CLL; previously received ≥1 therapy Cohort 2: Previously untreated CLL or SLL	Cohorts 1 and 2: Acalabrutinib 100 mg BID + obinutuzumab	Cohort 1: 37.8 months (16.9-44.9 months) Cohort 2: 36.0 months (0.9-41.5 months)	Cohort 1: 26/19 21M/5F 62.5 years (42-76 years) Cohort 2: 19/17 11M/8F 61.0 years (42-75 years)	(Note: Efficacy data are included for Cohort 2 only) Primary: • INV-assessed ORR (PR or better) Secondary: • INV-assessed CR rate, time to response, DOR, PFS, and time to CR • TTNT • OS • MRD-negative CR rate (data not included in this SCE)

Study No. of Sites Location	Study Dates Enrollment Total/Planned	Study Design Study Objective	Diagnosis	Study Treatments	Duration of Acalabrutinib Treatment, Median (Range)	Subjects Treated/Continuing Treatment Sex (M/F) Median Age (Range)	Efficacy Endpoints
15-H-0016 1 site US	12 January 2015 to 07 Dec 2018 (data cutoff) 48/48	Phase 2, open-label, single-center, randomized Efficacy, safety, and pharmacodynamics	R/R or previously untreated CLL/SLL with 17p deletion, TP53 mutation, or NOTCH-1 mutation	Acalabrutinib 100 mg BID or 200 mg QD	R/R CLL: 25.0 months (1.8-46.4 months) Previous untreated CLL: 26.4 months (5.5-42.1 months)	R/R CLL: 32/24 23M/9F 64 years (48-83 years) Previous untreated CLL: 16/12 10M/6F 63.5 years (45- 81 years)	Primary: • INV-assessed ORR (PR or better) Secondary: • INV-assessed DOR, time to progression, time to initial response, and PFS • OS

BID=twice daily; BR=bendamustine+rituximab; CLL=chronic lymphocytic leukemia; CR=complete response; DOR=duration of response; F=female; INV=investigator; IR=idelalisib+rituximab; IRC=independent Review Committee; M=male; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; PRO=patient-reported outcome; QD=once daily; R/R=relapsed/refractory; SCE=Summary of Clinical Efficacy; SLL= small lymphocytic lymphoma; TTNT=time to next treatment.

2.4.2. Pharmacokinetics

Methods

Plasma and urine concentrations of acalabrutinib and plasma concentrations of its metabolite ACP-5862 were determined with LC-MS/MS methods. Standard non-compartment analysis was performed in all studies where rich sampling was applied.

PBPK modelling and simulations using Simcyp were undertaken to predict the DDI potential between acalabrutinib and CYP3A modulators, including effect on the active metabolite ACP-5862, and to assess the inhibition potential of acalabrutinib and ACP-5862 on CYP3A4 or CYP2C8 substrates.

A population PK analysis was undertaken to characterize the pharmacokinetics of acalabrutinib and ACP-5862 in healthy subjects and subjects with B-cell malignancies including CLL and identify covariate effects on the PK parameters; estimate acalabrutinib/ACP-5862 individual empirical Bayes estimates and exposures to enable subsequent exposure-efficacy and exposure-safety analyses in subjects with B-cell malignancies.

Data from 12 clinical studies were integrated in the population PK analysis: 5 Phase 1 studies in healthy subjects (ACE-HV-001, -004, -112, and -113) and 8 Phase 1b/2/3 studies in subjects with B-

cell malignancies (ACE-CL-001, -CL-003, -CL-007, ACE-LY-002, -003, -004, -MY-001, and -WM-001). The pooled analysis dataset comprised acalabrutinib and ACP-5862 plasma concentrations (metabolite measurements were not available across all clinical studies) and relevant covariates from 138 healthy subjects and 575 subjects with B cell malignancies.

Acalabrutinib concentration-time data was best characterized by a 2-compartment structural model with transit chain absorption (5 transit compartments and first-order absorption) and linear elimination. The model was parameterized in terms of MTT, Ka, CL/F, Vc/F, apparent inter-compartmental clearance (Q/F), and Vp/F. Between occasion variability (BOV) was included on MTT and F1 and between subject variability (BSV) was estimated for CL/F, Vc/F and Vp/F. The estimated population means of CL/F, Vc/F, Q/F, Vp/F, MTT and Ka were: 133.7 L/h, 30.95 L, 20.93 L/h, 109.5 L, 0.4587 hours, and 1.478 hours-1, respectively. BSV in CL/F, Vc/F and Vp/F were 24 (% coefficient of variation [CV]), 270(%CV) and 34 (%CV), respectively. BOV in MTT and F1 were 118 (%CV) and 56(%CV), respectively.

ACP-5862 concentration-time data was best characterized by a 2-compartment structural model with a first-order production rate of 0.4*CL/F and linear elimination. The model was parameterized in terms of apparent clearance (CLM/F), apparent volume of central compartment (VcM/F), apparent intercompartmental clearance (QM/F), and apparent volume of peripheral compartment (VpM/F). BSV was estimated for all four parameters. The estimated population means of CLM/F, VcM/F, QM/F, and VpM/F were: 21.7 L/h, 22.6 L, 26.7 L/h, and 89.2 L, respectively. BSV in CLM/F, VcM/F, QM/F, and VpM/F were 12 (%CV), 47 (%CV), 41 (%CV), and 19 (%CV), respectively.

Proton-pump inhibitors (PPI) were included as covariates on F1. The baseline ECOG score and health status were included as covariates on CL/F. In addition, health status was included as covariate on Vp/F.

Absorption

The absolute bioavailability of acalabrutinib following a single 100 mg oral dose was 25.3% (range 20.7% to 31.3% in individual subjects) (study ACE-HV-009).

The absorption of acalabrutinib is rapid with maximum plasma concentrations occurring generally between 0.5 and 1.5 hours after single and repeated doses.

Based on the aqueous solubility across the physiological pH range, acalabrutinib has low solubility, but the solubility is high in acidic conditions up to pH 4 (e.g., normal gastric pH).

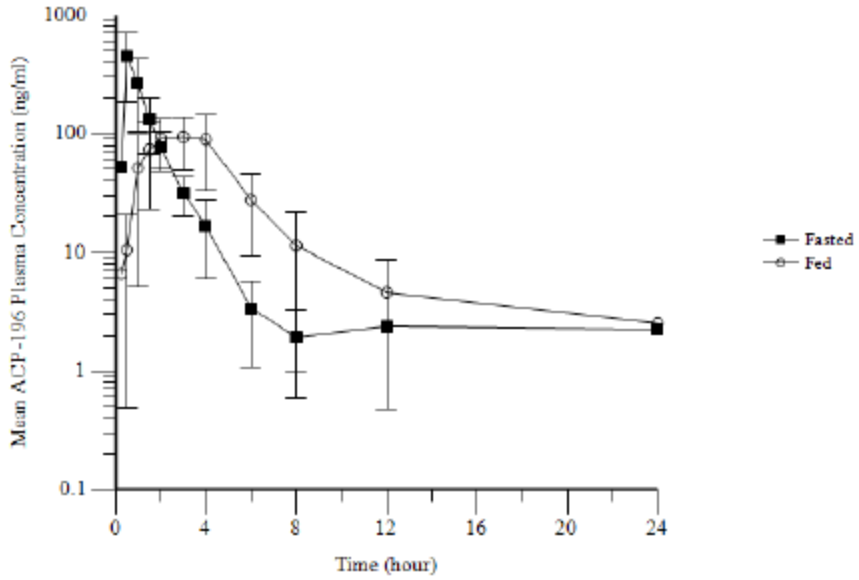
- *Bioequivalence*

No bioequivalence study has been performed. An initial "blend in capsule" formulation was used in early clinical studies and initial stages of pivotal studies, but the commercially representative "capsule" formulation was used in the pivotal phase 3 studies.

- *Food interaction*

The effect of food on the initial "blend in capsule" formulation was investigated in study ACE-HV-001. There was a significant decrease in C_{max} (69% decrease) and a delay in t_{max} from 0.5 to 2.5 hours when the product was taken with a high-fat meal compared to the fasted state, while there was no significant effect on AUC (results slightly outside BE acceptance criteria).

Figure 9: Mean ACP-196 Plasma Concentration (ng/mL) versus Time (hour) Data After 75 mg ACP-196 Administration in Fed (○) and Fasted (■) State, Log Scale



- *Effect of gastric pH*

Acalabrutinib is a weakly basic drug that exhibits 2 basic moieties (pKa=3.5 and 5.8) and one acidic moiety at pKa 12.1. Its solubility is pH-dependent across the physiological pH range. Based on a dose of 100 mg, acalabrutinib can be described as highly soluble in aqueous media at pH 4 and below but with low solubility above pH 4. Thus, acalabrutinib is soluble in the stomach, and in vivo absorption is decreased by substances that increase gastric pH (such as PPIs, H2-receptorantagonists and antacids), (see also section on Drug – drug interactions).

Helicobacter pylori infection

The healthy subject study population was enriched in Hispanic subjects, a population known to have an increased incidence of *H. pylori* infection, which might influence the PK of drugs that have pH-dependent dissolution. Therefore, the *H. pylori* status in healthy subjects was tested in several healthy volunteer studies. There was no consistent effect of *H. pylori* infection on acalabrutinib exposure.

Distribution

The volume of distribution (Vz) of acalabrutinib was 98.0 L (42.8%) (geometric mean [CV%]), and the volume of distribution at steady state (Vss) was 34.2 L (40.2%) after an IV microtracer dose (<10 µg; ≤1 µCi) of [^{14}C]acalabrutinib (Study ACE-HV-009). The Vz/F was 344 L (36.2%) (geometric mean [CV%]), after the oral acalabrutinib dose coadministered with the 14C-labeled IV tracer dose in Study ACE-HV-009.

Plasma protein binding has been evaluated for acalabrutinib and its metabolite ACP-5862 with ultracentrifugation using low-binding polycarbonate tubes. The fraction unbound was 2.5% for acalabrutinib and 1.4% for ACP-5862.

The *in vitro* mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for the metabolite ACP-5862. In the mass balance study, the blood/plasma ratio of total radioactivity was 0.86 based on $AUC_{0\text{-}12\ h}$, and increased over time, likely due to covalent binding to BTK in blood cells.

Elimination

The main route of elimination for acalabrutinib is metabolism followed by excretion in faeces.

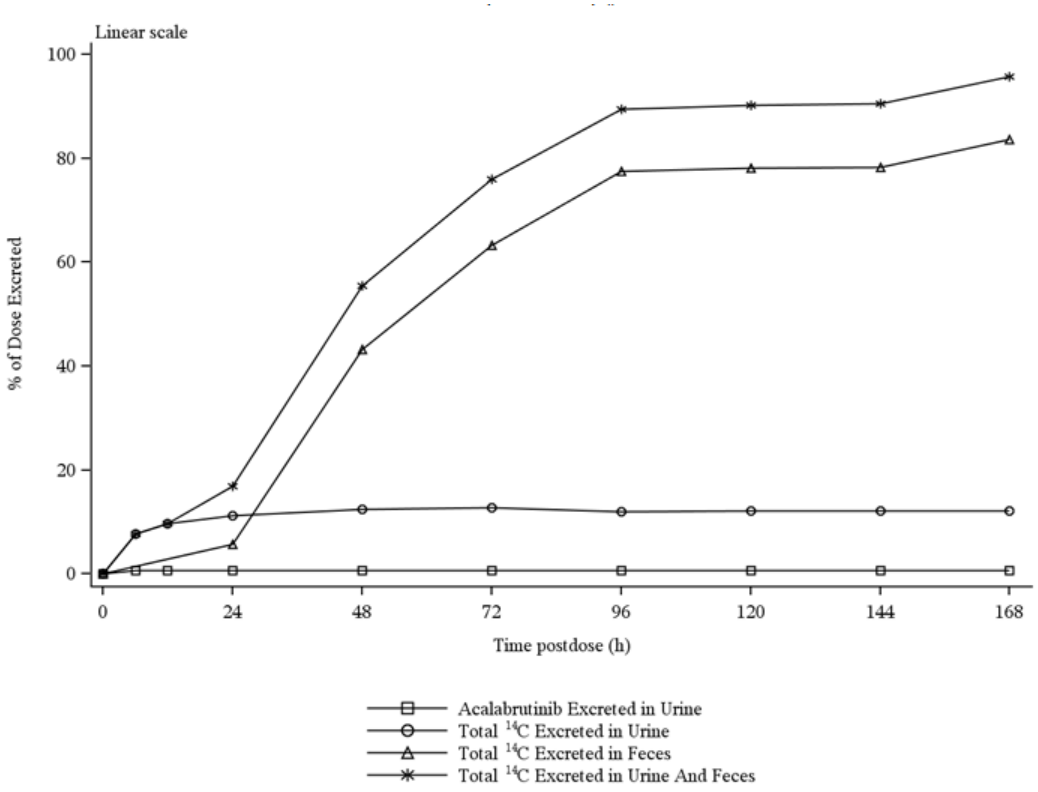
Based on study ACE-HV-009 (cohort 1, IV tracer dose), total CL and CLr for acalabrutinib (geometric mean [CV%]) was 39.4 L/h (30.6%) and 0.654 L/h (55.6%), respectively. The apparent clearance (CL/F) after the oral administration of 100-mg (capsule) acalabrutinib was 163 L/h (CV 35.7%), and CL_R was 1.33 L/h (CV 32.8%).

The terminal $t_{1/2}$ of acalabrutinib (geometric mean [CV%]) was similar between oral and IV doses, 1.57 (0.60%) hours for oral administration and 1.78 (0.46%) hours for IV administration (Cohort 1; Study ACE HV 009), ie approximately 1-2 hours. After single or repeated oral 100-mg acalabrutinib doses the mean terminal $t_{1/2}$ of acalabrutinib ranged from 0.965 hour to 2.64 hours in healthy subjects.

- *Mass balance*

Cohort 2 of study ACE-HV-009 was a single-dose mass balance study conducted in 6 healthy volunteers (4 male and 2 female) in the fasted state. Each subject received a single oral 100 mg dose of acalabrutinib (1 mg/ml oral solution) containing a microtracer (<10 µg, ≤1 µCi [^{14}C]acalabrutinib). The majority of the total radioactivity was eliminated in the faeces, with geometric mean (CV%) recoveries of total radioactivity in urine and faeces of 12.0% (15.9%) and 83.5% (5.1%), respectively. Less than 1% (0.5%) of the dose was excreted as unchanged acalabrutinib in urine. Acalabrutinib accounted for 1.2% of the excreted dose in faeces.

Figure 10: Arithmetic Mean Cumulative % of Acalabrutinib and Total 14C Excreted in Urine and Faeces after an Oral Dose (n=5)



Cohort 2: 100-mg acalabrutinib Oral Dose with microtracer

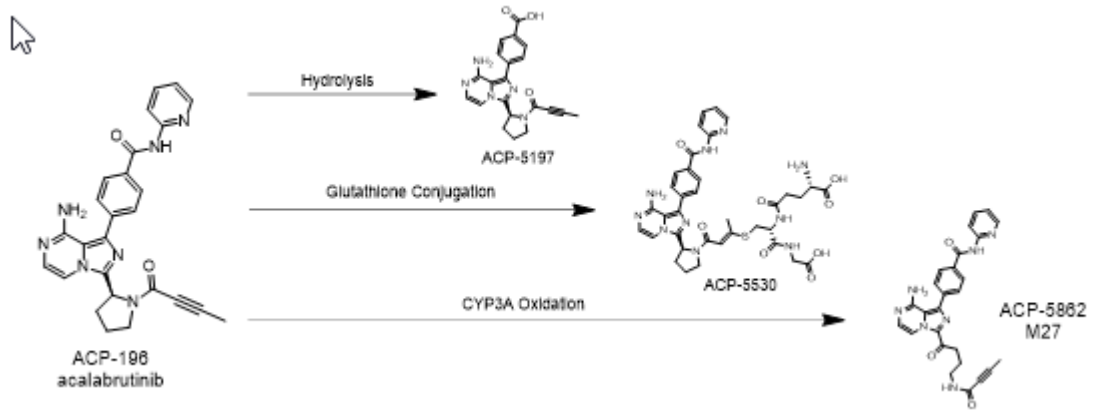
- *Metabolism*

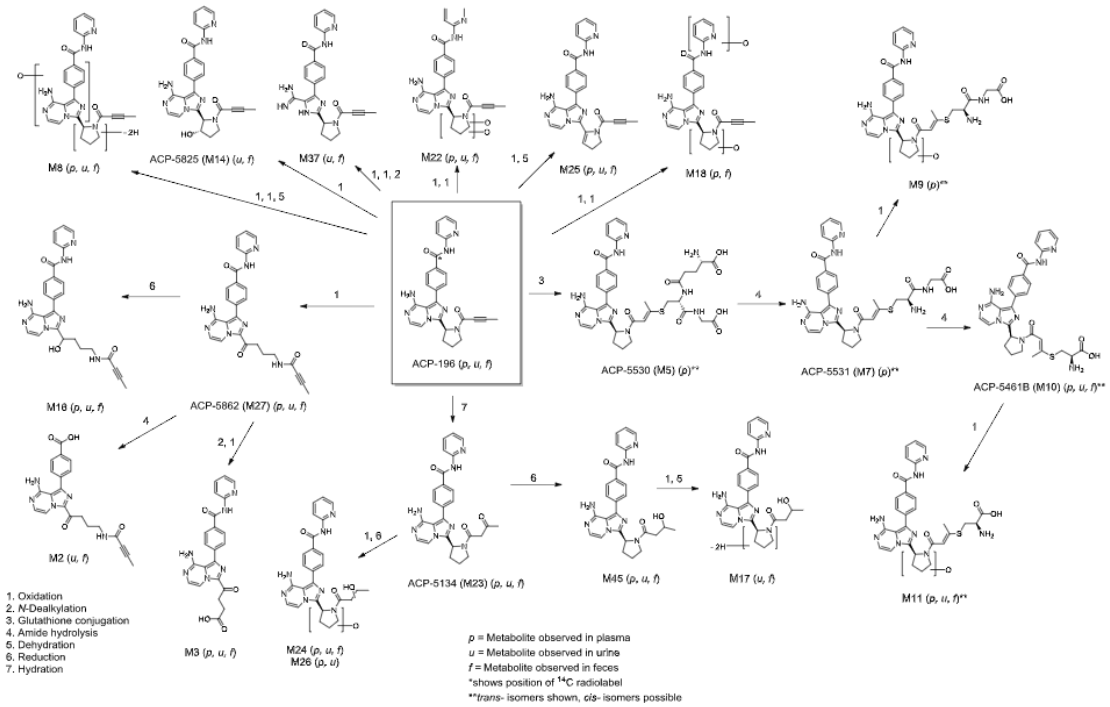
CYP3A-mediated oxidation is the major route of metabolism in humans. Glutathione conjugation and amide hydrolysis are minor metabolism pathways. In vitro reaction phenotyping data indicated conjugation of acalabrutinib with GSH is mediated primarily by human glutathione transferases M1 and M2 (GSTM1, GSTM2).

In vitro data shows that the formation of the major metabolite ACP-5862 from acalabrutinib are mediated by CYP3A4. Also the metabolism of the metabolite ACP-5862 appears to be mediated by CYP3A4.

Acalabrutinib was extensively metabolised following an oral dose of 14C-acalabrutinib, with 15 metabolites identified in plasma, urine and faeces. In plasma, parent acalabrutinib accounted for 8.6% of total radioactivity and the most abundant metabolite was M27 (ACP-5862), representing 34.7% of total radioactivity. M27 was the only single human metabolite representing >10% of radioactivity and was about 4-fold the amount of parent acalabrutinib. The next most abundant plasma metabolite components after M27 were 10.8% (M7, M8, M9, M10, and M11, collectively) of radioactivity in the plasma profile. In urine, parent acalabrutinib accounted for 0.5% of excreted dose. The most abundant metabolite component co-eluted and was 2.7% of excreted dose, representing mainly M7, M10, and M11, collectively. Metabolite M27 (ACP-5862) represented 0.5% of excreted dose. In faeces, parent acalabrutinib accounted for 1.2% of excreted dose. The most abundant metabolite component co-eluted and was 12.1% of excreted dose, representing M22, M45, and M23, collectively.

Figure 11: Proposed metabolism scheme. Upper panel: primary metabolic route. Lower panel: Proposed complete biotransformation pathways of ACP-196 in human.



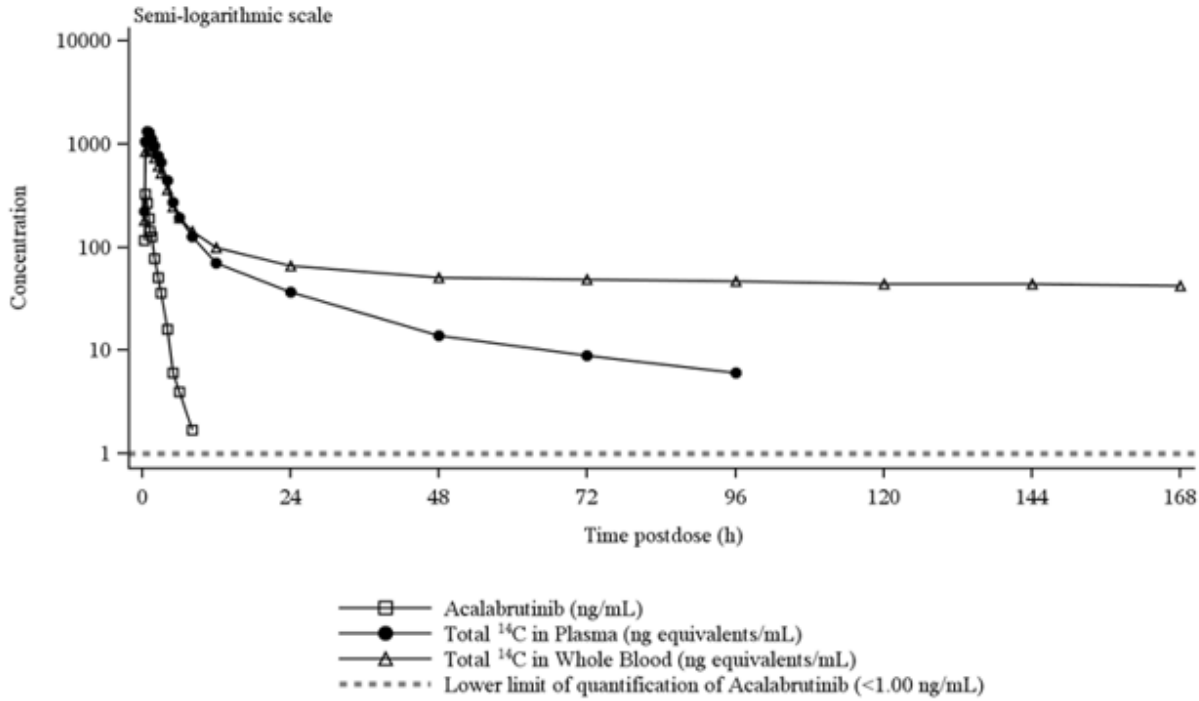


Note: Pathways are proposed based on general knowledge of metabolism and do not imply definitive pathways. Direct experimentation was not performed.

The mean acalabrutinib (ACP-196) to total ^{14}C radioactivity ratio was 0.0635 for $AUC_{0-\infty}$ indicating that acalabrutinib contributed only a small proportion of total ^{14}C radioactivity exposure with the majority of total ^{14}C radioactivity arising from metabolites.

The mean terminal $t_{1/2}$ of total radioactivity in plasma was 46.5 hours while the half-life for parent drug was 1.47 hours. The $t_{1/2}$ value for total radioactivity in whole blood was >2 times the sampling interval in 5 of the 6 subjects in Cohort 2, and mean half-life was not calculated. See *Figure 12*.

Figure 12: Mean Concentration Profiles for Acalabrutinib after an Oral Dose in Plasma, Total ^{14}C in Plasma, and Whole Blood (n=6; ACE-HV-009)



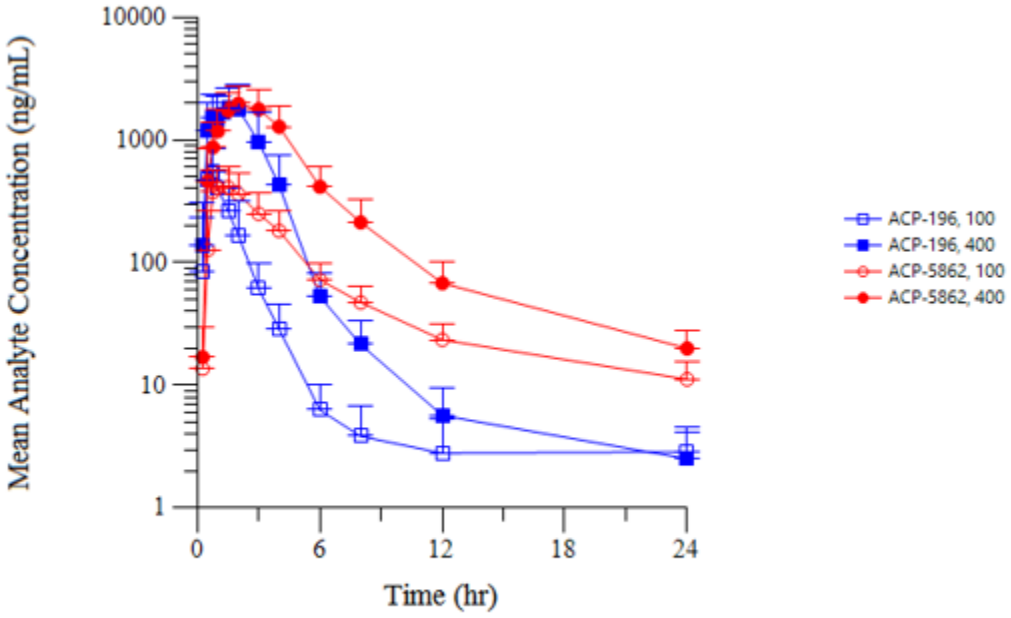
Cohort 2: 100-mg acalabrutinib Oral Dose with microtracer

Acalabrutinib has one chiral centre, and is the pure (S)-enantiomer. No data was provided on inter-conversion.

- *Pharmacokinetics of metabolites*

A longer $t_{1/2}$ and higher AUC or $AUC_{0\text{-last}}$ for the metabolite were observed relative to parent drug, with no meaningful accumulation of ACP-5862 after repeated BID dosing. In this study, the metabolite exposure increased roughly proportional to the increase in dose from 100 to 400 mg (while parent drug increased more than dose-proportional), the metabolite to parent (M/P) ratio of AUC values were 2.36 following a single dose of 100-mg acalabrutinib and the half-life was similar for metabolite as for parent (2.54 hours for metabolite and 2.64 hours for parent drug after the 100-mg dose). In study ACE-CL-001 the half-life for the metabolite was around 2 hours, compared to around 1 hour for the parent drug. In study ACE- ACE-HV-113, the half-life was clearly longer for parent than for metabolite (6.8 hours vs 1.9 hours), the M/P ratio of AUC was 2.69 and tmax was 1 hour.

Figure 13: Group Mean Plasma ACP-5862 and Acalabrutinib Concentration versus Time Profiles Following Acalabrutinib Administration (Log/Linear Scale; ACE-HV-005)



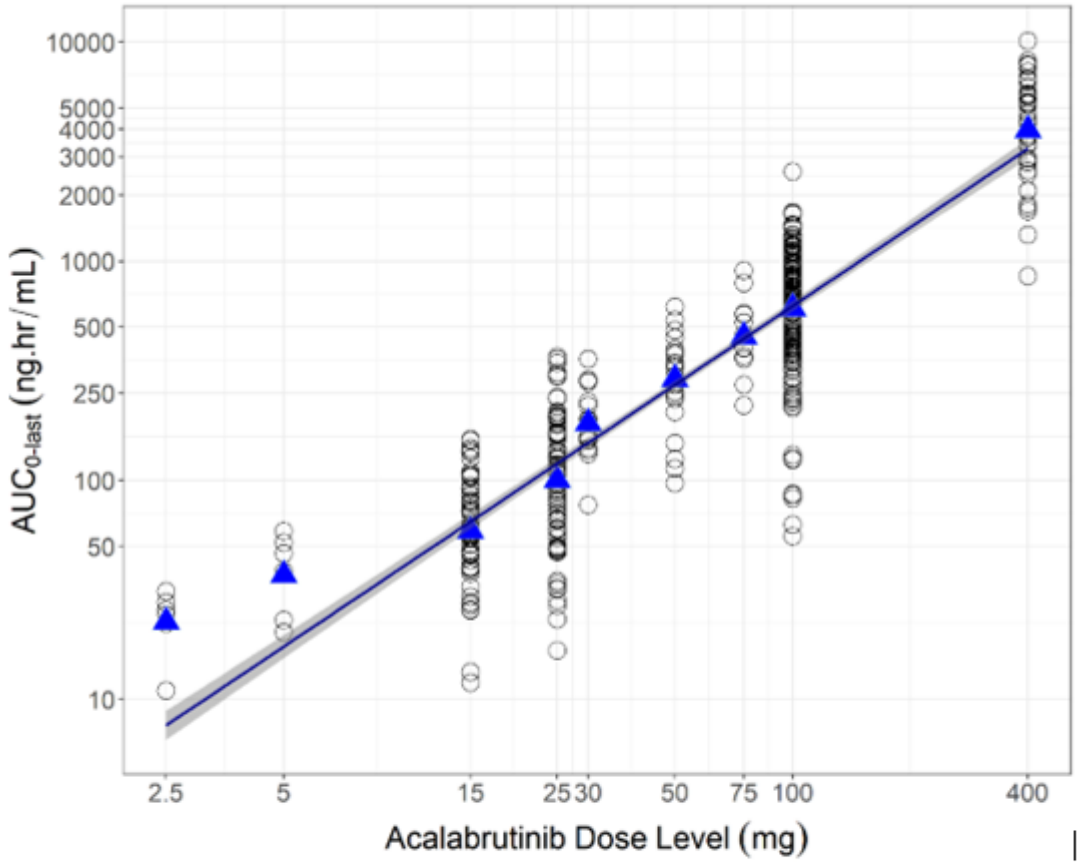
ACP-196=acalabrutinib; hr=hour.
Note: Analyte, ACP-196 Dose (mg) administered; Error bars represent standard deviation.

Dose-proportionality and time dependency

In study ACE-HV-001, increases in AUC relative to the increases in dose administered were linear between 2.5 mg and 100 mg while the increase in mean C_{max} values was greater than dose proportional over the studied dose range. In study ACE-HV-005, the increase in AUCs was greater than proportional between 100 mg and 400 mg in healthy subjects, where mean plasma acalabrutinib $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ were 5.9-, and 7-fold higher, respectively, after oral administration of 400 mg compared to 100 mg acalabrutinib. C_{max} was closer to dose proportional, 3.6-fold higher after 400 mg compared to 100 mg. In study ACE-CL-001, there was a less than dose-proportional increase of AUC and C_{max} with increasing dose in the interval 100 QD to 400 mg QD and a roughly proportional increase in AUC and C_{max} in the interval 100 mg BID to 200 mg BID.

A cross-study comparison of $AUC_{0\text{-}last}$ over the acalabrutinib dose range 2.5 mg to 400 mg from the noncompartmental analyses in healthy subjects is presented below. Over the dose range of 2.5 mg to 400 mg, the increase of acalabrutinib exposure ($AUC_{0\text{-}last}$) was slightly greater than dose-proportional (slope estimate of 1.18 based on power model analysis). Based on population PK modelling, acalabrutinib exposure increased proportional to dose over the dose range 75 mg to 250 mg.

Figure 14: Acalabrutinib $AUC_{0\text{-}last}$ versus Dose Levels in Healthy Subjects (Monotherapy)



$AUC_{0\text{-}last}$=area under the curve from time 0 to the last observation.
Note: $AUC_{0\text{-}last}$ and dose were natural log-transformed for the slope estimation of the power model analysis. The solid blue line denotes the expected geometric mean and the grey shading denotes the 90% prediction limits; the open circles denote the calculated individual $AUC_{0\text{-}last}$ values; solid triangles denote the calculated arithmetic mean for each dose level. Intercept 1.00 (90% CI: 0.82, 1.18); slope 1.18 (90% CI: 1.14, 1.22).
Source: Population PK report D8220C00009; data from monotherapy arms from Studies ACE-HV-001, -004, -005, -007, -008, -111, -112 and -113.

No accumulation of acalabrutinib is observed during repeated dosing, which is in line with expectations based on the short half-life (1-2 hours) and dosing interval. There is no sign of time-dependency in the PK of acalabrutinib. There are no signs of auto-induction of acalabrutinib clearance.

Pharmacokinetics in target population

In the population PK analysis, predicted median (90%PI) acalabrutinib AUC24h,ss and maximum plasma concentration at steady state (Cmax,ss) values for the reference population following acalabrutinib 100 mg BID (subject with B-malignancies, ECOG ≤1, without concomitant intake of PPIs) were 1668 (1094-2536) ng*h/mL and 461 (199.8-783.3) ng/mL. The popPK analysis detected a difference between healthy subjects and patients in acalabrutinib clearance (CL/F), where healthy subjects have slightly higher clearance. Furthermore ECOG 2+ status had a statistically significant effect on acalabrutinib clearance where patients with ECOG 2+ had slightly lower clearance. In terms of exposure this translates into that healthy subjects, acalabrutinib AUC24h,ss was 1135 (745.7–1732) ng*h/mL and Cmax,ss: 348.3 (165.3–578.9) ng*h/mL, which is a decrease by 32% and 24%, respectively. In subjects with B-cell malignancies and ECOG ≥2 acalabrutinib AUC24h,ss was 2012

(1319-3056) ng*h/mL and Cmax,ss: 527.7 (214.5–909.3) ng*h/mL, which is an increase by 21% and 14%, respectively.

The model predicted ACP-5862 AUC24h,ss and Cmax,ss for the reference population at 100 mg BID were 4175 (3256-5430) ng*h/mL and 461.3 (263.7- 678.4) ng/mL, respectively. Health status did not translate into the same impact on exposures of ACP-5862. In healthy subjects, ACP-5862 AUC24h,ss was 4177(3255–5432) ng/mL*h and Cmax,ss: 491.7 (289.2– 710.1) ng/mL, which is a change of 0% and 7%, respectively. In subjects with B-cell malignancies and ECOG ≥2 AUC24h,ss was 4177 (3256-5430) and Cmax,ss: 444.2 (251.7– 658.9), which is an decrease by 0% and 4%, respectively.

Special populations

- *Renal impairment*

A formal clinical study to investigate the impact of renal impairment on the pharmacokinetics of acalabrutinib/ACP-5862 has not been performed. In Study ACE-HV-009 the renal excretion of acalabrutinib was negligible (<2% after both oral and IV administration). The mean recovery of total radioactivity in urine was 12.0% (range 10.3% to 14.7%); the majority of total radioactivity was excreted in faeces. Based on the population PK analysis, including data for acalabrutinib [ACP-5862] from 408 [185] subjects with mild renal impairment (eGFR 60 to <89 mL/min/1.73 m^2), 109 [50] subjects with moderate renal impairment (eGFR 30 to <59 mL/min/1.73 m^2), and 2 [1] subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and 192 [68] subjects with normal renal function (≥90 mL/min/1.73 m^2), there was a trend of slightly increasing acalabrutinib exposure with decreasing renal function but not in ACP-5862, however no statistically significant effect of renal function on clearance was detected. Subjects with eGFR <30 mL/min/1.73 m^2 (end stage renal disease or on dialysis) were not included in the clinical trials. The applicant concludes that acalabrutinib can be administered to subjects with mild and moderate renal impairment (eGFR ≥30 mL/min) without any dose adjustments. The effects of severe renal impairment (very limited data) or hemodialysis on the pharmacokinetics of acalabrutinib/ACP-5862 have not been studied.

- *Hepatic impairment*

Two studies investigated the effect of impaired hepatic function: Study ACE-HI-001 (investigating the effect of mild and moderate HI on acalabrutinib exposure) and study ACE-HI-102 (investigating the effect of severe HI on acalabrutinib and ACP-5862 exposure).

In study ACE-HI-001, acalabrutinib Cmax values were 1.90-fold greater in subjects with mild hepatic insufficiency and similar (1.02-fold) in subjects with moderate hepatic insufficiency compared to subjects with normal hepatic function. $AUC_{0\text{-last}}$ values were 1.90-fold greater in subjects with mild hepatic insufficiency and 1.48-fold in subjects with moderate hepatic insufficiency, compared to subjects with normal hepatic function.

In study ACE-HI-102, geometric mean total acalabrutinib C_{max}, $AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$ values were 4.92 -fold, 5.16 -fold and 5.28 -fold, respectively, greater in subjects with severe hepatic insufficiency compared to subjects with normal hepatic function. Geometric mean unbound acalabrutinib C_{max} and $AUC_{0\text{-last}}$ values were 3.77 -fold and 3.55 -fold, respectively, greater in subjects with severe hepatic insufficiency compared to subjects with normal hepatic function.

Geometric mean total and unbound ACP-5862 C_{max}, $AUC_{0\text{-inf}}$ and and $AUC_{0\text{-last}}$ values in subjects with severe hepatic insufficiency were similar to those in subjects with normal hepatic function (between 0.88- to 1.01-fold of healthy subjects).

Thus, a 5-fold increase in C_{max} and total exposure of acalabrutinib was seen in subjects with severe hepatic impairment. The exposure of the active metabolite ACP-5862 was however similar in subjects with severe hepatic impairment as in healthy volunteers. See *Figure 15* and *Figure 16*.

Figure 15: Arithmetic Mean Total Plasma Acalabrutinib Concentrations Versus Time in Subjects with Severe Hepatic Impairment and with Normal Hepatic Function (Semi-Log Scale) (Pharmacokinetic Population)

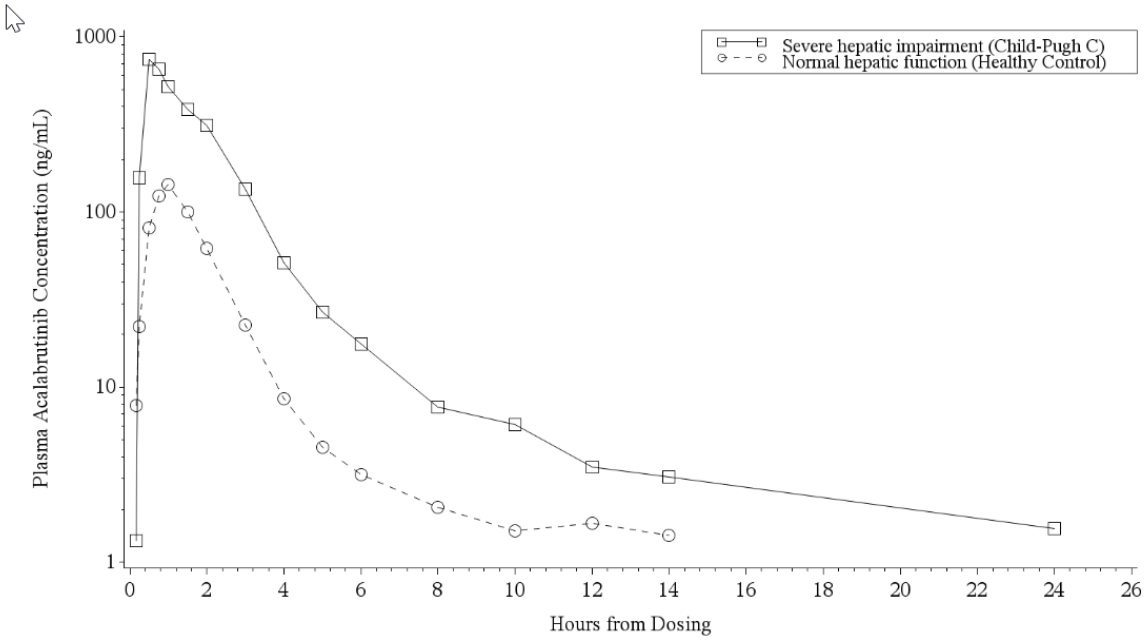
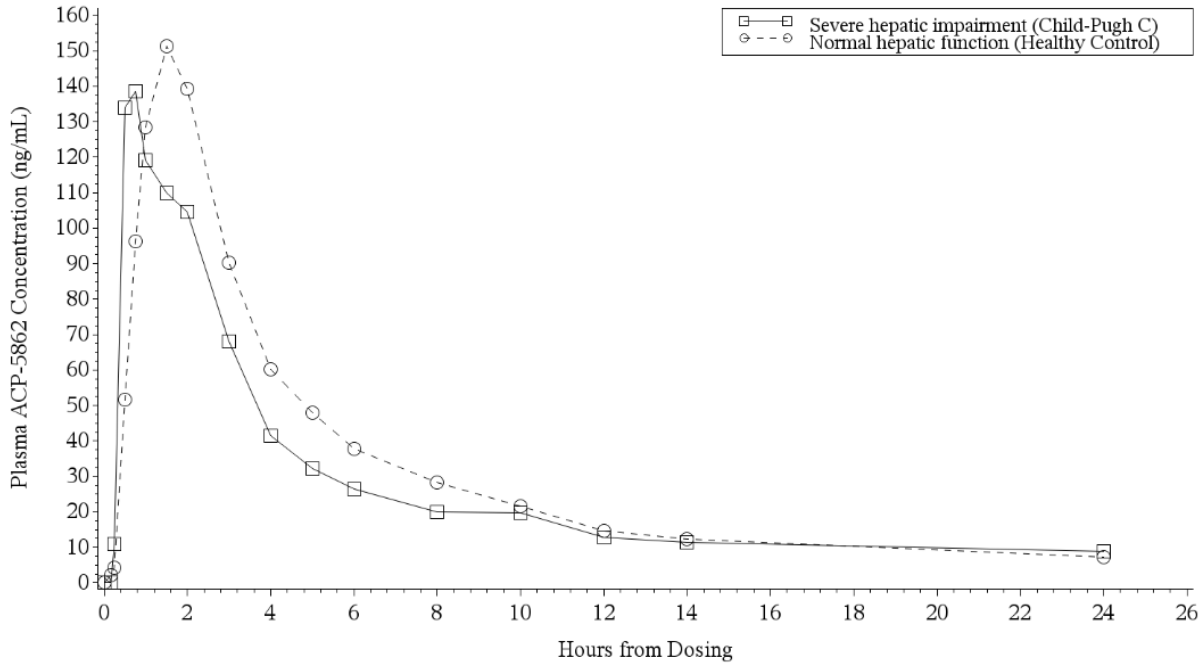


Figure 16: Arithmetic Mean Total Plasma ACP-5862 Concentrations Versus Time in Subjects with Severe Hepatic Impairment and with Normal Hepatic Function (Linear Scale) (Pharmacokinetic Population)



- *Sex, race/ethnicity, weight, age*

The effect of demographic covariates on acalabrutinib/ACP-5862 were investigated in the population PK analysis. According to the covariate analysis the effect of sex, race/ethnicity, body weight and age were not found to be statistically significant on any PK parameters. The population PK analysis, based on a population with a mean ± SD age of 61.0±14.5 years (range 18.0–90.0 years of age) for acalabrutinib, and 68.1±9.70 years (range 18.0–88.0 years of age) for ACP-5862. The pharmacokinetics of acalabrutinib/ACP-5862 has not been studied in subjects less than 18 years of age.

Table 19: Subject population in pharmacokinetic studies (based on data used in pop-PK analysis) by age group

	Age 65-74 No. of Older Subjects /Total	Age 75-84 No. of Older Subjects /Total	Age 85+ No. of Older Subjects /Total
Subjects	239/366	115/366	12/366
ACE-CL-001	46	19	–
ACE-LY-004	16	7	3
ACE-WM-001	17	12	4
ACE-LY-002	1	3	–
ACE-LY-003	4	1	–
ACE-MY-001	2	2	–
ACE-CL-003	1	3	–
ACE-CL-007	149	68	5
Total	239	115	12

Pharmacokinetic interaction studies

Acalabrutinib as victim of drug interactions

Acalabrutinib and the active metabolite ACP-5862 (formed via CYP3A4 metabolism) are substrates for CYP3A4, P-gp and BCRP *in vitro*.

Itraconazole (strong CYP3A4 and P-gp inhibitor) increased acalabrutinib C_{max} and AUC 3.7- and 5.1-fold respectively. No marked differences in half-life values were observed (3.3 vs 2.5 hours).

Following a single dose of rifampicin (inhibitor of OATP1B1/1B3, P-gp and BCRP), peak exposure of acalabrutinib was approximately 1.23-fold higher than with acalabrutinib alone and the overall exposure was 1.36- and 1.29-fold higher ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ respectively).

Multiple doses of rifampicin (strong CYP3A4 and P-gp inducer) decreased acalabrutinib C_{max} and AUC by 68 and 77% respectively. The half-life was somewhat shorter following rifampicin treatment, 0.8 vs 1.6 hours.

The active metabolite was not measured in the interaction studies, but the applicant has attempted to simulate metabolite exposure following treatment with strong (and moderate) CYP3A4 inhibitors and inducers and to suggest SmPC recommendations based on these simulations. However, the model was not sufficiently qualified and is not currently used to support any claims.

Absorption of acalabrutinib is affected by substances increasing gastric pH. Concomitant administration with calcium carbonate resulted in 75% lower C_{max} and 53% lower AUC of acalabrutinib. Following pre-treatment with omeprazole, acalabrutinib had 43% lower AUC_{0-t}, 36% lower AUC_{0-inf} and 72% lower Cmax. Proton-pump inhibitors (PPIs) were found to be a statistically significant covariate in the population PK analysis. The results indicate that acalabrutinib exposures were lower with concomitant PPI use (36% decrease).

Acalabrutinib as perpetrator of drug interactions

Based on *in vitro* data, for acalabrutinib inhibition cannot be completely excluded for intestinal CYP3A4 since the IC50 values for direct inhibition and TDI of CYP3A4 were below the cut-off value for interaction risk at the intestinal level (86 µM).

In vitro studies indicate that acalabrutinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1 or UGT2B7 at clinically relevant concentrations.

In vitro studies indicate that ACP-5862 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A1 or UGT2B7 at clinically relevant concentrations.

In vitro studies indicate that acalabrutinib induces CYP1A2.

Based on *in vitro* data, the risk of induction of intestinal CYP3A4 by acalabrutinib cannot be excluded since a 2.44-fold increase was seen in one donor at the highest concentration (50 µM) and the cut-off for intestinal enzymes are 86 µM.

For CYP2B6, induction by acalabrutinib was observed at the highest concentration but no signs of induction were seen at the lower concentrations which is most relevant, and consequently no evaluation of interaction potential of CYP2B6 *in vivo* is necessary.

ACP-5862 did not induce CYP1A2 or CYP2B6. For CYP3A4 induction was observed at the highest concentration but no signs of induction were seen at the lower concentrations which are most relevant.

For BCRP, *in vivo* inhibition by acalabrutinib cannot be excluded as the *in vitro* IC50 value of 40.9 µM is lower than the cut-off used for evaluation of intestinal interaction potential in vivo (0.1*Dose/250 mL = 86 µM).

Metabolite ACP-5862 was shown *in vitro* to be an inhibitor of MATE1 with an IC50 value of 0.2 µM.

Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 or MATE2-K at clinically relevant concentrations. Acalabrutinib does not inhibit MATE1 and ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

No study with oral contraceptives has been submitted.

Pharmacokinetics using human biomaterials

N/A

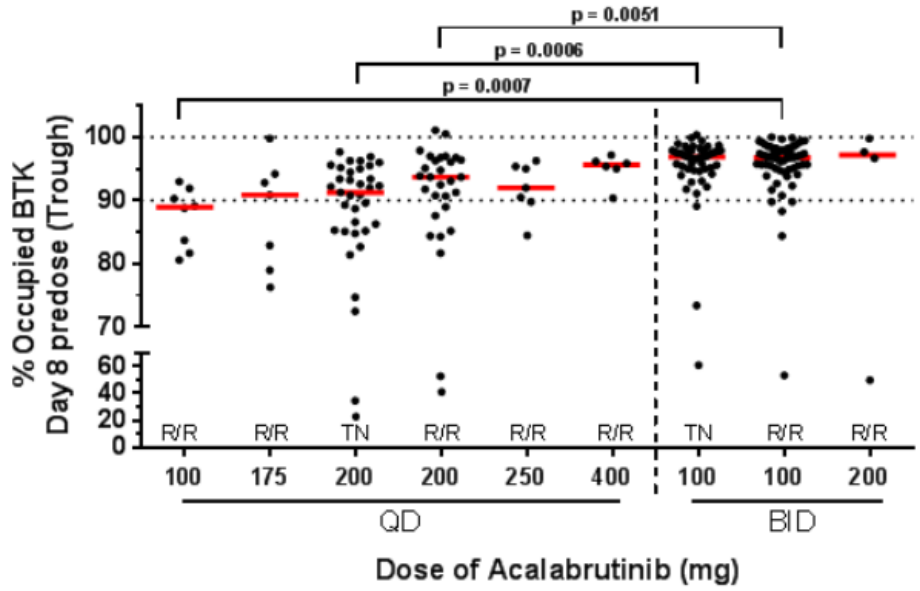
2.4.3. Pharmacodynamics

Mechanism of action

Dose-BTK occupancy relationship

BTK receptor occupancy relationships have been studied in healthy subjects and patients. As shown in *Figure 17*, results from ACE-CL-001 (Report 2016007) suggest that the 100-mg BID dose of acalabrutinib provided maximal BTK occupancy with least interpatient variability at trough for subjects with R/R and TN CLL.

Figure 17 BTK Occupancy (%) in Subjects with R/R and Treatment-Naive CLL at Trough (Acalabrutinib Css,min)



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 naïve.
a Horizontal lines depict median values; (unpaired, parametric, 2 tailed t-test used for statistical testing); values in red are p-values <0.05.
Source: Study ACE-CL-001

Primary and Secondary pharmacology

Exposure-efficacy relationship

The exposure metric used for the exposure-response analyses was steady state cumulative AUC estimated over 24h (AUC24h,ss). To account for contribution of the major active metabolite, ACP-5862, to overall efficacy and safety, acalabrutinib and ACP-5862 molar exposures were adjusted with respective BTK potency and protein binding, and expressed as total active AUC24h,ss (exposure metric for the total active moiety), as shown below:

$$Total\ Active\ AUC_{24h,ss} = AUC_{parent} * fu_{parent} + AUC_{metabolite} * \frac{MW_{parent}}{MW_{metabolite}} * fu_{metabolite} * 0.5$$

Only data from the ongoing pivotal study ACE-CL-007 in subjects with previously untreated CLL (n=274) were included in the exposure-response analysis for efficacy outcomes. In this study, subjects received oral doses of acalabrutinib 100-mg BID.

Exposure-safety relationship

Exposure-safety analyses were performed on a pooled dataset (overall population; n=573) and predefined subsets of subjects with B-cell malignancies who received acalabrutinib as monotherapy or in combination, across 8 clinical studies. In the studies, acalabrutinib was administered orally as once-daily (QD; 100 mg, 175 mg, 200 mg, and 250 mg) or twice-daily (BID; 100 mg and 200 mg) regimens. The relationships between acalabrutinib $AUC_{24h,ss}$ and the incidence of selected AEs (percentage of subjects with a specific AE) are shown below. Acalabrutinib $AUC_{24h,ss}$ were comparable regardless of whether Grade ≥2 or Grade ≥3 any AEs were present or absent. With the exception of Grade ≥2 infection, there were no trends between higher acalabrutinib exposures and the selected ECIs. These results (in the overall population) were consistent across all safety sub-populations, including CLL Naive, Total CLL, CLL Mono, CLL Combo, and Mono HemMalig.

Figure 18 Box Plot of Acalabrutinib $AUC_{24h,ss}$ by AEs in Subjects with B-Cell Malignancies (Overall Population)

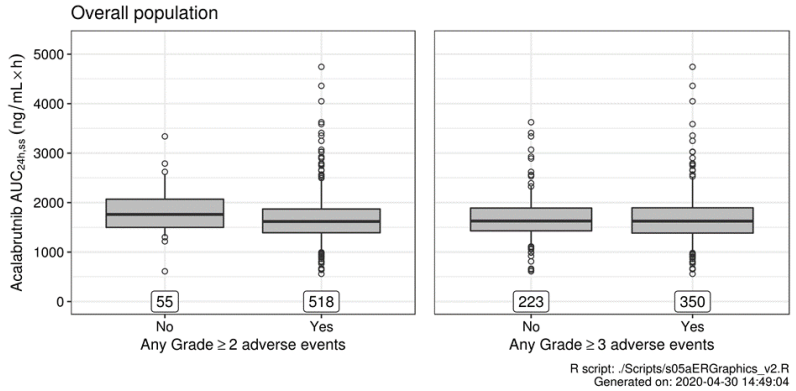
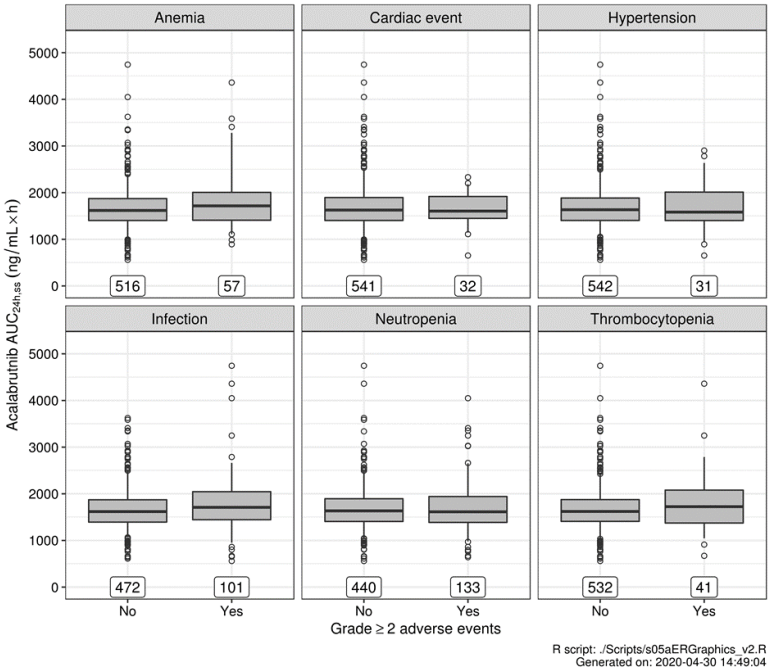
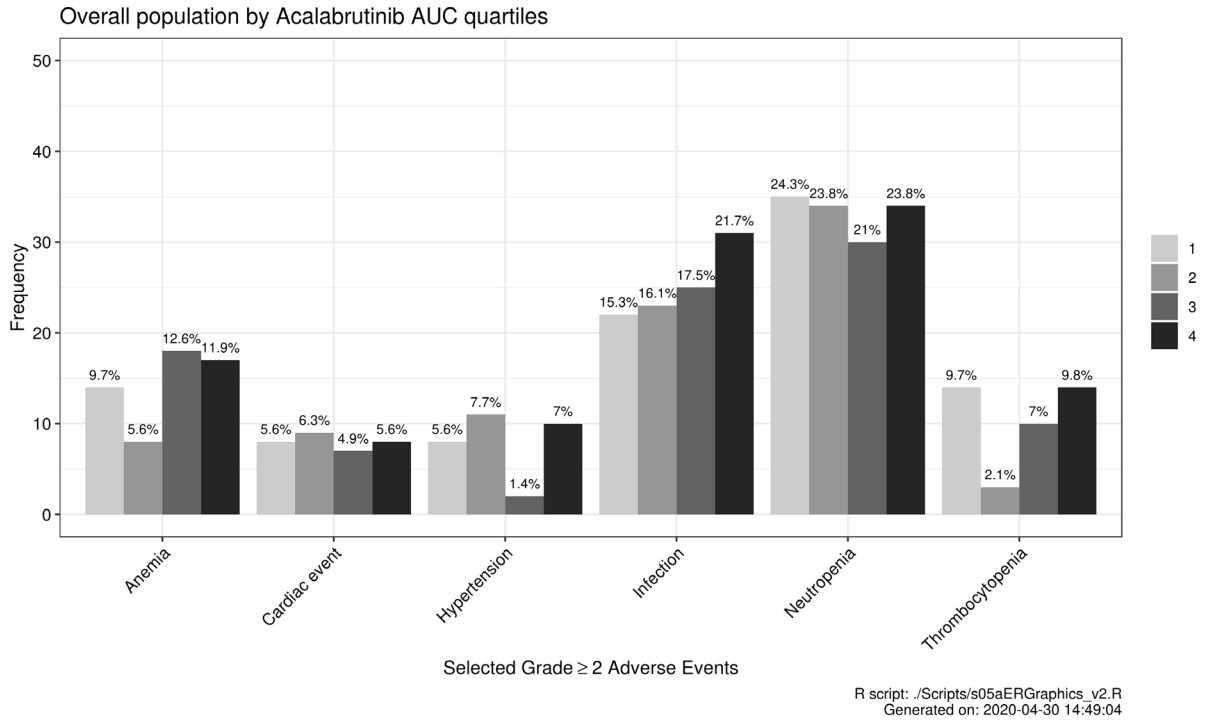


Figure 19 Box Plot of Acalabrutinib $AUC_{24h,ss}$ Stratified by Selected Grade ⩾2 AEs of Clinical Interest (Overall Population)



AE=adverse event; AUC24h,ss=area under the concentration-time curve at steady-state conditions for a 24-hour dosing interval. The numbers under the categories on the x-axis indicate the number of subjects who experienced the selected AE (Yes) and the number of subjects who did not experience the AE (No). For the boxplot, the ends of the box represent the 25th and 75th percentiles of the AUC24h,ss distribution and the middle line shows the median of the distribution. The whiskers outside the box indicate the 5th and 95th percentiles of the AUC24h,ss distribution. Data below the 5th and above the 95th percentile are shown as open circles.

Figure 20 Incidence of Selected Grade ⩾2 AEs of Clinical Interest Stratified by Quartile of Acalabrutinib AUC24h,ss (Overall Population)



AE=adverse event; AUC24h,ss=area under the concentration-time curve at steady-state conditions for a 24-hour dosing interval.

Exposure (AUC24h,ss) quartiles have been computed for acalabrutinib treated subjects in the overall Safety Population. The shaded bars represent the four quantiles (quartiles) of AUC24h,ss with 1=first quartile, 2=second quartile, 3=third quartile, and 4=fourth quartile.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of acalabrutinib and its active metabolite, M27 (ACP-5862), were studied in healthy subjects and in patients with B-cell malignancies. Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and ACP-5862 exhibit almost linear PK across a dose range of 75 to 250 mg. Population PK modelling suggests that the PK of acalabrutinib and ACP-5862 is similar across patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including, CLL), the geometric mean steady state daily area under the plasma concentration over time curve (AUC24h) and maximum plasma concentration (Cmax) for acalabrutinib were 1679 ng•h/mL and 438 ng/mL, respectively, and for ACP-5862 were 4166 ng•h/mL and 446 ng/mL, respectively. The metabolite, M27 is approximately 50% less potent than acalabrutinib but with higher plasma exposure (AUC 2-3-fold higher than parent). The metabolite was not measured in for example the interaction studies, which is a great weakness, attempts to simulate metabolite exposure following co-administration with CYP3A4 inhibitors/inducers as discussed where the active moiety concept was used.

A physiologically based pharmacokinetic model approach has been used to describe the effects of CYP3A4 inhibition and induction, both with acalabrutinib as a victim and perpetrator. Furthermore, the PBPK model has been used to investigate the behaviour of the active metabolite in combination with CYP3A4 inhibition/induction. A population PK analysis has been used to mainly describe covariate

effects; demographic as well as intrinsic/extrinsic factors. The results from the analysis indicate that the final model describes patient PK data well but there are some indications of model misspecification for the healthy subject data. As the main objective was to describe CLL patient PK the final PK model as presented is accepted.

The time to peak plasma concentrations (T_{max}) was 0.5-1.5hours for acalabrutinib, and 1.0 hour for ACP-5862. The absolute bioavailability of Calquence is estimated to 25.3%. It can be concluded that the degree of absorption is larger than what the absolute bioavailability would indicate, and together the available data show that the degree of absorption is rather high, but it cannot be clearly concluded that the absorption can be classified as complete according to the BCS concept (above 85%).

There was a significant decrease in C_{max} by 69% and a delay in t_{max} by 1-2 hours when the product was taken with a high-fat meal compared to the fasted state, while there was no significant effect on AUC (results slightly outside BE acceptance criteria). The food effect study was not performed with the commercial formulation but with the previous blend in capsule formulation, however, based on a cross-study comparison the effect of omeprazole seems to be lower on the final formulation compared to the earlier formulation. Thus it is not considered likely that the effect of food (due to increased pH) would be larger on the commercial formulation than on the earlier formulation. It is agreed that acalabrutinib can be taken with or without food, since the effect of food on C_{max} is not likely to be clinically relevant and considering the food recommendations in the phase 3 studies (see section 5.2 of the SmPC).

Reversible binding to human plasma protein was 97.5% for acalabrutinib and 98.6% for ACP-5862. The *in vitro* mean blood-to-plasma ratio was 0.8 for acalabrutinib and 0.7 for ACP-5862. The mean steady state volume of distribution (V_{ss}) was approximately 34 L for acalabrutinib.

In vitro, acalabrutinib is predominantly metabolised by CYP3A enzymes, and to a minor extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major metabolite in plasma, that was further metabolized primarily by CYP3A-mediated oxidation, with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

In vitro studies indicate that acalabrutinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1 or UGT2B7 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.

In vitro studies indicate that ACP-5862 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A1 or UGT2B7 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.

In vitro studies indicate that acalabrutinib and ACP-5862 are P-gp and BCRP substrates. Co-administration with BCRP inhibitors is however unlikely to result in clinically relevant drug interactions. Co-administration with an OATP1B1/1B3 inhibitor (600 mg rifampin, single dose) resulted in an increase in acalabrutinib C_{max} and AUC by 1.2-fold and 1.4-fold (N=24, healthy subjects), respectively, which is not clinically relevant. Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 and MATE2-K at clinically relevant concentrations. Acalabrutinib may inhibit intestinal BCRP, while ACP-5862 may inhibit MATE1 at clinically relevant concentrations (see section 4.5). Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Following a single oral dose of 100 mg acalabrutinib, the terminal elimination half-life ($t_{1/2}$) of acalabrutinib was) 1 to 2 hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was approximately 7 hours. The mean apparent oral clearance (CL/F) was 134 L/hr for acalabrutinib and 22 L/hr for ACP-5862 in patients with B-cell malignancies.

The elimination pathways of acalabrutinib have been sufficiently elucidated. Following administration of a single 100 mg radiolabelled [^{14}C]-acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the faeces and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged acalabrutinib; thus metabolism is the main elimination pathway.

The plasma protein binding results are from different studies and according to the CHMP guideline on DDI (CPMP/EWP/560/95 Rev1) it is recommended to determine the protein binding in the same study if the protein binding of parent and metabolite is high so as not to introduce inter-study variability. In addition, the studied concentration interval (1, 3 and 10 µM) is high compared to plasma concentrations seen in clinical studies (Cmax of 466 ng/ml = 1 µM). New plasma protein binding data including acalabrutinib and its metabolite ACP-5862 in the same study using clinically relevant concentration range of acalabrutinib and ACP-5862 should be submitted post-approval as recommended by the CHMP.

The mean terminal $t_{1/2}$ of total radioactivity in plasma was 46.5 hours while the half-life for parent drug was 1.47 hours, indicating presence of metabolites with longer half-life than parent drug. In whole blood, the terminal half-life could not be calculated but is clearly long - likely due to covalent binding of acalabrutinib to BTK in blood cells. M27 is a major metabolite (representing 34.7% of total radioactivity), that needs to be screened for enzyme inhibitory potential, but no other metabolites need to be further characterised. Approximately 67% of the total radioactivity in plasma is identified. This is considered acceptable since the metabolite M27 contributing more than 10% of the AUC of drug related material has been structurally characterised. The non-identified drug radioactivity is likely numerous trace amount metabolites.

Based on population PK analysis, age (>18 years of age), sex, race (Caucasian, African American) and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862. No pharmacokinetic studies were performed with Calquence in patients under 18 years of age.

Given the differences in exposures (AUC and C_{max}) between the capsule and blend-in-capsule formulations, the impact of formulation was evaluated in the population PK model and its inclusion did not statistically improve the model performance and parameter precision. The simulation-based analysis showed that no significant impact on the exposure metrics is expected due to the influence of formulation effect, demonstrating the lack of any clinically relevant effect.

There is a tendency to more than dose-proportional increase in exposure with increasing dose in the dose range 2.5 to 400 mg (although the study Study ACE-CL-001 showed less than dose-proportional increase in the dose range 100 QD to 400 mg QD). However, there seems to be no major deviation from dose-proportionality in the dose range 75 to 250 mg.

Renal clearance following IV administration was 0.654 L/h and filtration (fu*GFR) is expected to be around 0.2 L/h, thus active renal secretion seems to be included in the renal elimination of acalabrutinib. However, renal clearance of unchanged parent drug is a very minor elimination pathway and thus any effect on renal transporters is not likely to affect the elimination of acalabrutinib. *In vivo* interconversion of acalabrutinib to the other enantiomer is unlikely to be clinically relevant.

It can be agreed that no dedicated renal study is needed, since renal elimination is a minor pathway. A large proportion of the patients in the pop PK analysis had mild RI, so this is covered in the safety population (see discussion on Clinical safety). Based on population PK analysis, no clinically relevant PK difference was observed in 408 subjects with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2 as estimated by MDRD), 109 subjects with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2) relative to 192 subjects with normal renal function (eGFR greater than or equal to 90 mL/min/1.73m^2). The PK of acalabrutinib has not been characterised in patients

with severe renal impairment (eGFR less than 29 mL/min/1.73m^2) or renal impairment requiring dialysis. Patients with creatinine levels greater than 2.5 times the institutional ULN were not included in the clinical studies (see SmPC section 4.2 and 5.2).

Acalabrutinib is metabolised in the liver. In dedicated hepatic impairment (HI) studies, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by 1.9-fold, 1.5-fold and 5.3-fold in subjects with mild (n=6) (Child-Pugh A), moderate (n=6) (Child-Pugh B) and severe (n=8) (Child-Pugh C) hepatic impairment, respectively. Subjects in the moderate HI group were however not significantly affected in markers relevant for the elimination capacity of drugs, so the effect of moderate hepatic impairment was likely underestimated in this study. Based on a population PK analysis, no clinically relevant difference was observed between subjects with mild (n=79) or moderate (n=6) hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST) relative to subjects with normal (n=613) hepatic function (total bilirubin and AST within ULN) (see SmPC section 4.2).

Subjects in the moderate HI group were however mainly affected in aspects not primarily related to elimination capacity of drugs (such as encephalopathy and ascites) and not in markers that are likely to be relevant for the elimination capacity of drugs (such as albumin, bilirubin and prothrombin time), so the effect of moderate HI is likely underestimated in the submitted study. The number of subjects with moderate (and severe) HI in the population PK-analysis was very low, and thus this analysis cannot contribute much in concluding about the effect of moderate HI. Acalabrutinib is not recommended in severe HI, but can be given without dose adjustment in patients with mild and moderate HI; the risk of increased exposure of acalabrutinib in patients with moderate HI that are affected in markers relevant for the elimination capacity, was analysed in two subjects from the moderate HI cohorts (Child-Pugh B) that were affected regarding albumin, and two subjects from the severe HI cohorts that were closest to the Child-Pugh B classification. The expected daily exposure following normal dosing (based on the mean $AUC_{0\text{-last}}$ obtained for these 4 subjects) is within the established exposure-safety relationship. However, the variability is large and the data is based on very few subjects. Thus, as a precaution a recommendation to monitor patients with moderate hepatic impairment closely for signs of toxicity has been included in the SmPC (see section 4.2 and 4.4).

The effect of severe HI on the parent drug acalabrutinib was similar to the effect of a strong CYP34 inhibitor on acalabrutinib exposure. The applicant has simulated metabolite exposure with concomitant CYP3A4 inhibition, where a significant decrease in metabolite exposure was predicted, in contrast to the metabolite results from the study in severe HI where the metabolite exposure was unchanged. One explanation for this deviation in results could be that in patients with severe HI, intestinal CYP3A4 metabolism would likely not be affected, while concomitant treatment with CYP3A4 inhibitors would also affect intestinal CYP3A4 metabolism. However, this discrepancy contributes to the doubts regarding the PBPK model and the uncertainty regarding the effect of CYP3A4 inhibition on metabolite exposure and also regarding the relative contribution of intestine versus liver to the metabolism.

There is an ongoing study that will provide information regarding the effect of moderate CYP3A inhibitors on parent as well as on metabolite exposure. Until data from this study is available, and considering the safety profile as well as the uncertainty regarding the lower limit of exposure in relation to efficacy, the suggested recommendation to use the normal dose but monitor patients closely for adverse reactions in case of concomitant treatment with moderate CYP3A4 inhibitors can be agreed. The results from the currently ongoing drug-drug interaction (DDI) study (ACE-HV-115; evaluating the pharmacokinetics of acalabrutinib and ACP-5862 administered alone or in combination with moderate CYP3A4 inhibitors fluconazole or isavuconazole), the updated PBPK model based on the results of Study ACE-HV-115 and possible suggested revisions of recommendations for co-administering acalabrutinib with CYP3A inhibitors should be submitted post-approval as recommended by the CHMP. It is not assumed that any revisions regarding recommendations for CYP3A inducers will

be possible based on this study and the revised model. Concomitant use with strong CYP3A4 inducers should be avoided (see SmPC section 4.5).

Concomitant use of PPIs is not recommended, and for antacids and H2-blockers, staggered dosing is suggested. The effect of antacids on gastric pH has short duration, and thus administration of acalabrutinib 2 hours after administration of an antacid will likely not result in clinically relevant effects on the bioavailability of acalabrutinib due to effects on gastric pH. Also, since acalabrutinib is quickly absorbed, administration of antacids (or H2 blockers with slower onset of effect than antacids) 2 hours after acalabrutinib administration will also likely not result in clinically relevant effects on the bioavailability of acalabrutinib. It is not entirely clear if a 10 hour interval between a H2 blocker and the next acalabrutinib dose is sufficient in order to completely avoid an effect on acalabrutinib absorption, but this limit is considered reasonable and will likely not result in clinically relevant effects on acalabrutinib exposure. (see section 4.5 of the SmPC).

The in vitro results of acalabrutinib as a substrate for OATP1B1, OATP1B3, OAT1, OAT3 or OCT2 is inconclusive since the tested concentrations are too high and may saturate the transporters. The risk of interaction with OATP1B1 or OATP1B3 inhibitors do not need to be repeated as an in vivo study with rifampicin has been performed showing a small not clinically relevant interaction. In vitro studies for the transporters OAT1, OAT3 and OCT2 do not need to be repeated since the renal secretion is estimated to be <25%.

Acalabrutinib and ACP-5862 are substrates for BCRP, but available data do not suggest that BCRP transport in the gut would limit the absorption of acalabrutinib to a large extent, given the signs of fairly high degree of absorption, linear pharmacokinetics in the clinical dose range. In addition, available pharmacogenetic data do not indicate that a clinically relevant effect of BCRP inhibitors is likely. Thus, in the SmPC it is stated that a clinically relevant interaction is unlikely.

Based on a cross-study comparison, the exposure of the sensitive CYP3A4 substrate venetoclax was in the same range following co-administration with acalabrutinib as without acalabrutinib, indicating no large potential for acalabrutinib to inhibit intestinal CYP3A4 in vivo. However, the risk of a weak inhibition of CYP3A substrates cannot be completely excluded and a warning is included in section 4.5 of the SmPC.

Co-administration of acalabrutinib with CYP1A2 substrates (e.g. theophylline, caffeine) may decrease their exposure, which is reflected in the SmPC.

Based on in vitro DDI data for acalabrutinib, a risk for induction of intestinal CYP3A4 could not be excluded. However, considering the totality of data (vague in vitro signal, venetoclax data and no signs of auto-induction of acalabrutinib clearance) it´s considered unlikely that acalabrutinib will induce intestinal CYP3A4 and result in clinically relevant interactions when co-administered with CYP3A substrates.

Acalabrutinib is not teratogenic according to preclinical studies but causes embryo/foetal toxicity. It should therefore not be used during pregnancy, and women of childbearing potential should be advised to avoid becoming pregnant. The proposed indication is not expected to include women of childbearing potential to a large extent. Based on the submitted data it is unlikely that acalabrutinib will induce intestinal CYP3A4 and result in clinically relevant interactions when co-administered with CYP3A substrates, and thus efficacy of oral contraceptives is not expected to be affected during acalabrutinib treatment (see SmPC section 4.5 and 4.6).

The dose-BTK occupancy analyses across doses and populations indicate that the proposed 100 mg BID dose result in a consistent high occupancy (>95%) with the least amount of variability between individuals.

The exposure-efficacy relationship has been analysed with total active AUC, where the concentration of the active metabolite has been adjusted for the relative potency which is accepted. Furthermore, the applicant states that a wide range of exposure has been used in the exposure-efficacy analysis. However only one dose level was included in study ACE-CL-007 which makes it difficult to separate the exposure effect from other confounding factors. Although no apparent relationship between exposure and efficacy was detected, as the exposure range was related to one dose level the exposure-efficacy results should be interpreted with caution.

An increase in acalabrutinib exposure of up to approximately 2.5-fold can be expected to be safe and well-tolerated and that a decrease in exposure of up to approximately 50% can be expected to have no clinically relevant impact on efficacy. The exposure-safety analyses indicate that acalabrutinib is safe over a wide exposure range based on a pooled dataset which included several dose levels and multiple safety endpoints. Model-based exposure-safety analyses (logistic regression) were subsequently performed between $AUC_{24h,ss}$ and infections, where no statistically significant relationship was detected. Overall, it is agreed that no alarming exposure-safety relationships were detected. In the exposure-safety analyses, the exposure range was (min to max) AUC0-24h of 559.2 – 4744 ng*h/mL for a dose range of 100 mg once daily to 200 mg twice daily, including the highest dose of 400 mg once daily. Hence, it is indicated that an $AUC24_{h,ss}$ up to approximately 4500 ng/mL*h remains safe. However, the lower limit of exposure in relation to efficacy remains unknown.

The CHMP recommended that additional long-term stability data for the metabolite should be submitted post-approval. Overall, the presented dosing rationale to support the fixed 100-mg BID acalabrutinib dose seems reasonable.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology aspects of acalabrutinib are sufficiently studied; all relevant information is included in the SmPC. Further, the CHMP recommends that the applicant submits:

- The results from the currently ongoing drug-drug interaction (DDI) study (ACE-HV-115; evaluating the pharmacokinetics of acalabrutinib and ACP-5862 administered alone or in combination with moderate CYP3A4 inhibitors fluconazole or isavuconazole), the updated PBPK model based on the results of Study ACE-HV-115 and possible suggested revisions of recommendations for co-administering acalabrutinib with CYP3A inhibitors should be submitted.
- Additional long-term stability data for the metabolite ACP-5862, up to 1224 days (i.e., 75 additional days), in order to cover the maximum storage from collection to extraction for the metabolite (1224 days in study ACE-CL-007) should also be submitted.

2.5. Clinical efficacy

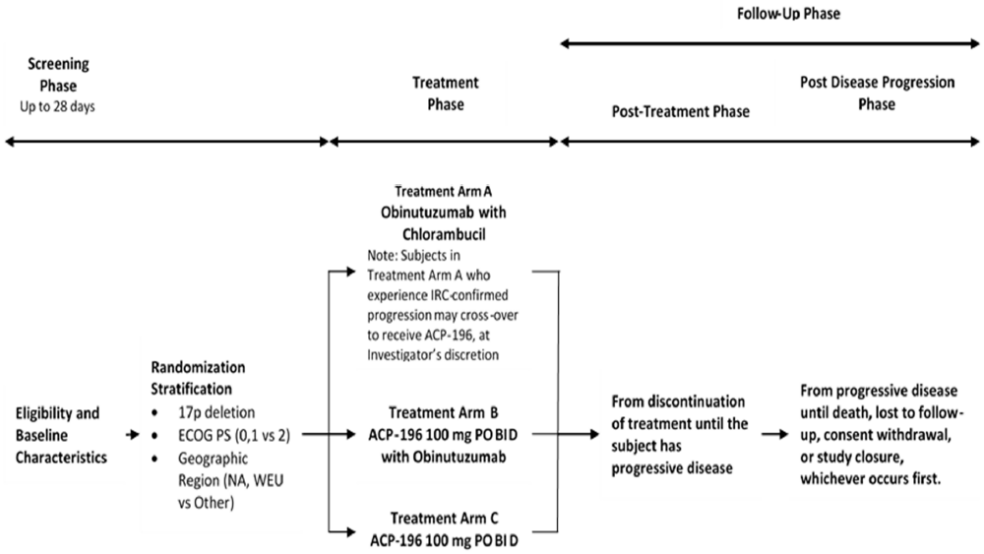
2.5.1. Dose response study(ies)

See Clinical Pharmacology section and supportive study 001.

2.5.2. Main studies

Study ACE-CL-007

A Randomized, Multicentre, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP- 196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia.



Study Participants

Key inclusion criteria

Enrolled previously untreated subjects who were unfit based on the inclusion criterion of age ≥65 years or age <65 years with a Cumulative Illness Rating Score Geriatric (CIRS-G) score of >6 or a creatinine clearance of 30-69 mL/min (using the Cockcroft-Gault equation). Additional inclusion criteria were:

- adult men and women with documented CD20-positive CLL that met the following published diagnostic IWCLL 2008 criteria (Hallek et al. 2008)
- met at least 1 of the IWCLL 2008 criteria for requiring treatment
- ANC ≥0.75x109/L or ≥0.50x109/L in subjects with documented bone marrow involvement
- platelet count ≥50x109/L, or ≥30x109/L in subjects with documented bone marrow involvement. Subjects with transfusion-dependent thrombocytopenia were excluded. In Study ACE-CL-309, platelets were to be ≥75x109/L for subjects receiving BR (in Arm B)
- estimated creatinine clearance of ≥30 mL/min (using Cockcroft-Gault equation)
- baseline ECOG performance status of ≤2.

Notable exclusion criteria

- Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at Screening.
- History of stroke or intracranial hemorrhage within 6 months before randomization.

- Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).
- Required or received anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days of first dose of study drug.
- Required treatment with proton-pump inhibitors.
- Required treatment with a strong CYP3A inhibitor/inducer: Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before Screening.

Treatments

Monotherapy or combination therapy with acalabrutinib until toxicity or PD were compared to a control therapy of fixed duration.

Objectives

The primary objective was to evaluate the efficacy of obinutuzumab+chlorambucil compared with acalabrutinib+obinutuzumab based on IRC assessment of PFS. The key secondary objective was to evaluate the efficacy of obinutuzumab+chlorambucil versus acalabrutinib monotherapy based on IRC-assessed PFS.

Other secondary objectives included evaluation of IRC-assessed ORR, OS, and TTNT

Outcomes/endpoints

The primary efficacy endpoint is progression-free survival (PFS) as assessed by IRC PFS, between the obinutuzumab+chlorambucil arm and acalabrutinib+obinutuzumab arm. It is defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause.

Table 20. Primary Efficacy Analysis of PFS-IRC Outcome

Situation	Date of Progression or Censoring	Outcome
PFS events include death or first IRC-confirmed disease progression that occurred at or prior to the data analysis cutoff date.		
Death before first disease assessment	Date of death	Event
IRC-confirmed PD or death between scheduled assessments	Earliest date of IRC confirmed PD or death	Event
All other cases will be censored as follows:		
No baseline tumor assessments	Randomization	Censored
No adequate post-baseline assessment	Randomization	Censored
No IRC-confirmed PD or death at the time of data cutoff (including subjects who had PD or died after cutoff)	Date of last adequate IRC assessment before data cutoff	Censored
No IRC-confirmed PD or death before study exit	Date of last adequate IRC assessment before data cutoff	Censored
No IRC-assessed PD or death before start of subsequent anticancer therapy	Date of the last adequate IRC assessment before start of subsequent anticancer therapy Therapy	Censored
IRC-assessed PD or death after start of subsequent anticancer therapy	Date of the last adequate IRC assessment before start of subsequent anticancer therapy	Censored
IRC-confirmed PD or death after 2 or more consecutively missed visits	Date of last adequate IRC assessment before the consecutively missed visits	Censored

Secondary endpoints

The key (first) secondary efficacy endpoint is PFS as assessed by IRC comparing between Arms A and C

Other secondary efficacy endpoints are listed below, and each will be compared between Arms B versus A and Arms C versus A in the ITT population.

• IRC-assessed ORR per IWCLL 2008 criteria	ORR was defined as the proportion of subjects who achieved a best response of CR, CRi, nPR, or PR at or before initiation of subsequent anticancer therapy. ORR including PRL was defined as the proportion of subjects who achieved a best response of CR, CRi, nPR, PR or PRL at or before initiation of subsequent anticancer therapy
• Time to Next Treatment (TTNT)	TTNT was defined as the time from randomization to start date of non-protocol specified subsequent anticancer therapy for CLL or death due to any cause, whichever came first. TTNT was analyzed in the same fashion as that for the primary efficacy analysis
• OS	OS was defined as the time from date of randomization to death due to any cause.

Exploratory efficacy endpoints for the comparison of Arms B versus A and Arms C versus A were:

- Investigator-Assessed PFS and ORR
- Investigator and IRC-Assessed ORR + PRL (partial response except for lymphocytosis)
- Improvement of Disease-Related Symptoms
- Sustained Hematologic Improvement

Assessment for tumor response and progression will be conducted in accordance with the IWCLL 2008 criteria until disease progression. Disease assessments will be done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter for all subjects (including subjects who discontinue from study treatment due to an AE or any reason) until confirmation of disease progression or death, consent withdrawal, or lost to follow up. Subjects from Arm A who have IRC-confirmed disease progression may be eligible to receive single agent acalabrutinib at 100 mg PO BID at investigator discretion.

Sample size

The study was expected to enrol approximately 510 subjects with a 1:1:1 randomization ratio between the 3 treatment arms (approximately 170 subjects per arm). The study was sized to achieve approximately 90% power to detect a hazard ratio (acalabrutinib + obinutuzumab/ obinutuzumab + chlorambucil) of 0.6 for PFS which, under the model assumptions, translates into a 67% relative and 17.8 months absolute increase in median PFS time: a median of 26.7 months for subjects in the obinutuzumab+chlorambucil arm vs. 44.5 months for subjects in the acalabrutinib+obinutuzumab arm.

Given the study assumptions, the minimum detectable treatment difference at the final analysis of PFS corresponds to a hazard ratio (HR) of approximately 0.735.

Randomisation

Randomisation was stratified by presence versus absence of 17p deletion by central laboratory, ECOG performance status (0, 1 versus 2) and geographic region (North America and Western Europe versus Other).

Blinding (masking)

This was an open-label study.

Statistical methods

The primary efficacy analysis was to compare PFS as assessed by IRC between obinutuzumab+chlorambucil (arm B) and acalabrutinib+obinutuzumab (arm A) in the ITT population using a stratified log rank test adjusting for randomization stratification factors.

The null and alternative hypotheses are as follows:

H_0: $PFS_{Arm\ B} = PFS_{Arm\ A}$

H_A: $PFS_{Arm\ B} \neq PFS_{Arm\ A}$

The test will be conducted to reject the null hypothesis in favor of the alternative while showing that Arm B is superior to Arm A.

Analyses using the ITT population included data only prior to treatment switch for obinutuzumab + chlorambucil subjects who crossed over to acalabrutinib monotherapy.

One interim analysis and one final analysis for PFS are planned. The data submitted from study ACE-CL-007 was from a pre-planned interim analysis.

The final analysis of PFS is planned to occur when a total of 167 PFS events have been observed, which is anticipated to occur at 49 months after the first subject is randomized.

The interim analysis of PFS will be conducted when approximately two-thirds of the final analysis PFS event goal (i.e., 111 events across Arms A and B) have been observed, which is expected to occur approximately 34 months after the first subject has been randomized.

Alternatively, a time-based interim analysis may be conducted if the required number of events have not occurred by 24 months after the last subject randomized.

The applicant split α into α1 and α2 for interim and final analyses. Secondary endpoints were tested in a hierarchical order separately for interim and final analyses.

Results

Participant flow

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab +Chlorambucil (N=177)**	**Total (N=535)**
Subjects randomized (ITT Population)	179 (100.0)	179 (100.0)	177 (100.0)	535 (100.0)
Treated with ≥1 study drug	179 (100.0)	178 (99.4)	169 (95.5)	526 (98.3)
Randomized but not treated[a]	0	1 (0.6)	8 (4.5)	9 (1.7)
Acalabrutinib				
Subjects treated with study drug	179 (100.0)	178 (99.4)	–	–
Subjects who discontinued study drug	33 (18.4)	36 (20.1)	–	–
Death	1 (0.6)	3 (1.7)	–	–
Lost to follow-up	0	1 (0.6)	–	–
Withdrawal of consent	1 (0.6)	1 (0.6)	–	–
AE/SAE	18 (10.1)	16 (8.9)	–	–
CLL progressive disease	6 (3.4)	7 (3.9)	–	–
Investigator's discretion	3 (1.7)	5 (2.8)	–	–
Pregnancy	0	0	–	–
Other	4 (2.2)[e]	3 (1.7)[f]	–	–
Chlorambucil				
Subjects treated with study drug	–	–	169 (95.5)	–
Subjects who discontinued study drug	–	–	169 (95.5)	–
Death	–	–	1 (0.6)	–
Lost to follow-up	–	–	1 (0.6)	–
Withdrawal of consent	–	–	1 (0.6)	–
AE/SAE	–	–	24 (13.6)	–
CLL progressive disease	–	–	4 (2.3)	–
Investigator's discretion	–	–	1 (0.6)	–
Pregnancy	–	–	0	–
Completed Study Regimen	–	–	137 (77.4)	–
Other	–	–	0	–

Obinutuzumab				
Subjects treated with study drug	179 (100.0)	–	169 (95.5)	–
Subjects who discontinued study drug	179 (100.0)	–	168 (94.9)[d]	–
Death	1 (0.6)	–	1 (0.6)	–
Lost to follow-up	0	–	1 (0.6)	–
Withdrawal of consent	0	–	0	–
AE/SAE	11 (6.1)	–	10 (5.6)	–
CLL progressive disease	2 (1.1)	–	3 (1.7)	–
Investigator's discretion	2 (1.1)	–	1 (0.6)	–
Pregnancy	0	–	0	–
Completed Study Regimen	163 (91.1)	–	152 (85.9)	–
Other	0	–	0	–
Subjects who discontinued all study treatment[b]	33 (18.4)	36 (20.1)	168 (94.9)	237 (44.3)
Subjects who exited study	16 (8.9)	22 (12.3)	32 (18.1)	70 (13.1)
Death	6 (3.4)	9 (5.0)	16 (9.0)	31 (5.8)
Lost to follow-up	1 (0.6)	3 (1.7)	2 (1.1)	6 (1.1)
Withdrawal of consent	6 (3.4)	9 (5.0)	12 (6.8)	27 (5.0)
Investigator's discretion	3 (1.7)	1 (0.6)	0	4 (0.7)
Other	0	0	2 (1.1)[g]	2 (0.4)
Time on study (months)[c]				
Mean (SD)	28.2 (7.18)	28.0 (7.75)	26.5 (9.40)	27.6 (8.18)
Median	28.5	28.4	28.0	28.3
Min, Max	1.7, 40.3	0.1, 40.8	0.0, 40.4	0.0, 40.8
Time from randomization to first dose (days)				
n	179	178	169	526
Mean (SD)	3.7 (2.40)	3.9 (2.45)	4.6 (3.27)	4.1 (2.75)
Median	3.0	3.0	4.0	3.0
Min, Max	1.0, 14.0	1.0, 15.0	1.0, 21.0	1.0, 21.0

Nine subjects were randomized but did not receive study drug; 1 subject in the acalabrutinib monotherapy arm (withdraw consent) and 8 subjects in the Obin+Clb arm (5 withdraw consent, 2 deaths (car accident and sepsis), and 1 ineligible per sponsor). Thus, given the open-label design of the study, biased early censoring, although limited, cannot be excluded.

Recruitment

The study enrolled 535 subjects at 142 centres in 18 countries between 14 September 2015 and 08 February 2017, and 526 subjects received study treatment. The regions with the highest percentage of enrolled subjects included North America (36.4%), Western Europe (26.7%), Central and Eastern Europe (25.0%), Australia and New Zealand (8.0%), and South America (3.7%).

Conduct of the study

There were 5 global protocol amendments undertaken, none deemed critical.

Protocol deviations

Table 10 Summary of Important Protocol Deviations (ITT Population)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	Arm C Acalabrutinib Monotherapy (N=179)	Arm A Obinutuzumab +Chlorambucil (N=177)	Total (N=535)
Subjects with any important protocol deviations	33 (18.4)	17 (9.5)	28 (15.8)	78 (14.6)
Informed consent	8 (4.5)	4 (2.2)	10 (5.6)	22 (4.1)
Study treatment administration/dispense[a]	8 (4.5)	6 (3.4)	8 (4.5)	22 (4.1)
Study procedures/assessments	9 (5.0)	2 (1.1)	6 (3.4)	17 (3.2)
Inclusion criteria	5 (2.8)	5 (2.8)	4 (2.3)	14 (2.6)
Concomitant medications	2 (1.1)	2 (1.1)	0	4 (0.7)
Missing endpoint assessments	3 (1.7)	0	1 (0.6)	4 (0.7)
Exclusion criteria	1 (0.6)	0	2 (1.1)	3 (0.6)
Withdrawal/termination criteria	2 (1.1)	0	0	2 (0.4)

Note: Subjects with >1 deviation were summarized once at each deviation.

[a] Refers to subjects under dosed, subjects administered invalid study drug, or subjects administered study drug incorrectly.

Table 14.2.1.3 Sensitivity Analysis of Progression Free Survival (PFS) by Independent Review Committee (IRC) Assessment ITT Population: Excluding Subjects with Important Protocol Deviation

	Acala + Obin (N=146)	Acala (N=162)	Chlb + Obin (N=149)
Subject Status			
Events - n(%)	10 (6.8%)	20 (12.3%)	82 (55.0%)
Death	4 (2.7%)	5 (3.1%)	10 (6.7%)
PD	6 (4.1%)	15 (9.3%)	72 (48.3%)
Censored - n(%)	136 (93.2%)	142 (87.7%)	67 (45.0%)
No event before data cutoff	127 (87.0%)	130 (80.2%)	52 (34.9%)
No post-baseline assessment	0	5 (3.1%)	8 (5.4%)
No event before taking subsequent anti-cancer therapy	3 (2.1%)	1 (0.6%)	2 (1.3%)
Death or PD after 2 or more consecutive missed visits	2 (1.4%)	3 (1.9%)	0
No event before study exit	4 (2.7%)	3 (1.9%)	5 (3.4%)
Progression Free Survival (months)			
Q1 (95% CI)	NE (NE , NE)	34.2 (33.1, NE)	14.4 (14.0, 16.7)
Median (95% CI)	NE (NE , NE)	NE (34.2, NE)	22.3 (19.8, 27.5)
Q3 (95% CI)	NE (NE , NE)	NE (34.2, NE)	NE (27.8, NE)
Min, Max	0.0+, 39.4+	0.0+, 39.4+	0.0+, 39.6+
Stratified Analysis[a]			
Hazard Ratio (95% CI)[b]	0.08 (0.04, 0.15)	0.15 (0.09, 0.25)	--
p-value[c]	<.0001	<.0001	--

Time to event (or time to censor for censored subjects) will be calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months are derived as days / 30.4375.
"+" indicates a value from a censored subject.
[a]Stratified by 17p deletion status (yes vs. no)
[b]Estimated based on stratified Cox Proportional Hazards model for Hazard Ratio (95% CI)
[c] Estimated based on stratified log-rank test for p-value
[d]Kaplan-Meier estimate of the proportion of subjects who were progression free at the timepoint.

Baseline data

The median age for all subjects was 70 years (range: 41-91 years) with 84% of subjects ≥65 years, and 61% were male. Del 17p, del 11q, unmutated IGHV, and TP53 mutation were noted in 9%, 18%, 63%, and 11% of subjects, respectively, and 70% of subjects had at least 1 of these chromosomal characteristics. Study arms look overall reasonably well balanced. Please refer to the B/R section for a discussion on the external validity of the study.

Numbers analysed

Analysis populations - Subjects Analysed (Analysis Sets)

	No. (%) of Subjects			
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	Arm C Acalabrutinib Monotherapy (N=179)	Arm A Obinutuzumab +Chlorambucil (N=177)	Total (N=535)
Intent to Treat Population	179 (100.0)	179 (100.0)	177 (100.0)	535 (100.0)
Safety Population	178 (99.4)	179 (100.0)	169 (95.5)	526 (98.3)

Outcomes and estimation

Primary Variable: PFS as Assessed by IRC

With a median follow-up of 28.5 months in the acalabrutinib+obinutuzumab arm (Arm B) and 28 months in the obinutuzumab+chlorambucil arm (Arm A), the median estimated PFS for acalabrutinib+obinutuzumab (Arm B) was not reached; the median estimated PFS for obinutuzumab+chlorambucil (Arm A) was 22.6 months (95% CI: 20.2–27.6). Based on the stratified analysis, acalabrutinib+obinutuzumab (Arm B) shown a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab+chlorambucil (Arm A), with a 90% reduction in risk of disease progression or death (HR=0.1 [95% CI: 0.06–0.17]; p<0.0001).

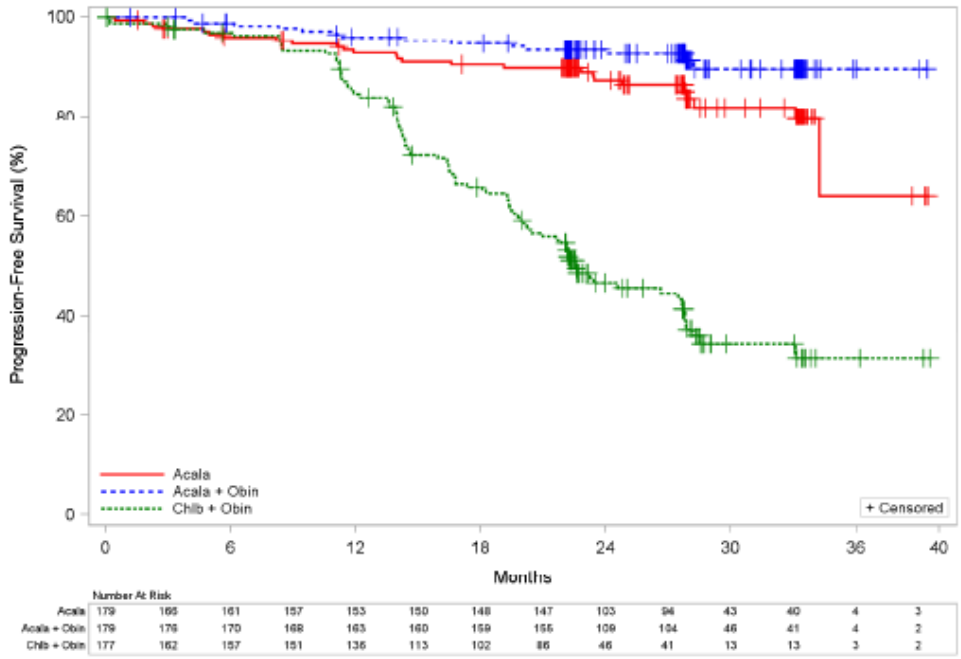
The KM estimate of the proportion of subjects without a PFS event at 12 months was 95.9% (95% CI: 91.7–98) for acalabrutinib+obinutuzumab (Arm B) and 84.6% (95% CI: 78–89.3) for obinutuzumab+chlorambucil (Arm A). The KM estimate of the proportion of subjects without a PFS event at 36 months was 89.6% (95% CI: 82–94.1) for acalabrutinib+obinutuzumab (Arm B) and 31.3% (95% CI: 21.8–41.3) for obinutuzumab+chlorambucil (Arm A).

Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

	No. (%) of Subjects	
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=177)
Subject Status		
Events	14 (7.8)	93 (52.5)
Death	5 (2.8)	11 (6.2)
Progressive Disease	9 (5.0)	82 (46.3)
Censored	165 (92.2)	84 (47.5)
No Event Before Data Cutoff	154 (86.0)	64 (36.2)
No Postbaseline Assessment	1 (0.6)	11 (6.2)
No Event Before Taking Subsequent Anti-Cancer Therapy	3 (1.7)	3 (1.7)
Death or Progressive Disease After 2 or More Consecutive Missed Visits	2 (1.1)	1 (0.6)
No Event Before Study Exit	5 (2.8)	5 (2.8)
Progression Free Survival (Months)		
Q1 (95% CI)	NE (NE, NE)	14.4 (13.9, 16.6)
Median (95% CI)	NE (NE, NE)	22.6 (20.2, 27.6)
Q3 (95% CI)	NE (NE, NE)	NE (33.1, NE)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified Analysis[a]		
Hazard Ratio (95% CI)[b]	0.10 (0.06, 0.17)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard Ratio (95% CI)[b]	0.10 (0.06, 0.18)	–
p-value[c]	<0.0001	–
KM Estimates of PFS[d] by Timepoint		
6 Months (95% CI)	98.9 (95.5, 99.7)	97.0 (92.9, 98.7)
12 Months (95% CI)	95.9 (91.7, 98.0)	84.6 (78.0, 89.3)
18 Months (95% CI)	94.8 (90.2, 97.2)	65.6 (57.7, 72.4)
24 Months (95% CI)	92.7 (87.4, 95.8)	46.7 (38.5, 54.6)
30 Months (95% CI)	89.6 (82.0, 94.1)	34.2 (25.3, 43.2)
36 Months (95% CI)	89.6 (82.0, 94.1)	31.3 (21.8, 41.3)

CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival; Q1=quartile 1; Q3=quartile 3.
a Stratified by 17p deletion status (yes vs. no).
b Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.
c Estimated based on stratified or unstratified log-rank test for p-value, respectively.
d KM estimate of the proportion of subjects who were progression free at the timepoint.
Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375. Note: "+" indicates a value from a censored subject. Source: Table 14.2.1.

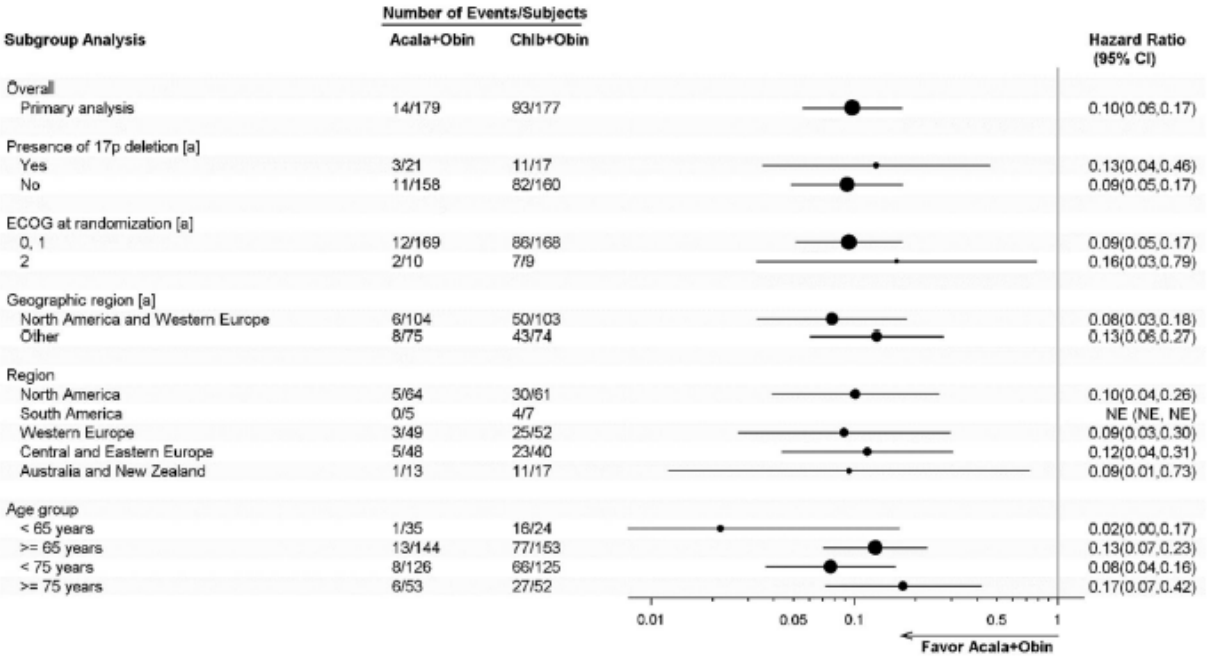
Figure. Kaplan-Meier Plot for Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

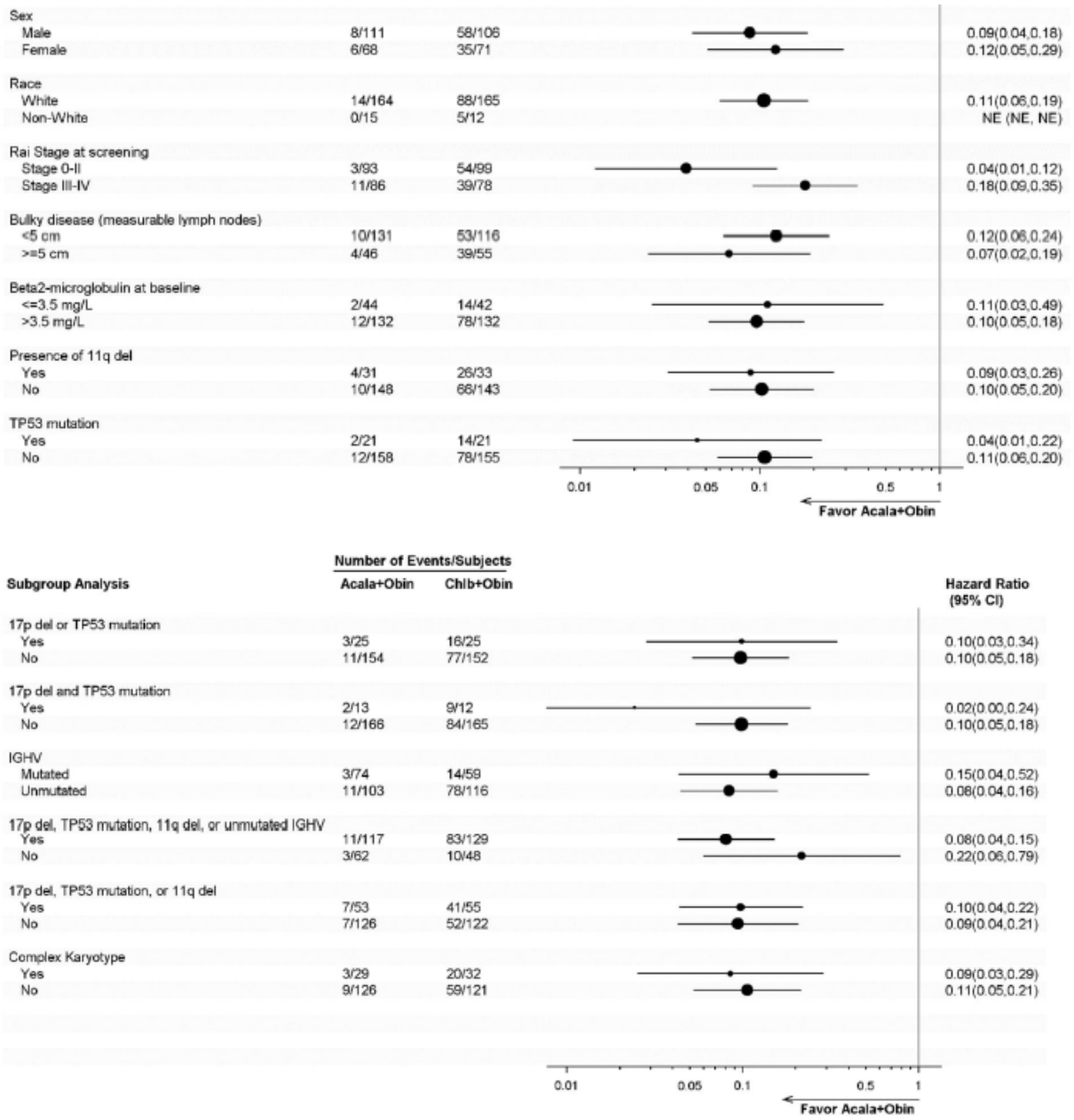


IRC=Independent Review Committee; ITT=intent-to-treat.

Subgroups analysis– Primary Endpoint

Figure. Forest Plot for Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint





ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat. Source: Figure 14.2.1.9.1.

Secondary Variables

PFS by IRC Assessment – Key Secondary Endpoint

The key secondary efficacy endpoint was IRC-assessed PFS comparing obinutuzumab+chlorambucil (Arm A) with acalabrutinib monotherapy (Arms C). With a median follow-up of 28.4 months in the acalabrutinib monotherapy arm (Arm C) and 28 months in the obinutuzumab+chlorambucil arm (Arm B), the median estimated PFS for acalabrutinib monotherapy (Arm C) was not reached; the median estimated PFS for obinutuzumab+chlorambucil (Arm A) was 22.6 months (95% CI: 20.2–27.6).

Based on the stratified analysis, acalabrutinib monotherapy showed a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with an 80% reduction in risk of disease progression or death (HR=0.2 [95% CI: 0.13–0.3]; p<0.0001).

The KM estimate of the proportion of subjects without a PFS event at 12 months was 92.9% (95% CI: 87.8–95.9) for acalabrutinib monotherapy and 84.6% (95% CI: 78–89.3) for obinutuzumab+chlorambucil. The KM estimate of the proportion of subjects without a PFS event at 36

months was 63.9% (95% CI: 29.4–84.9) for acalabrutinib monotherapy and 31.3% (95% CI: 21.8–41.3) for obinutuzumab+chlorambucil.

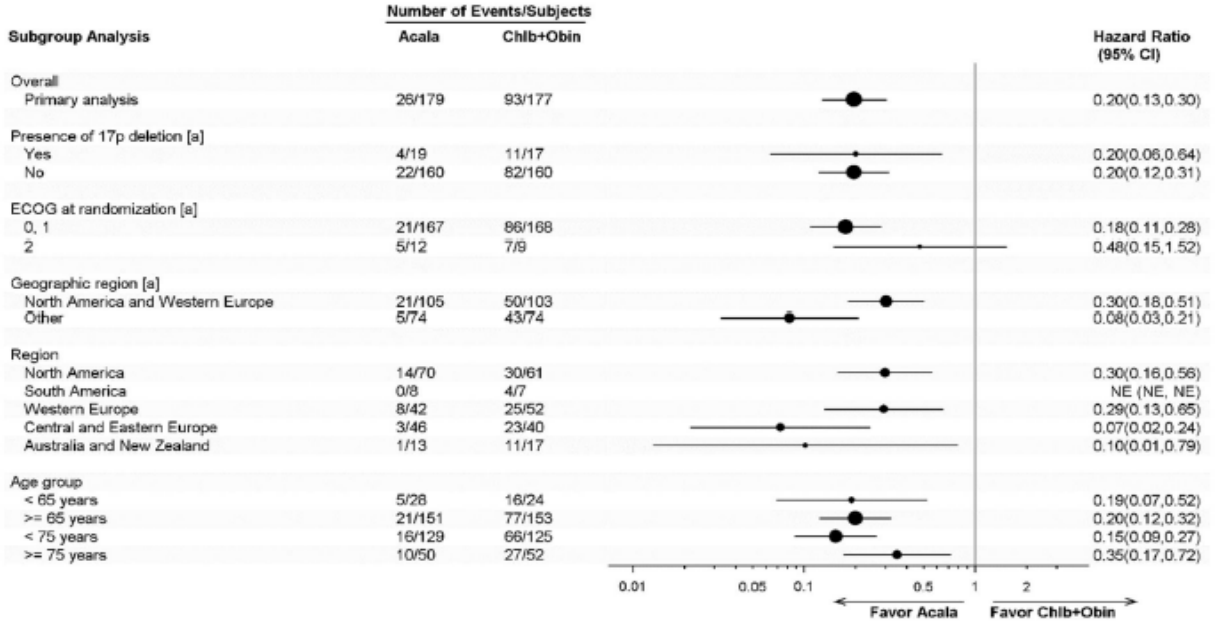
Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint

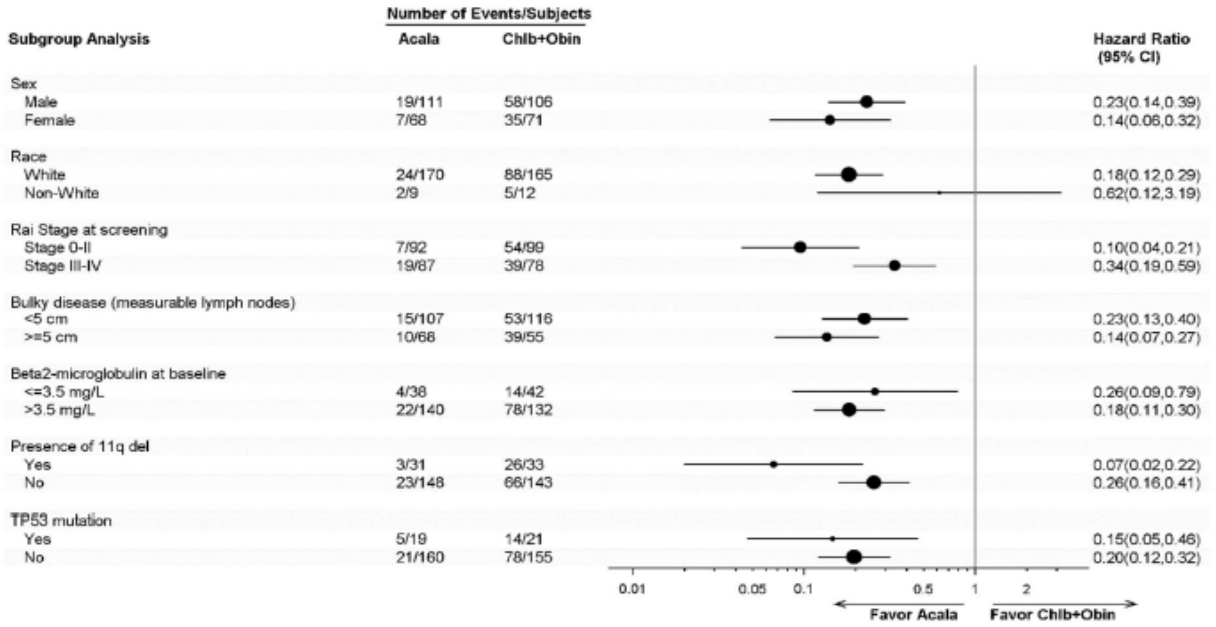
	No. (%) of Subjects	
	Arm C Acalabrutinib Monotherapy (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=177)
Subject Status		
Events	26 (14.5)	93 (52.5)
Death	6 (3.4)	11 (6.2)
Progressive Disease	20 (11.2)	82 (46.3%)
Censored	153 (85.5)	84 (47.5)
No Event Before Data Cutoff	139 (77.7)	64 (36.2)
No Postbaseline Assessment	5 (2.8)	11 (6.2)
No Event Before Taking Subsequent Anti-Cancer Therapy	2 (1.1)	3 (1.7)
Death or Progressive Disease After 2 or More Consecutive Missed Visits	3 (1.7)	1 (0.6)
No Event Before Study Exit	4 (2.2)	5 (2.8)
Progression Free Survival (Months)		
Q1 (95% CI)	34.2 (28.2, NE)	14.4 (13.9, 16.6)
Median (95% CI)	NE (34.2, NE)	22.6 (20.2, 27.6)
Q3 (95% CI)	NE (NE, NE)	NE (33.1, NE)
Min, Max	0.0+, 39.5+	0.0+, 39.6+
Stratified Analysis[a]		
Hazard Ratio (95% CI)[b]	0.20 (0.13, 0.30)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard Ratio (95% CI)[b]	0.20 (0.13, 0.31)	–
p-value[c]	<0.0001	–
KM Estimates of PFS[d] by Timepoint		
6 Months (95% CI)	95.9 (91.6, 98.0)	97.0 (92.9, 98.7)
12 Months (95% CI)	92.9 (87.8, 95.9)	84.6 (78.0, 89.3)
18 Months (95% CI)	90.5 (84.9, 94.1)	65.6 (57.7, 72.4)
24 Months (95% CI)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
30 Months (95% CI)	81.9 (73.3, 88.0)	34.2 (25.3, 43.2)
36 Months (95% CI)	63.9 (29.4, 84.9)	31.3 (21.8, 41.3)

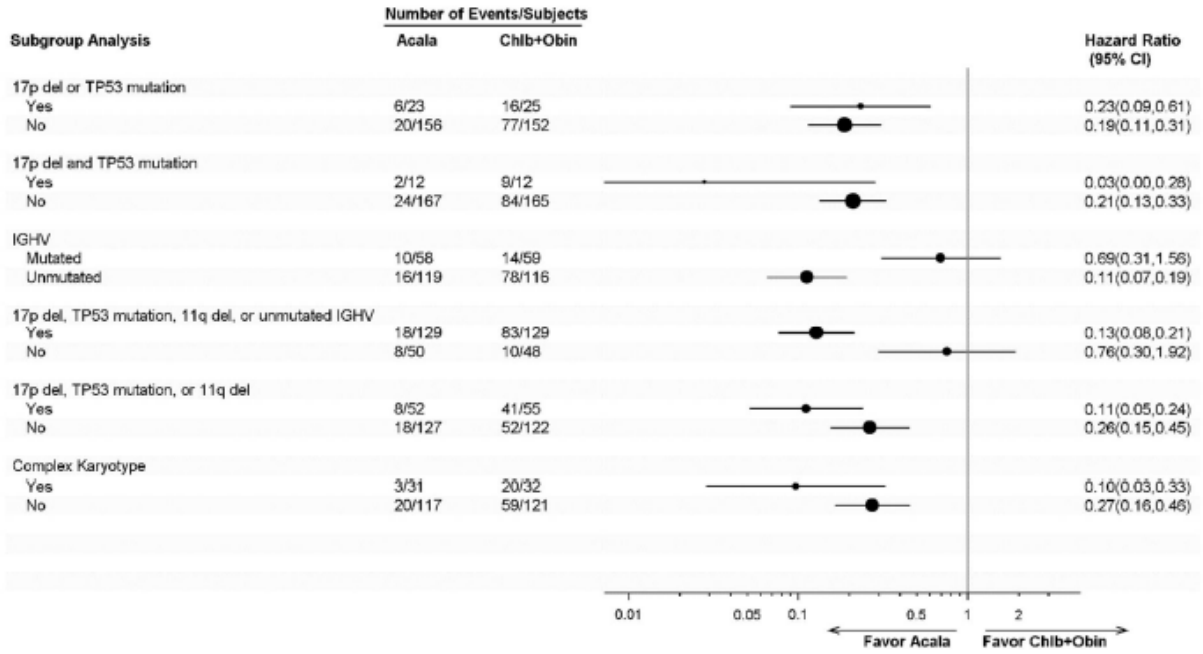
CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival; Q1=quartile 1; Q3=quartile 3.
a Stratified by 17p deletion status (yes vs. no).
b Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.
c Estimated based on stratified or unstratified log-rank test for p-value, respectively.
d KM estimate of the proportion of subjects who were progression free at the timepoint.
Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375.
Note: "+" indicates a value from a censored subject. Source: Table 14.2.1.

Examination of Subgroups – Key Secondary Endpoint

Forest Plot for Subgroup Analysis of Progression-Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint



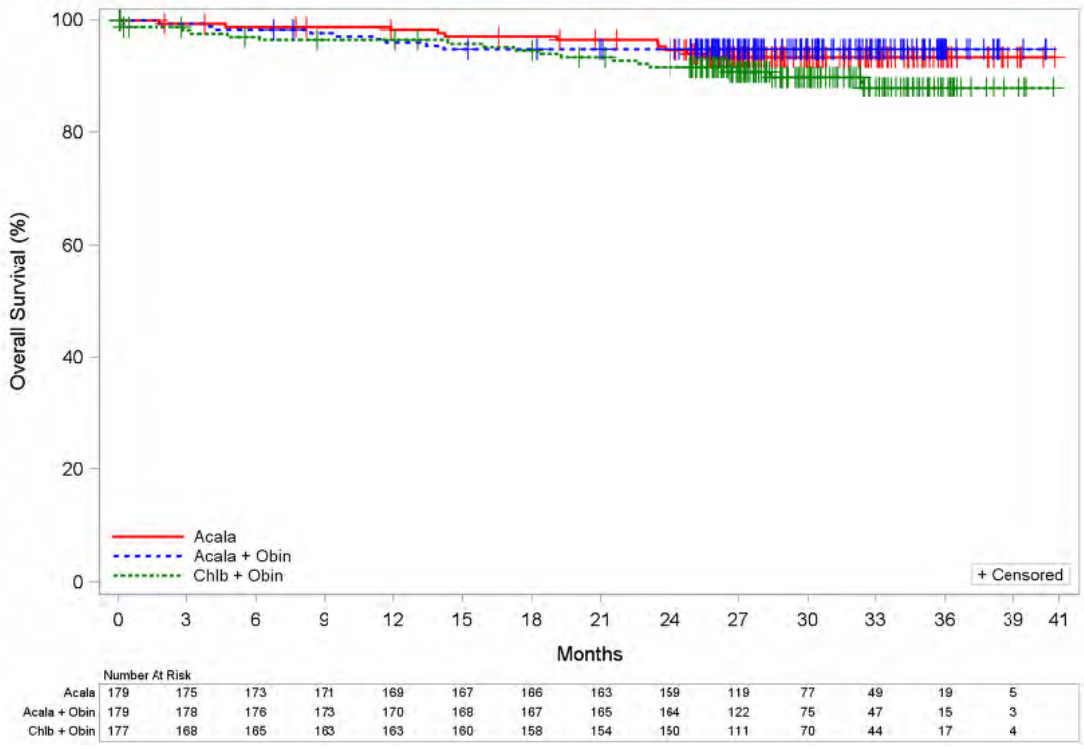




ECOG=Eastern Cooperative Oncology Group; del=deletion; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat. Source: Figure 14.2.1.9.2.

Overall Survival

The median OS was not reached in any of the treatment arms, with an HR of 0.47 (95% CI: 0.21–1.06; p=0.0577) for the acalabrutinib+obinutuzumab arm and an HR of 0.60 (95% CI: 0.28–1.27; p=0.1556) for the acalabrutinib monotherapy arm compared with obinutuzumab+chlorambucil arm



	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
Subject Status			
Events[a]	9 (5.0)	11 (6.1)	17 (9.6)
Death	9 (5.0)	11 (6.1)	17 (9.6)
Censored[b]	170 (95.0)	168 (93.9)	160 (90.4)
Alive	170 (95.0)	168 (93.9)	160 (90.4)
Overall Survival (months)			
Q1 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	1.7, 40.4+	0.1+, 40.8+	0.0+, 40.7+
Stratified Analysis[c]			
Hazard Ratio (95% CI)[d]	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	–
p-value[e]	0.0577	0.1556	–
KM Estimates of OS[f] by Timepoint			
6 Months (95% CI)	98.3 (94.9, 99.5)	98.9 (95.5, 99.7)	97.1 (93.2, 98.8)
12 Months (95% CI)	96.1 (91.9, 98.1)	98.3 (94.8, 99.4)	96.5 (92.4, 98.4)
18 Months (95% CI)	94.9 (90.5, 97.3)	97.1 (93.2, 98.8)	94.7 (90.1, 97.2)
24 Months (95% CI)	94.9 (90.5, 97.3)	94.7 (90.2, 97.2)	91.7 (86.3, 95.0)
30 Months (95% CI)	94.9 (90.5, 97.3)	93.5 (88.6, 96.3)	89.9 (83.9, 93.7)
36 Months (95% CI)	94.9 (90.5, 97.3)	93.5 (88.6, 96.3)	88.1 (80.7, 92.8)

CI=confidence interval; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; OS=overall survival; Q1=quartile 1; Q3=quartile 3.

[a] Included all deaths on study, including deaths after crossover for obinutuzumab+chlorambucil subjects who crossed over.

[b] Based on subject's last known date of alive on study.

[c] Stratified by 17p deletion status (yes vs. no).

[d] Estimated based on stratified Cox Proportional Hazards model for Hazard Ratio (95% CI).

[e] Estimated based on stratified log-rank test for p-value.

[f] KM estimate of proportion subjects who were alive at the timepoint.

Note: Time to event (or time to censor for censored subjects) was calculated as date of death (censoring date for censored subjects) – randomization date + 1; Months are derived as days / 30.4375.

Note: "+" indicates a value from a censored subject.

Richter's Transformation

One subject in the acalabrutinib+obinutuzumab arm, 5 subjects in the acalabrutinib monotherapy arm, and 1 subject in the obinutuzumab+chlorambucil arm had Richter's transformation during the study including the crossover period.

Time to Next Treatment (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	Arm C Acalabrutinib Monotherapy (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=177)
Subject Status			
Events	13 (7.3)	21 (11.7)	70 (39.5)
Death	8 (4.5)	10 (5.6)	15 (8.5)
Crossover Treatment	0	0	45 (25.4)
Subsequent Anticancer Therapy	5 (2.8)	11 (6.1)	10 (5.6)
Censored	166 (92.7)	158 (88.3)	107 (60.5)
No event before data cutoff	166 (92.7)	158 (88.3)	107 (60.5)
Time to Next Treatment (months)			
Q1 (95% CI)	NE (NE, NE)	NE (NE, NE)	19.9 (17.2, 21.5)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (28.9, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	1.3, 40.3+	0.1+, 40.1+	0.0+, 39.6+
Stratified Analysis[a]			
Hazard Ratio (95% CI)[b]	0.14 (0.08, 0.26)	0.24 (0.15, 0.40)	–
p-value[c]	<0.0001	<0.0001	–
KM Estimates of TTNT[d] by Timepoint			
6 Months (95% CI)	97.8 (94.2, 99.2)	96.6 (92.6, 98.5)	95.3 (90.9, 97.6)
12 Months (95% CI)	94.9 (90.5, 97.3)	94.3 (89.7, 96.9)	92.9 (87.9, 95.9)
18 Months (95% CI)	93.2 (88.4, 96.1)	92.6 (87.5, 95.6)	78.5 (71.5, 84.0)
24 Months (95% CI)	93.2 (88.4, 96.1)	90.2 (84.7, 93.8)	67.0 (59.2, 73.6)
30 Months (95% CI)	93.2 (88.4, 96.1)	87.9 (81.8, 92.1)	55.5 (46.5, 63.5)
36 Months (95% CI)	90.0 (80.0, 95.2)	86.3 (79.2, 91.1)	50.2 (40.3, 59.3)

CI=confidence interval; ITT=intent-to-treat; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; Q1=quartile 1; Q3=quartile 3; TTNT=time to next treatment.
a Stratified by 17p deletion status (yes vs. no).
b Estimated based on stratified Cox Proportional Hazards model for Hazard Ratio (95% CI).
c Estimated based on stratified log-rank test for p-value.
d Kaplan-Meier estimates of proportion of subjects who have not received next treatment at timepoint.
Note: Time to event (or time to censor for censored subjects) was calculated as date of death (censoring date for censored subjects) – randomization date + 1; Months were derived as days / 30.4375. Source: Table 14.2.3.

Exploratory Variables

Investigator-Assessed PFS and ORR

Based on the stratified analysis, both acalabrutinib+obinutuzumab and acalabrutinib monotherapy demonstrated a statistically significant improvement in investigator-assessed PFS compared with obinutuzumab+chlorambucil (HR=0.12 [95% CI: 0.07–0.21]; p<0.0001) and (HR=0.16 [95% CI: 0.1–0.27]; p<0.0001), respectively. The unstratified analysis was also statistically significant for both treatment arms (p<0.0001). As of the data cut-off date, the median estimated PFS for acalabrutinib+obinutuzumab and acalabrutinib monotherapy was not reached; the median estimated PFS for obinutuzumab+chlorambucil was 27.8 months (95% CI: 22.6–28.8).

The KM estimate of the proportion of responders without an investigator-assessed PFS event at 12 months was 95.4% (95% CI: 91.1–97.7) for acalabrutinib+obinutuzumab, 94.7% (95% CI: 90.1–97.2) for acalabrutinib monotherapy, and 85.5% (95% CI: 79.1–90) for obinutuzumab+chlorambucil. The KM estimate of the proportion of responders without a PFS event at 36 months was 90.9% (95% CI: 85.3–94.5), 87.6% (95% CI: 81–92.1), and 36.9% (95% CI: 26.6–47.1) for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil, respectively.

Concordance between IRC-Assessed and Investigator-Assessed Progressive Disease

The overall concordance rates between the IRC-assessed and investigator-assessed progressive disease for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil were 96.6%, 93.3%, and 89.3%, respectively.

Concordance between IRC-and Investigator-Assessed Progressive Disease (ITT Population)

	No. (%) of Subjects		
	PD by Investigator		
Progressive Disease by IRC	**Yes**	**No**	**Total**
Arm B: Acalabrutinib+ Obinutuzumab (N=179)			
Yes	6 (3.4)	3 (1.7)	9 (5.0)
No	3 (1.7)	167 (93.3)	170 (95.0)
Total	9 (5.0)	170 (95.0)	179 (100.0)
Overall concordance rate	96.6	–	–
Arm C: Acalabrutinib Monotherapy (N=179)			
Yes	10 (5.6)	10 (5.6)	20 (11.2)
No	2 (1.1)	157 (87.7)	159 (88.8)
Total	12 (6.7)	167 (93.3)	179 (100.0)
Overall concordance rate	93.3	–	–
Arm A: Obinutuzumab+ Chlorambucil (N=177)			
Yes	69 (39.0)	13 (7.3)	82 (46.3)
No	6 (3.4)	89 (50.3)	95 (53.7)
Total	75 (42.4)	102 (57.6)	177 (100.0)
Overall concordance rate	89.3	–	–

Investigator-Assessed ORR

Investigator-assessed ORR (CR+CRi+nPR+PR) and ORR including partial response with lymphocytosis (CR+CRi+nPR+PR+PRL) were consistent with the analysis of the secondary variable (IRC-assessed ORR and ORR including PRL).

Per investigator assessment, CR was achieved in 38 subjects in the acalabrutinib+obinutuzumab arm, 13 subjects in acalabrutinib monotherapy arm, and 23 subjects in the obinutuzumab+chlorambucil arm. PR was achieved in 117 (65.4%) subjects in the acalabrutinib+obinutuzumab arm, 138 (77.1%) subjects in the acalabrutinib monotherapy arm, and 112 (63.3%) subjects in the obinutuzumab+chlorambucil arm.

The investigator-assessed ORR for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 96.1% (95% CI: 92.1–98.1), 89.4% (95% CI:84.0–93.1), and 82.5% (95% CI: 76.2–87.4), respectively. The investigator-assessed ORR difference between acalabrutinib+obinutuzumab and obinutuzumab+chlorambucil was 13.6%(95% CI: 7.3–19.9), which was statistically significant (p<0.0001). The investigator-assessed ORR difference between acalabrutinib monotherapy and obinutuzumab+chlorambucil was 6.9% (95% CI: -0.3–14.1) (p=0.0522).

The investigator-assessed ORR including PRL for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil was 96.6% (95% CI: 92.9–98.5), 92.2% (95% CI:

87.3–95.3), and 82.5% (95% CI: 76.2–87.4). Per the investigator assessment, PRL was achieved in 1 subject in the acalabrutinib+obinutuzumab arm, 5 subjects in the acalabrutinib monotherapy arm, and no subjects in the obinutuzumab+chlorambucil arm. The investigator-assessed ORR including PRL difference between acalabrutinib+obinutuzumab and obinutuzumab+chlorambucil was 14.2% (95% CI: 8.0–20.4), which was statistically significant (p<0.0001). The investigator-assessed ORR difference between acalabrutinib monotherapy and obinutuzumab+chlorambucil was 9.7% (95% CI: 2.8–16.5), which was also statistically significant (p=0.0048).

Concordance Between IRC-Assessed and Investigator-Assessed CR/CRi and Best Overall Response

The overall concordance rates between the IRC-assessed and investigator-assessed CR/Cri for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil were 86%, 92.7%, and 90.4%, respectively. Overall rates between the IRC-assessed and investigator-assessed best overall response for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil were 97.8%, 92.7%, and 83.6%, respectively.

Improvement of Disease-Related Symptoms

The number of subjects with constitutional symptoms (fatigue, fever, night sweats, or weight loss) present at baseline was similar for acalabrutinib+obinutuzumab, acalabrutinib monotherapy, and obinutuzumab+chlorambucil at baseline (96, 104, and 88 subjects, respectively). There was a trend toward an improvement in (absence of) constitutional symptoms during treatment across all 3 treatment arms for any constitutional symptoms, as well as for individual constitutional symptoms.

Sustained Hematologic Improvement

Sustained hematologic improvement was a hematologic improvement that persisted continuously ≥56 days (8 weeks) without blood transfusion or growth factors. Among subjects with cytopenia(s) at baseline, sustained hematologic improvement was similar in the acalabrutinib+obinutuzumab arm and acalabrutinib monotherapy arm, but lower in the obinutuzumab+chlorambucil for ANC (88.9%, 90.0%, and 50.0%, respectively), hemoglobin (77.6%, 64.7%, and 49.3%, respectively), and platelet count (81.8%, 87.9%, and 50.0%, respectively).

Minimal Residual Disease Analysis:

Peripheral blood or bone marrow MRD negativity was observed in 56% (24/43) of subjects with investigator-assessed CR/CRi who were treated with acalabrutinib in combination with obinutuzumab. In the acalabrutinib monotherapy arm, 7%(1/14) of subjects with investigator-assessed CR/CRi were MRD negative in peripheral blood, whereas 61%(14/23) of subjects treated with chlorambucil+obinutuzumab were MRD negative in peripheral blood or bone marrow as assessed by flow cytometry.

Overall, there was a 79% concordance (27 of 34 samples) of MRD status between peripheral blood and bone marrow as assessed by flow cytometry.

Ancillary analyses

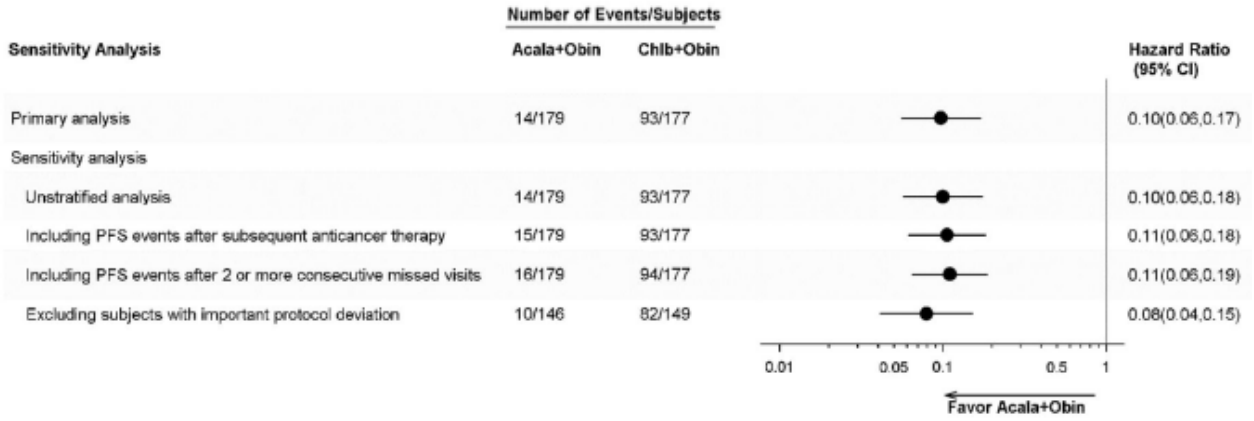
Sensitivity Analyses - Primary Endpoint

The following sensitivity analyses were performed for acalabrutinib+obinutuzumab (Arm B) compared with obinutuzumab+chlorambucil (Arm A): unstratified analysis, inclusion of PFS without censoring for subsequent anticancer therapy, inclusion of PFS events after 2 or more consecutively missed visits, and exclusion of subjects with important protocol deviations.

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar PFS for acalabrutinib+obinutuzumab (Arm B) compared with obinutuzumab+chlorambucil (Arm A) (stratified: HR=0.11 [95% CI: 0.06–0.18]; p<0.0001 and unstratified: HR=0.11 [95% CI: 0.06–0.19]; p<0.0001).

All other sensitivity analyses were also consistent with the primary analysis, with HR ranging from 0.08–0.11, which was statistically significant for all analyses (p<0.0001).

Figure. Forest Plot for Sensitivity Analysis of Progression Free Survival by IRC Assessment (ITT Population)– Primary Endpoint



IRC=Independent Review Committee; ITT=intent-to-treat; PFS=progression-free survival. Source: Figure 14.2.1.8.1.

Sensitivity Analyses of Progression-Free Survival by IRC Assessment (ITT Population) – Primary Endpoint

Sensitivity Analysis	No. (%) of Subjects	
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=177)
Include PFS Without Censoring for Subsequent Anticancer Therapy		
Events	15 (8.4)	93 (52.5)
Death	6 (3.4)	11 (6.2)
Disease Progression	9 (5.0)	82 (46.3)
Censored	164 (91.6)	84 (47.5)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	22.6 (20.2, 27.8)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.11 (0.06, 0.18)	–
p-value[c]	<0.0001	–
Unstratified Analysis		
Hazard ratio (95% CI)[b]	0.11 (0.06, 0.19)	–
p-value[c]	<0.0001	–
Include PFS Events After ≥2 Consecutively Missed Visits		
Events	16 (8.9)	94 (53.1)
Death	7 (3.9)	12 (6.8)
Disease Progression	9 (5.0)	82 (46.3)
Censored	163 (91.1)	83 (46.9)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	22.6 (20.2, 27.6)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.11 (0.06, 0.19)	–
p-value[c]	<0.0001	–
Exclude Subjects with Important Protocol Deviation		
Events	10/146 (6.8)	82/149 (55.0)
Death	4/146 (2.7)	10/149 (6.7)
Disease Progression	6/146 (4.1)	72/149 (48.3)
Censored	136/146 (93.2)	67/149 (45.0)
Progression-free survival (months)		
Median (95% CI)	NE (NE, NE)	22.3 (19.8, 27.5)
Min, Max	0.0+, 39.4+	0.0+, 39.6+
Stratified analysis[a]		
Hazard ratio (95% CI)[b]	0.08 (0.04, 0.15)	–
p-value[c]	<0.0001	–

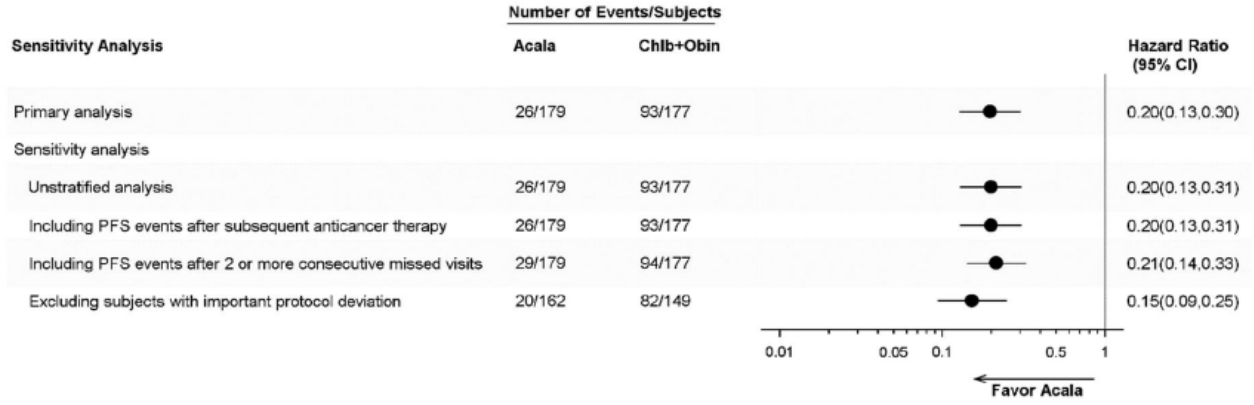
CI=confidence interval; IRC=Independent Review Committee; ITT=intent-to-treat; Max=maximum; Min=minimum; NE=not estimable; PFS=progression-free survival.
a Stratified by 17p deletion status (yes vs. no).
b Estimated based on stratified or unstratified Cox Proportional Hazards model for Hazard Ratio (95% CI), respectively.
c Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Note: Time to event (or time to censor for censored subjects) was calculated as date of disease progression or death (censoring date for censored subjects) – randomization date + 1. Months were derived as days / 30.4375. Note: "+" indicates a value from a censored subject. Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.3.

Stratification Factors for Analysis of PFS by Independent Review Committee (IRC) ITT Population

	Acala + Obin (N=179)	Acala (N=179)	Chlb + Obin (N=177)
Primary Analysis			
Presence of 17p del (Yes)			
Number of Subjects (%)	21 (11.7%)	19 (10.6%)	17 (9.6%)
Number of PFS Events[a] (%)	3 (1.7%)	4 (2.2%)	11 (6.2%)
Presence of 17p del (No)			
Number of Subjects (%)	158 (88.3%)	160 (89.4%)	160 (90.4%)
Number of PFS Events[a] (%)	11 (6.1%)	22 (12.3%)	82 (46.3%)

Sensitivity Analyses – Key Secondary Endpoint

Forest Plot for Sensitivity Analysis of Progression Free Survival by IRC Assessment (ITT Population) – Key Secondary Endpoint



IRC=Independent Review Committee; ITT=intent-to-treat; PFS=progression-free survival. Source: Figure 14.2.1.8.2.

IRC-assessed ORR

Best Overall Response by IRC Assessment (ITT Population)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	Arm C Acalabrutinib Monotherapy (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=177)
Best Overall Response			
CR	23 (12.8)	1 (0.6)	8 (4.5)
CRi	1 (0.6)	0	0
nPR	1 (0.6)	2 (1.1)	3 (1.7)
PR	143 (79.9)	150 (83.8)	128 (72.3)
PRL	0	2 (1.1)	0
Stable Disease	4 (2.2)	8 (4.5)	15 (8.5)
Non-PD	1 (0.6)	0	2 (1.1)
NED	0	0	1 (0.6)
Progressive Disease	0	3 (1.7)	0
UNK[a]	6 (3.4)	12 (6.7)	12 (6.8)
Not Evaluable[b]	0	1 (0.6)	8 (4.5)
ORR (CR+CRi+nPR+PR)	168 (93.9)	153 (85.5)	139 (78.5)
95% CI[c]	(89.3, 96.5)	(79.6, 89.9)	(71.9, 83.9)

	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=179)	**Arm C Acalabrutinib Monotherapy (N=179)**	**Arm A Obinutuzumab+ Chlorambucil (N=177)**
ORR Difference (vs. obinutuzumab+chlorambucil)	15.3	6.9	–
95% CI[c]	(8.3, 22.3)	(-1.0, 14.9)	–
p-value[d]	<0.0001	0.0763	–
ORR+PRL (CR+CRi+nPR+PR+PRL)	168 (93.9)	155 (86.6)	139 (78.5)
95% CI[c]	(89.3, 96.5)	(80.8, 90.8)	(71.9, 83.9)
ORR+PRL Difference (vs. obinutuzumab+chlorambucil)	15.3	8.1	–
95% CI[c]	(8.3, 22.3)	(0.2, 15.9)	–
p-value[d]	<0.0001	0.0376	–

CI=confidence interval; CR=complete response; CRi=CR with incomplete blood count recovery; IRC=Independent Review Committee; ITT=intent-to-treat; NED=no evaluable disease; Non-PD=not meeting criteria for progressive disease and not UNK; nPR=nodular partial response; ORR=overall response rate; PR=partial response; PRL=partial response with lymphocytosis; UNK=unknown.
a "UNK" category included 17 subjects with IRC global assessment as "Not Applicable" whereas their IRC timepoint assessments included "PR" at either a single timepoint or at nonconsecutive timepoints.
b These 9 subjects with no evaluable disease were those 9 subjects who were randomized to study drug but did not receive study drug (Section 10.1).
c 95% confidence interval based on Normal approximation (with use of Wilson's score).
d Based on Cochran-Mantel-Haenzel test with adjustment for 17p deletion status (yes vs no).
Note: CR, Cri, nPR, and PR were based on IRC global assessment; other response categories are derived from IRC assessment at each timepoint. Source: Table 14.2.2.

Overall Response Rate by IRC Assessment by for Selected Subgroups (ITT Population)

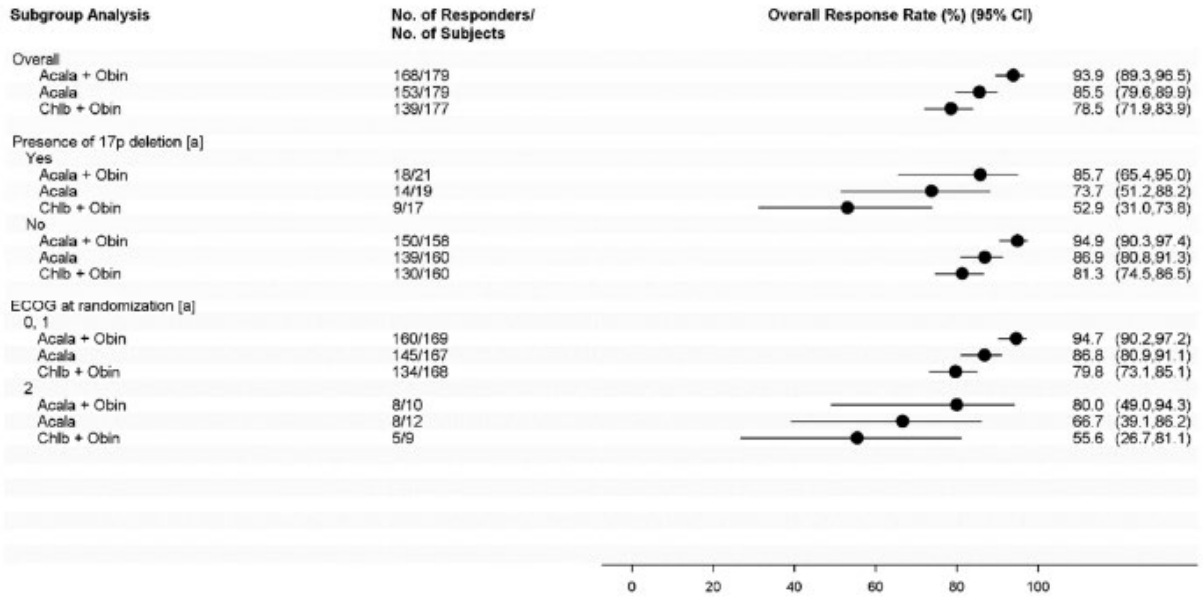
	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=179)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=177)	
	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)	Responders/ Subjects	ORR (%) (95% CI)
Overall	168/179	93.9 (89.3, 96.5)	153/179	85.5 (79.6, 89.9)	139/177	78.5 (71.9, 83.9)
Presence of 17p deletion[a]						
Yes	18/21	85.7 (65.4, 95.0)	14/19	73.7 (51.2, 88.2)	9/17	52.9 (31.0, 73.8)
No	150/158	94.9 (90.3, 97.4)	139/160	86.9 (80.8, 91.3)	130/160	81.3 (74.5, 86.5)
ECOG PS at randomization						
0, 1	160/169	94.7 (90.2, 97.2)	145/167	86.8 (80.9, 91.1)	134/168	79.8 (73.1, 85.1)
2	8/10	80.0 (49.0, 94.3)	8/12	66.7 (39.1, 86.2)	5/9	55.6 (26.7, 81.1)
Age group						
<65	35/35	100 (90.1, 100)	23/28	82.1 (64.4, 92.1)	17/24	70.8 (50.8, 85.1)
≥65	133/144	92.4 (86.8, 95.7)	130/151	86.1 (79.7, 90.7)	122/153	79.7 (72.2, 85.3)
<75	123/126	97.6 (93.2, 99.2)	114/129	88.4 (81.7, 92.8)	95/125	76.0 (67.8, 82.6)
≥75	45/53	84.9 (72.9, 92.1)	39/50	78.0 (64.8, 87.2)	44/52	84.6 (72.5, 92.0)
Sex						
Male	107/111	96.4 (91.1, 98.6)	94/111	84.7 (76.8, 90.2)	85/106	80.2 (71.6, 86.7)
Female	61/68	89.7 (80.2, 94.9)	59/68	86.8 (76.7, 92.9)	54/71	76.1 (65.0, 84.5)
Race						
White	153/164	93.3 (88.4, 96.2)	146/170	85.9 (79.9, 90.3)	130/165	78.8 (71.9, 84.3)
Non-white	15/15	100 (79.6, 100)	7/9	77.8 (45.3, 93.7)	9/12	75.0 (46.8, 91.1)
Rai stage at screening						
Stage 0-II	92/93	98.9 (94.2, 99.8)	85/92	92.4 (85.1, 96.3)	82/99	82.8 (74.2, 89.0)
Stage III-IV	76/86	88.4 (79.9, 93.6)	68/87	78.2 (68.4, 85.5)	57/78	73.1 (62.3, 81.7)
Bulky disease						
<5 cm	123/131	93.9 (88.4, 96.9)	95/107	88.8 (81.4, 93.5)	92/116	79.3 (71.1, 85.7)
≥5 cm	43/46	93.5 (82.5, 97.8)	57/68	83.8 (73.3, 90.7)	43/55	78.2 (65.5, 87.1)
B2-microglobin at baseline						
≤3.5 mg/L	43/44	97.7 (88.2, 99.6)	31/38	81.6 (66.6, 90.8)	27/42	64.3 (49.2, 77.0)
>3.5 mg/L	124/132	93.9 (88.5, 96.9)	121/140	86.4 (79.8, 91.1)	109/132	82.6 (75.2, 88.1)
Complex karyotype						
Yes	27/29	93.1 (78.0, 98.1)	26/31	83.9 (67.4, 92.9)	20/32	62.5 (45.3, 77.1)
No	118/126	93.7 (88.0, 96.7)	98/117	83.3 (76.0, 89.4)	98/121	81.0 (73.1, 87.0)
Presence of 11q deletion						
Yes	31/31	100 (89.0, 100)	27/31	87.1 (71.1, 94.9)	27/33	81.8 (65.6, 91.4)
No	137/148	92.6 (87.2, 95.8)	126/148	85.1 (78.5, 90.0)	111/143	77.6 (70.1, 83.7)
TP53 mutation						
Yes	18/21	85.7 (65.4, 95.0)	16/19	84.2 (62.4, 94.5)	10/21	47.6 (28.3, 67.6)
No	150/158	94.9 (90.3, 97.4)	137/160	85.6 (79.4, 90.2)	128/155	82.6 (75.8, 87.7)
IgHV						
Mutated	68/74	91.9 (83.4, 96.2)	44/58	75.9 (63.5, 85.0)	48/59	81.4 (69.6, 89.3)
Unmutated	98/103	95.1 (89.1, 97.9)	107/119	89.9 (83.2, 94.1)	89/116	76.7 (68.3, 83.5)
17p deletion, TP53 mutation, 11q deletion, or unmutated IgHV						
Yes	110/117	94.0 (88.2, 97.1)	114/129	88.4 (81.7, 92.8)	97/129	75.2 (67.1, 81.8)
No	58/62	93.5 (84.6, 97.5)	39/50	78.0 (64.8, 87.2)	42/48	87.5 (75.3, 94.1)

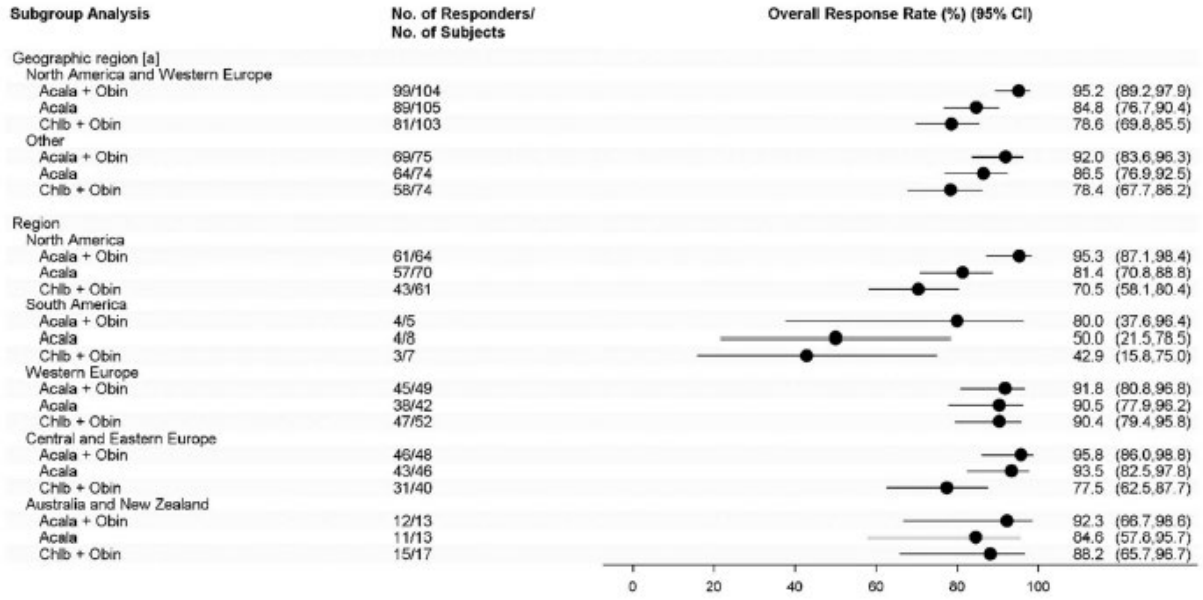
ECOG PS=Eastern Cooperative Oncology Group performance status; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat.

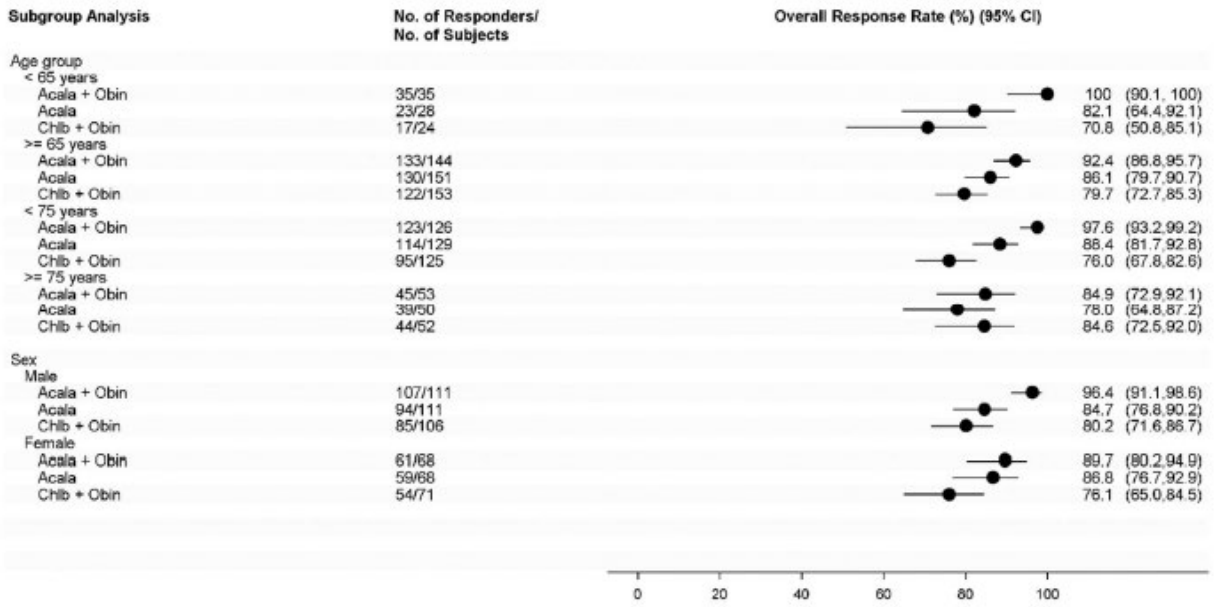
[a] Per Interactive voice/web response system (IXRS) record.

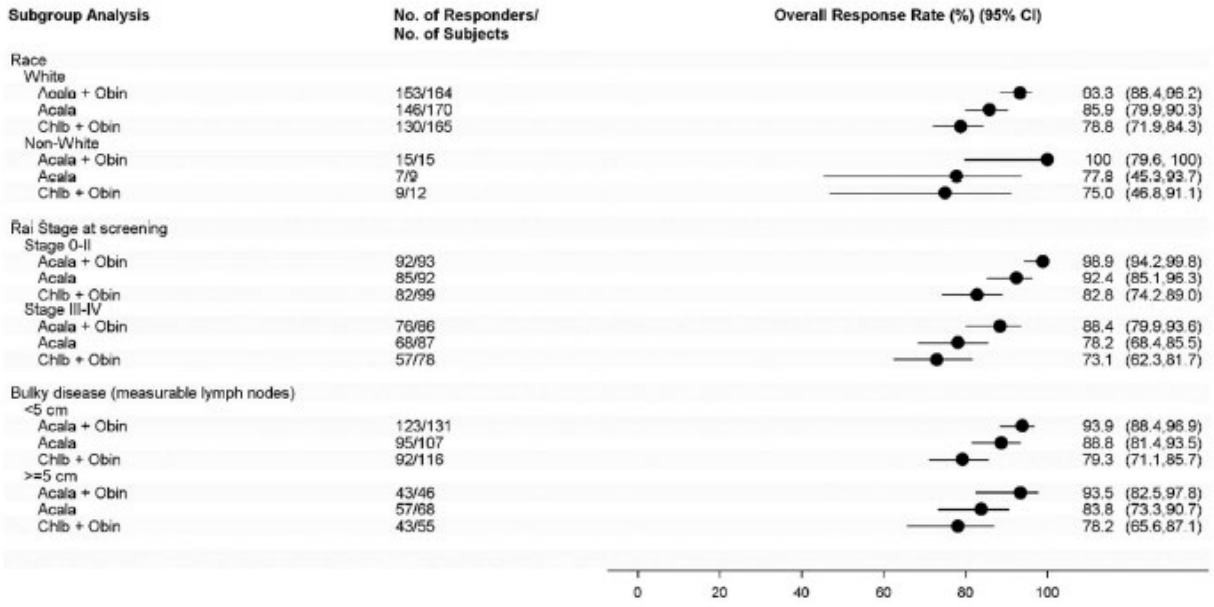
Source: Figure 14.2.2.1.

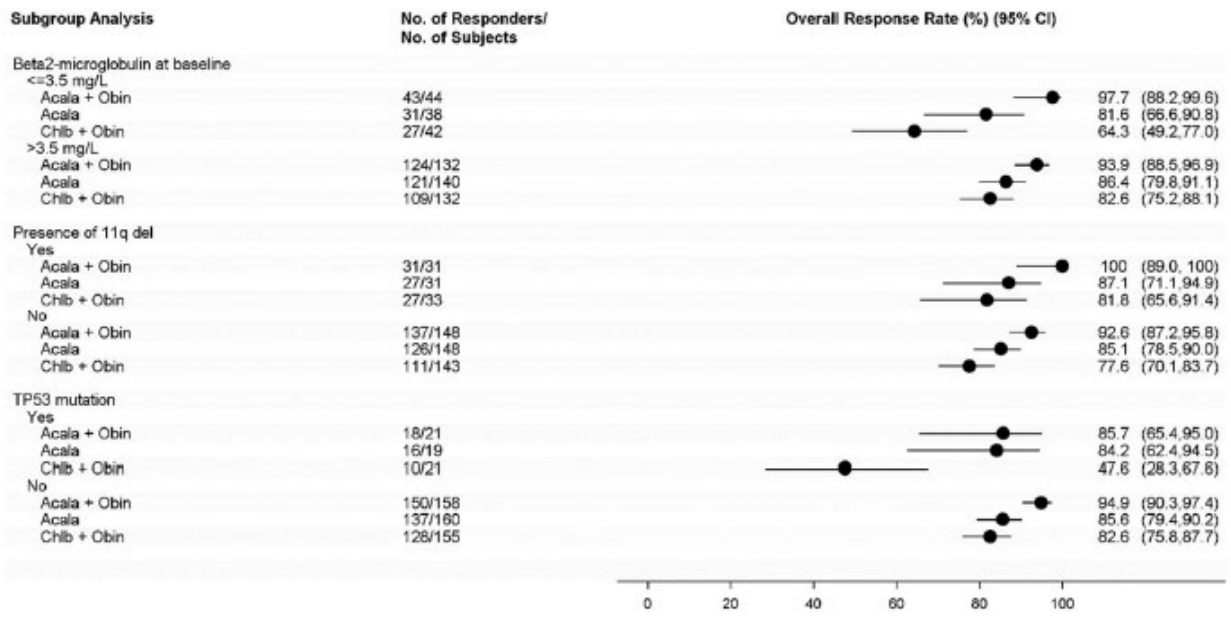
Forest Plot of Subgroup Analysis for Overall Response Rate by IRC Assessment (ITT Population)

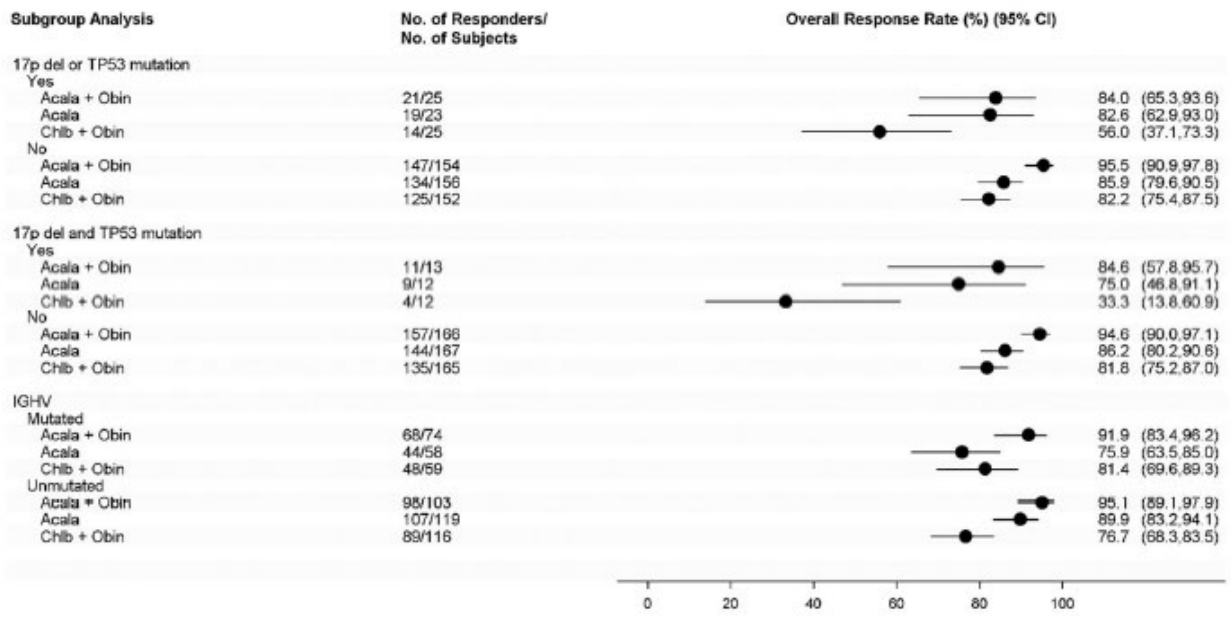


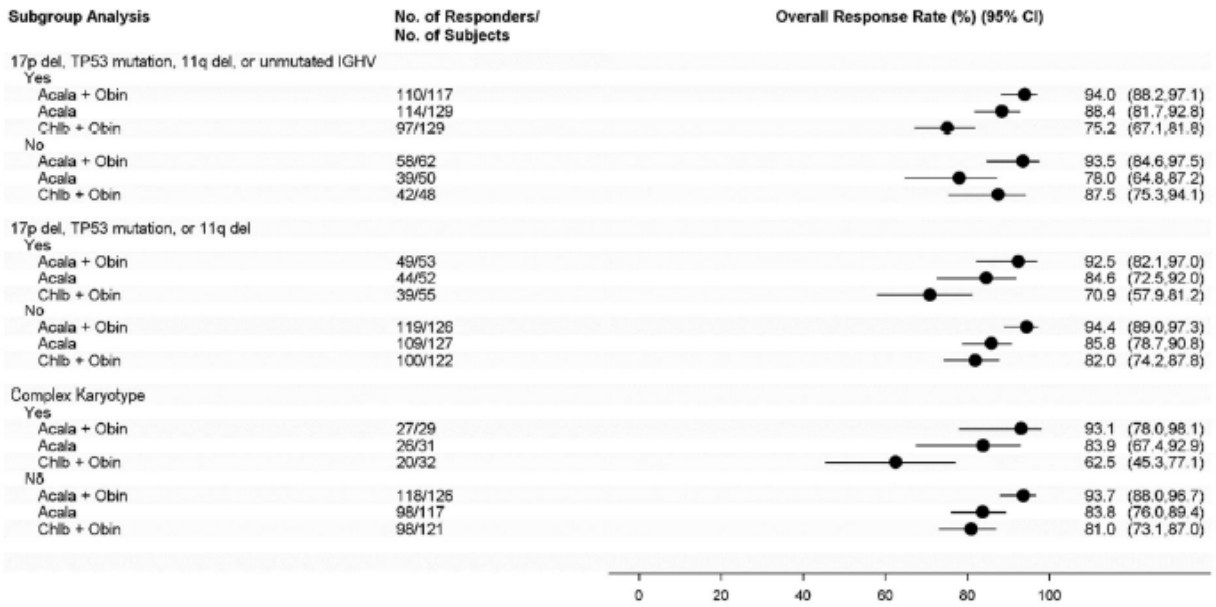



Subgroup Analysis
No. of Responders/ No. of Subjects
Overall Response Rate (%) (95% CI)
Age group
< 65 years
Acala + Obin 35/35 100 (90.1, 100)
Acala 23/28 82.1 (64.4,92.1)
Chlb + Obin 17/24 70.8 (50.8,85.1)
>= 65 years
Acala + Obin 133/144 92.4 (86.8,95.7)
Acala 130/151 86.1 (79.7,90.7)
Chlb + Obin 122/153 79.7 (72.7,85.3)
< 75 years
Acala + Obin 123/126 97.6 (93.2,99.2)
Acala 114/129 88.4 (81.7,92.8)
Chlb + Obin 95/125 76.0 (67.8,82.6)
>= 75 years
Acala + Obin 45/53 84.9 (72.9,92.1)
Acala 39/50 78.0 (64.8,87.2)
Chlb + Obin 44/52 84.6 (72.5,92.0)
Sex
Male
Acala + Obin 107/111 96.4 (91.1,98.6)
Acala 94/111 84.7 (76.8,90.2)
Chlb + Obin 85/106 80.2 (71.6,86.7)
Female
Acala + Obin 61/68 89.7 (80.2,94.9)
Acala 59/68 86.8 (76.7,92.9)
Chlb + Obin 54/71 76.1 (65.0,84.5)
0
20
40
60
80
100


Subgroup Analysis
No. of Responders/ No. of Subjects
Overall Response Rate (%) (95% CI)
Race
White
Acala + Obin 153/164 93.3 (88.4,96.2)
Acala 146/170 85.9 (79.9,90.3)
Chlb + Obin 130/165 78.8 (71.9,84.3)
Non-White
Acala + Obin 15/15 100 (79.6, 100)
Acala 7/9 77.8 (45.3,93.7)
Chlb + Obin 9/12 75.0 (46.8,91.1)
Rai Stage at screening
Stage 0-II
Acala + Obin 92/93 98.9 (94.2,99.8)
Acala 85/92 92.4 (85.1,96.3)
Chlb + Obin 82/99 82.8 (74.2,89.0)
Stage III-IV
Acala + Obin 76/86 88.4 (79.9,93.6)
Acala 68/87 78.2 (68.4,85.5)
Chlb + Obin 57/78 73.1 (62.3,81.7)
Bulky disease (measurable lymph nodes)
<5 cm
Acala + Obin 123/131 93.9 (88.4,96.9)
Acala 95/107 88.8 (81.4,93.5)
Chlb + Obin 92/116 79.3 (71.1,85.7)
>=5 cm
Acala + Obin 43/46 93.5 (82.5,97.8)
Acala 57/68 83.8 (73.3,90.7)
Chlb + Obin 43/55 78.2 (65.6,87.1)
0
20
40
60
80
100


Subgroup Analysis
No. of Responders/ No. of Subjects
Overall Response Rate (%) (95% CI)
Beta2-microglobulin at baseline
<=3.5 mg/L
Acala + Obin 43/44 97.7 (88.2,99.6)
Acala 31/38 81.6 (66.6,90.8)
Chlb + Obin 27/42 64.3 (49.2,77.0)
>3.5 mg/L
Acala + Obin 124/132 93.9 (88.5,96.9)
Acala 121/140 86.4 (79.8,91.1)
Chlb + Obin 109/132 82.6 (75.2,88.1)
Presence of 11q del
Yes
Acala + Obin 31/31 100 (89.0, 100)
Acala 27/31 87.1 (71.1,94.9)
Chlb + Obin 27/33 81.8 (65.6,91.4)
No
Acala + Obin 137/148 92.6 (87.2,95.8)
Acala 126/148 85.1 (78.5,90.0)
Chlb + Obin 111/143 77.6 (70.1,83.7)
TP53 mutation
Yes
Acala + Obin 18/21 85.7 (65.4,95.0)
Acala 16/19 84.2 (62.4,94.5)
Chlb + Obin 10/21 47.6 (28.3,67.6)
No
Acala + Obin 150/158 94.9 (90.3,97.4)
Acala 137/160 85.6 (79.4,90.2)
Chlb + Obin 128/155 82.6 (75.8,87.7)
0
20
40
60
80
100


Subgroup Analysis
No. of Responders/ No. of Subjects
Overall Response Rate (%) (95% CI)
17p del or TP53 mutation
Yes
Acala + Obin 21/25 84.0 (65.3,93.6)
Acala 19/23 82.6 (62.9,93.0)
Chlb + Obin 14/25 56.0 (37.1,73.3)
No
Acala + Obin 147/154 95.5 (90.9,97.8)
Acala 134/156 85.9 (79.6,90.5)
Chlb + Obin 125/152 82.2 (75.4,87.5)
17p del and TP53 mutation
Yes
Acala + Obin 11/13 84.6 (57.8,95.7)
Acala 9/12 75.0 (46.8,91.1)
Chlb + Obin 4/12 33.3 (13.8,60.9)
No
Acala + Obin 157/166 94.6 (90.0,97.1)
Acala 144/167 86.2 (80.2,90.6)
Chlb + Obin 135/165 81.8 (75.2,87.0)
IGHV
Mutated
Acala + Obin 68/74 91.9 (83.4,96.2)
Acala 44/58 75.9 (63.5,85.0)
Chlb + Obin 48/59 81.4 (69.6,89.3)
Unmutated
Acala + Obin 98/103 95.1 (89.1,97.9)
Acala 107/119 89.9 (83.2,94.1)
Chlb + Obin 89/116 76.7 (68.3,83.5)
0
20
40
60
80
100



[a] Per Interactive voice/web response system (IXRS) record. ECOG=Eastern Cooperative Oncology Group; del=deletion; IgHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; ITT=intent-to-treat. Source: Figure 14.2.2.1.

Summary of main efficacy results

The following table summarise the efficacy results from the main study ACE-CL-007 in previously untreated CLL supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for ELEVATE-TN Trial (ACE-CL-007)

Title: A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia		
Study identifier	**EUDRACT 2014-005582-73 (ACE-CL-007)**	
Design	randomized, global, multicenter, open-label, 3-arm Phase 3 study will evaluate the efficacy and safety of Arm A (Chlorambucil + Obinutuzumab), Arm B (Acalabrutinib BID + Obinutuzumab) and Arm C (Acalabrutinib BID monotherapy) in subjects with previously untreated CLL. Subjects randomized based on the following stratification factors: • Presence versus absence of 17p deletion mutation (17p del). • Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1 vs 2. • Geographic region (North America and Western Europe versus Other).	
	Duration of Run-in phase:	Not applicable
	Duration of main phase:	The end of trial is defined as the point when the last subject on the study has documented disease progression or death, or has been lost of follow up, whichever occurs first. The anticipated study duration is 4.5 years including enrollment time
	Duration of Extension phase:	Not applicable

Hypothesis	Superiority The study is expected to randomize approximately 510 subjects. Subjects will be randomized in a 1:1:1 ratio to Arm A, Arm B, or Arm C. Approximately 170 subjects will be randomized to each arm. The sample size calculation is driven by hypothesis test between Arm B and Arm A. The study is sized to achieve approximately 90% power to detect a hazard ratio (Arm B/Arm A) of 0.60 for PFS assuming a median PFS of 26.7 months for subjects in Arm A (Goede 2014) versus 44.5 months for subjects in Arm B.		
Treatments groups	Treatment Arm A: Obinutuzumab in Combination with Chlorambucil		Obinutuzumab IV infusions will be administered over a total of 6 treatment cycles. On C1D1, subjects will receive obinutuzumab 100 mg. On C1D2, subjects will receive 900 mg. On C1D8 and 15, subjects will receive 1000 mg. On D1 of C2 to C6, subjects will receive 1000 mg. Chlorambucil will be orally administered at a dose of 0.5 mg/kg on D1 and D15 of C1 through C6 (n=177)
	Treatment Arm B: Acalabrutinib BID in Combination with Obinutuzumab		Acalabrutinib will be orally administered at 100 mg BID starting on C1D1. Daily administration of acalabrutinib will continue until disease progression or unacceptable toxicity. Obinutuzumab will be administered as described above for Arm A, starting on C2D1 for a maximum of 6 cycles (n=179)
	Treatment Arm C: Acalabrutinib BID Monotherapy		Acalabrutinib will be orally administered at 100 mg BID starting on C1D1, and will continue until disease progression or unacceptable toxicity (n=179)
Endpoints and definitions	Primary endpoint	Treatment of adult patients with previously untreated CLL/SLL	To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib in combination with obinutuzumab (Arm B), based on IRC assessment of PFS per IWCLL 2008 criteria, in subjects with previously untreated CLL.
	Secondary endpoints	Treatment of adult patients with previously untreated CLL/SLL	To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) based on IRC assessment of PFS per IWCLL 2008 criteria. To compare obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib plus obinutuzumab (Arm B), and obinutuzumab plus chlorambucil (Arm A) versus acalabrutinib monotherapy (Arm C) in terms of: • IRC-assessed ORR per IWCLL 2008 criteria; • TTNT (defined as the time from randomization to institution of non-protocol specified treatment for CLL); and • OS.

	Safety and exploratory endpoints	Treatment of adult patients with previously untreated CLL/SLL	Safety: Incidence of adverse events (AEs) and serious adverse events (SAEs) and changes in laboratory measurements and vital signs from baseline. Exploratory: • Investigator-assessed PFS and ORR per IWCLL 2008 criteria • Clonal evolution (which will be assessed at baseline, after 6 months [24 weeks] of treatment, and at disease progression). The proportion of subjects with new cytogenetic abnormalities (eg, 11q del, 17p del, 13q del or trisomy 12), detected by FISH, will be determined. • Improvement and/or resolution of disease-related symptoms • Hematologic improvement in the subset of subjects with cytopenia(s) at baseline • PRO by the FACIT-Fatigue • PRO by EORTC QLQ-C30 and EQ-5D • MRU • PK characteristics of acalabrutinib alone and in combination with obinutuzumab • Potential predictive biomarkers and mechanisms of resistance for the disease • Molecular remission, as measured by MRD negativity, will be evaluated • Performance of DNA-based compared with flow cytometric-based methods for MRD • Extent and durability of MRD status on clinical outcomes following investigator-confirmed CR
Database lock	08 Feb 2019 data cut-off; 09 Apr 2019 data extract		

Results and Analysis	
Analysis description	**Primary Analysis**
One interim analysis to be performed at 24 months after last subject randomized	To evaluate the efficacy of obinutuzumab in combination with chlorambucil (Arm A) compared with acalabrutinib in combination with obinutuzumab (Arm B) based on IRC assessment of progression-free survival (PFS). PFS, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first. The primary efficacy analysis will be performed using a stratified log-rank test adjusting for randomization stratification factors. The estimate of the hazard ratio (Arm B/Arm A) and its corresponding 95% CI will be computed using a Cox Proportional Hazards model stratified by randomization stratification factors. KM curve was used to estimate the distribution of PFS. Intent-to-treat population is the primary analysis population.
Analysis description	**Secondary Analysis**

One interim analysis to be performed at 24 months after last subject randomized	1. PFS as assessed by IRC comparing between Arms A and C 2. ORR as assessed by IRC between Arms B and A 3. ORR as assessed by IRC between Arms C and A 4. OS between Arms B and A 5. OS between Arms C and A To control the overall Type I error α at 0.05 level, the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundary were used to split α into α1 and α2 for interim and final analyses, respectively. The nominal α1 and α2 levels would be determined based on the actual information fraction at the time of the interim analysis. Within each analysis, the fixed sequence procedure would be utilized to adjust for multiple comparisons. The secondary endpoint would be tested in the order as specified above. Intent-to-treat population is the primary analysis population.

	Acalabrutinib plus Obinutuzumab N=179	**Acalabrutinib Monotherapy N=179**	**Obinutuzumab plus Chlorambucil N=177**
Progression-Free Survival [a]			
Number of events (%)	14 (8)	26 (15)	93 (53)
PD, n (%)	9 (5)	20 (11)	82 (46)
Death events, n (%)	5 (3)	6 (3)	11 (6)
Median (95% CI), months [b]	NE	NE (34, NE)	22.6 (20, 28)
HR[c] (95% CI)	0.1 (0.06, 0.17)	0.2 (0.13, 0.3)	-
p-value [d]	< 0.0001	< 0.0001	-
Overall Response Rate[a] (CR + CRi + nPR + PR)			
ORR, n (%)	168 (94)	153 (86)	139 (79)
(95% CI)	(89, 97)	(80, 90)	(72, 84)
p-value [e]	< 0.0001	0.0763	-
CR, n (%)	23 (13)	1 (1)	8 (5)
CRi, n (%)	1 (1)	0	0
nPR, n (%)	1 (1)	2 (1)	3 (2)
PR, n (%)	143 (80)	150 (84)	128 (72)

ITT=intent-to-treat; CI=confidence interval; HR=hazard ratio; NE=not estimable; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response.
[a] Per 2008 International Workshop on CLL (IWCLL) criteria.
[b] Kaplan-Meier estimate.
[c] Based on a stratified Cox-Proportional-Hazards model. Both hazard ratios are compared with the obinutuzumab and chlorambucil arm.
[d] Based on a stratified log-rank test, with an alpha level of 0.012 derived from alpha spending function by the O'Brien-Fleming method.
[e] Based on a stratified Cochran–Mantel–Haenszel test, for the comparison with the obinutuzumab and chlorambucil arm.

Study ACE-CL-309

A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia.

Methods

Study Participants

Key inclusion criteria

Subjects were required to have received at least one prior systemic therapy for CLL to be eligible to enrol. Prior exposure to a B-cell lymphoma (BCL)-2 inhibitor (e.g., venetoclax/ABT-199) or a B-cell receptor (BCR) inhibitor (e.g., BTK inhibitors or PI3K inhibitors) was not allowed. Further:

- adult men and women with documented CD20-positive CLL that met the following published diagnostic IWCLL 2008 criteria (Hallek et al. 2008)
- met at least 1 of the IWCLL 2008 criteria for requiring treatment
- ANC ≥0.75x109/L or ≥0.50x109/L in subjects with documented bone marrow involvement
- platelet count ≥50x109/L, or ≥30x109/L in subjects with documented bone marrow involvement. Subjects with transfusion-dependent thrombocytopenia were excluded. In Study ACE-CL-309, platelets were to be ≥75x109/L for subjects receiving BR (in Arm B)
- estimated creatinine clearance of ≥30 mL/min (using Cockcroft-Gault equation)
- baseline ECOG performance status of ≤2.

Exclusion criteria

Prior exposure to a B-cell lymphoma (BCL)-2 inhibitor (e.g., venetoclax/ABT-199) or a B-cell receptor (BCR) inhibitor (e.g., BTK inhibitors or PI3K inhibitors). Prior bendamustine is allowed if investigator's choice for treatment in Arm B is idelalisib with rituximab. Bendamustine retreatment is allowed if the prior response to bendamustine lasted >24 months. Additional criteria were:

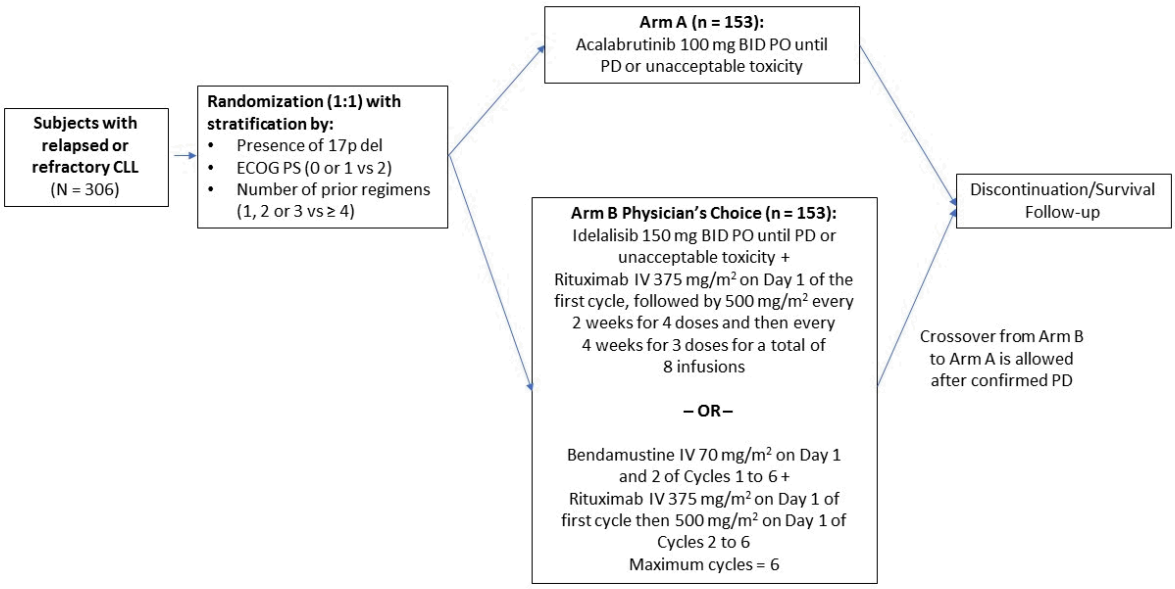
- Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at Screening.
- History of stroke or intracranial hemorrhage within 6 months before randomization.
- Known history of a bleeding diathesis (e.g., hemophilia, von Willebrand disease).
- Required or received anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days of first dose of study drug.
- Required treatment with proton-pump inhibitors.
- Required treatment with a strong CYP3A inhibitor/inducer: Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before Screening.

Treatments

Arm A: Monotherapy with acalabrutinib until toxicity or PD were compared

Arm B: control therapy at physician's choice either BR for fixed duration or IR until toxicity or PD.

Figure 21: Treatment schemes in ACE 309



Objectives

Primary Objective was to evaluate the efficacy of acalabrutinib monotherapy (Arm A) compared with IR or BR (Arm B) based on IRC assessment of PFS per IWCLL 2008 criteria (Hallek et al. 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson et al. 2012), hereafter referred to as IWCLL 2008 criteria, in subjects with R/R CLL.

Secondary Objectives

To evaluate Arm A compared with Arm B in terms of: Investigator-assessed PFS per **IWCLL 2008 criteria** Investigator- and IRC-assessed **ORR** per IWCLL 2008 criteria (defined as the proportion of subjects who achieve a best response of CR, CRi, nPR, or PR) **OS;** PROs by **FACIT-Fatigue** ; Investigator- and IRC-assessed **DOR** (defined as the time from the first documentation of objective response to the earlier time of disease progression or death from any cause) **; TTNT** (defined as the time from randomization to institution of non-protocol-specified treatment for CLL)

Safety Objective

Incidence and severity of **AEs and SAEs**

Exploratory Objectives

To evaluate Arm A compared with Arm B in terms of: Improvement and/or resolution of disease-related symptoms; PROs by EORTC QLQ-C30 and EQ-5D-5L ; MRU ; Potential predictive biomarkers and mechanisms of resistance for the disease

Outcomes/endpoints

Primary endpoint: PFS, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first. KM curve was used to estimate the distribution of PFS

Secondary endpoints:

PFS, defined as the time from date of randomization to the date of first investigator assessed disease progression or death due to any cause, whichever comes first. KM curve was used to estimate the distribution of PFS.

Best overall response was defined as the best response as assessed by the investigator or IRC on or before the initiation of subsequent anticancer therapy.

OS was defined as the time from date of randomization to death due to any cause.

Change from baseline in GFS at Week 24 and Week 48, proportion of subjects with improvement/stable/deterioration in GFS, and time to first clinically meaningful improvement in GFS.

DOR determined by IRC and by investigators was analyzed in the same fashion as PFS described above

TTNT was analyzed in the same fashion as PFS described above.

Sample size

The study was expected to enrol approximately 306 subjects with a 1:1 randomization ratio between Arm-A and Arm-B. With an event-driven design, the final analysis of PFS was planned when a total of 119 IRC-assessed PFS events had been observed.

Randomisation

Subjects in this study were randomized in a 1:1 ratio into the 2 treatment arms using an interactive voice/web response system (IXRS). Randomization was stratified by the following factors: Presence of 17p deletion; ECOG performance status (0 or 1 versus 2); Number of prior therapies (1, 2, or 3 versus ≥4).

Blinding (masking)

This was an open label trial.

Statistical methods

In analysis of PFS as assessed by IRC subjects were censored at treatment switch. Sensitivity analysis without censoring for subsequent anticancer therapy was however performed. In the primary analyses of IRC PFS, there were no subjects who were censored due to consecutively missing 2 or more visits.

In arm A 3 patients withdrew consent, and in arm B 10 patients withdrew consent. The number of patients randomised but not treated was 1 in arm A and 2 in arm B.

The data submitted from study ACE-CL-309 was from a pre-planned interim analysis. The applicant split α into α1 and α2 for interim and final analyses. Secondary endpoints were tested in a hierarchical order separately for interim and final analyses. It is worth noting that since the test of ORR was not statistically significant (p= 0.2248), it will not be possible to formally test OS in the final analysis.

A cut-off was determined for the interim analysis when approximately 79 IRC-assessed PFS events had occurred. A snapshot of the database occurred after all data through the visit cutoff date had been entered and cleaned. The interim analysis was conducted based on a snapshot of the database, which

included all available PFS events up to the visit cut-off date. The interim analysis was conducted using Lan and DeMets alpha-spending function with O'Brien-Fleming boundaries (O'Brien and Fleming 1979; Lan and DeMets 1983).

Table 21: summary of the planned PFS analyses

Analysis	No. of IRC-assessed PFS events	Efficacy stopping boundary[a]	Estimated timing[b]
Interim	79	p<0.012 or observed HR <0.57	19 months
Final	119	p<0.046 or observed HR <0.69	27 months

a p-value was based on 2-sided log-rank test.
b Time from the enrollment of first subject to data cutoff.
HR=hazard ratio; IRC=Independent Review Committee; PFS=progression-free survival.

If the primary efficacy endpoint achieved statistical significance, then selected secondary endpoints were to be tested in a manner that would preserve the overall Type I error rate at the 2-sided significance level of 0.05. The DMC members used their expertise, experience, and judgment to evaluate the safety data from the study on a regular basis and to recommend to the sponsor whether the study should continue or be stopped early for safety. No formal statistical rules recommending early stopping for safety were planned.

If the study did not cross the boundary at the interim analysis, the study was to proceed to final analysis. A visit cutoff date was to be determined when approximately 119 IRC-assessed PFS events had occurred.

To control the overall Type I error at 0.05 level, the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundary was used to split α into α1 and α2 for the interim and final analyses, respectively. The nominal α1 and α2 levels were determined based on the actual information fraction at the time of the interim analysis. If the primary endpoint achieved statistical significance, tests of key secondary endpoints of IRC-assessed ORR and OS were to be performed in a sequential hierarchical manner based on a closed testing procedure specified as: 1. IRC-assessed ORR; 2. OS

If the primary endpoint of IRC-assessed PFS achieved statistical significance at the interim analysis, the IRC-assessed ORR was to be tested at an α level of 0.05, given that almost all responses would have been observed at that time (thus the interim and final analyses of IRCassessed ORR would be the same). If the IRC-assessed ORR achieved statistical significance, the OS was to be tested at the same α level spent for the primary endpoint of IRC-assessed PFS at interim and final analyses, respectively.

Results

Participant flow

	No. (%) of Subjects			
	Arm A	Arm B		
	Acalabrutinib (N=155)	Total (N=155)	IR (N=119)	BR (N=36)
Subjects randomized (Intent-to-Treat Population)	155 (100.0%)	155 (100.0%)	119 (100.0%)	36 (100.0%)
Treated with investigational product (Safety Population)	154 (99.4%)	153 (98.7%)	118 (99.2%)	35 (97.2%)
Randomized but not treated[a]	1 (0.6%)	2 (1.3%)	1 (0.8%)	1 (2.8%)
Acalabrutinib				
Subjects on study drug	124 (80.0%)	0	0	0
Subjects who discontinued study drug	30 (19.4%)	0	0	0
Primary reason for study drug discontinuation				
Adverse event	17 (11.0%)	0	0	0
Death	1 (0.6%)	0	0	0
Investigator discretion	1 (0.6%)	0	0	0
Progressive disease	10 (6.5%)	0	0	0
Other[b]	1 (0.6%)	0	0	0
Idelalisib				
Subjects on study drug	0	42 (27.1%)	42 (35.3%)	0
Subjects who discontinued study drug	0	76 (49.0%)	76 (63.9%)	0
Primary reason for study drug discontinuation				
Adverse event	0	58 (37.4%)	58 (48.7%)	0
Investigator discretion	0	2 (1.3%)	2 (1.7%)	0
Progressive disease	0	11 (7.1%)	11 (9.2%)	0
Withdrawal of consent	0	1 (0.6%)	1 (0.8%)	0
Other[c]	0	4 (2.6%)	4 (3.4%)	0

Bendamustine				
Subjects on study drug	0	0	0	0
Subjects who discontinued study drug	0	35 (22.6%)	0	35 (97.2%)
Primary reason for study drug discontinuation				
Adverse event	0	4 (2.6%)	0	4 (11.1%)
Completed treatment	0	30 (19.4%)	0	30 (83.3%)
Progressive disease	0	1 (0.6%)	0	1 (2.8%)
Rituximab				
Subjects on study drug	0	0	0	0
Subjects who discontinued study drug	0	153 (98.7%)	118 (99.2%)	35 (97.2%)
Primary reason for study drug discontinuation				
Adverse event	0	20 (12.9%)	14 (11.8%)	6 (16.7%)
Completed treatment	0	123 (79.4%)	95 (79.8%)	28 (77.8%)
Investigator discretion	0	3 (1.9%)	3 (2.5%)	0
Progressive disease	0	2 (1.3%)	1 (0.8%)	1 (2.8%)
Withdrawal of consent	0	1 (0.6%)	1 (0.8%)	0
Other[c]	0	4 (2.6%)	4 (3.4%)	0
Subjects who discontinued all study treatment[d]	30 (19.4%)	111 (71.6%)	76 (63.9%)	35 (97.2%)
Subjects who exited study[e]	18 (11.6%)	28 (18.1%)	21 (17.6%)	7 (19.4%)
Primary reason for study exit				
Death	15 (9.7%)	18 (11.6%)	13 (10.9%)	5 (13.9%)
Withdrawal of consent	3 (1.9%)	10 (6.5%)	8 (6.7%)	2 (5.6%)
Time on study (months)[a]				
Mean (SD)	15.81 (3.54)	15.05 (4.45)	15.11 (4.34)	14.84 (4.84)
Median	16.10	15.74	16.07	15.49
Min, Max	0.53, 22.41	0.03, 22.05	0.03, 22.05	0.53, 20.80

One subject in the acalabrutinib arm and two in the IR/BR arm withdrew consent before receiving any study treatment. Within the control arm, 119 subjects were assigned to IR and 36 to BR. The assignment per investigator's choice was performed pre-randomisation.

Thirty-five subjects (11%) in the control arm (29 subjects (19%) previously on IR and 6 subjects (4%) previously on BR) crossed over to acalabrutinib monotherapy.

Withdrawal of consent was more commonly noted in the control arm, 6.5% *vs* 1.9%.

Recruitment

The study enrolled and randomized 310 subjects at 102 centres in 25 countries between 01 December 2016 and 17 January 2018, and 307 subjects received study treatment. Countries with the highest percentage of enrolled subjects were Poland (22.3%), Czech Republic (19.4%), Ukraine (8.1%), Russian Federation (5.2%), Italy (4.8%), Spain (4.5%), Canada (4.2%), and Australia (3.9%).

Conduct of the study

Protocol amendments were not considered significant.

Baseline data

The median age for all subjects was 67 years (range: 32-90) with 63% of subjects ≥65 years old. Most subjects were enrolled in Central and Eastern Europe (64%) or Western Europe (21%). The median

time from initial CLL diagnosis to randomization in the study was 79.0 months. 17p deletion, 11q deletion, unmutated IGHV, and TP53 mutation were seen in 16%, 27%, 78%, and 24% of subjects, respectively, and 88% of subjects had at least one of these chromosomal characteristics.

Median number of prior therapies were 1 in the experimental arm and 2 in the control arm. Median time since the most recent therapy in the study was 24 months.

Numbers analysed

Table 22: Analysis Sets

	No. (%) of Subjects		
	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)	Total (N=310)
ITT Population	155 (100.0%)	155 (100.0%)	310 (100.0%)
Safety Population	154 (99.4%)	153 (98.7%)	307 (99.0%)

Outcomes and estimation

Study 309

- Primary endpoint: IRC-assessed PFS for control *vs* acalabrutinib monotherapy using a two-sided log-rank test, stratified by randomization stratification factors.

With a median-follow up of 16 months and an event rate of only 44% in the control arm IRC-assessed PFS showed a HR of 0.31 [95% CI: 0.20, 0.49]; p<0.0001, in favour of the experimental arm. This estimation is based on 19 PD events and 8 deaths in the experimental arm, with the corresponding figures for the control arm being 59 and 9, respectively. The median estimated PFS for the experimental arm was not reached; the median estimated PFS for the control arm was 16.5 months (95%CI: 14.0, 17.1).

The subgroup analyses consistently favour the experimental arm. It is noted that the point estimate for PFS HR is 0.21 for the subgroup of subjects with del 17p or TP53 mutation (n=87) while 0.36 in the complementary group.

Updated results (cutoff 1 August 2019) based on investigator's assessment: With a median follow-up of 22.1 months (range: 0.53-29.11) in the acalabrutinib arm and 21.9 months (range: 0.03-27.73) in the IR/BR arm, and event rates of 58% in the control arm and 23% in the experimental arm, the PFS HR was 0.27 [95% CI: 0.18, 0.40]; p<0.0001. The outcome is supported by the performed sensitivity analyses. The median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.8 months (95% CI: 14.1, 22.4).

With 6 months longer follow-up, and an acceptable PFS maturity of 58% in the control arm, outcomes remain essentially stable. For the SmPC 5.1, the inferential as well as the updated analysis should be presented.

Table 23: Updated results per the 1 August 2019 cut-off:

Efficacy Addendum
Acalabrutinib (ACP-196)-ACE-CL-309

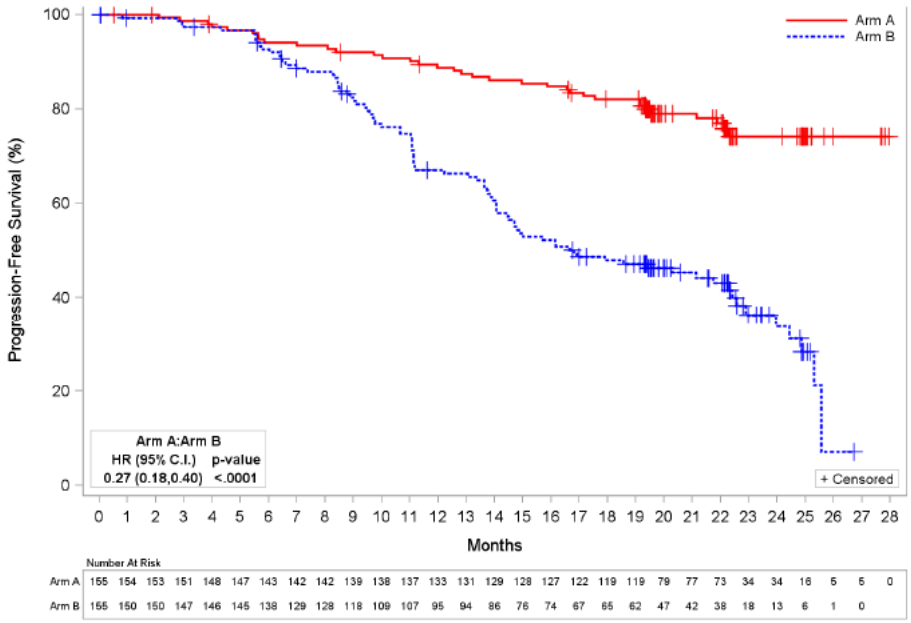
Key ACE-CL-309 Efficacy Addendum Findings	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subject Disposition		
Subjects randomized (Intent-to-Treat Population)[a]	155 (100.0)	155 (100.0)
Subjects treated with Investigational Product[a]	154 (99.4)	153 (98.7)
Subjects randomized but not treated[a,b]	1 (0.6)	2 (1.3)
Subjects who discontinued all study treatment,[c] no (%)	42 (27.1)	125 (80.6)
Subjects who exited study,[d] no. (%)	24 (15.5)	37 (23.9)
Primary reason for study exit		
Death, no. (%)	21 (13.5)	26 (16.8)
Withdrawal of consent, no. (%)	3 (1.9)[e]	11 (7.1)
Time on study,[d] months		
Mean (SD)	21.30 (5.20)	20.03 (6.45)
Median	22.14	21.91
Min[a], Max	0.53, 29.11	0.03, 27.73
Efficacy Assessments		
Investigator Assessed Progression-free survival (PFS): Censoring at Subsequent Anticancer Therapy[e, f]		
Events,[g] no. (%)	35 (22.6)	90 (58.1)
Death	12 (7.7)	11 (7.1)
Disease progression	23 (14.8)	79 (51.0)
Median PFS in months [95% CI]	NE [NE, NE]	16.8 [14.1, 22.4]
Stratified analysis, versus Arm B		
Hazard ratio (95% CI)[h]	0.27 (0.18, 0.40)	—
p-value[i]	<0.0001	—
Investigator Assessed Overall Response Rate (ORR)[j]		
ORR (CR+CRi+nPR+PR), no. (%) [95% CI][k]	124 (80.0) [73.0, 85.5]	130 (83.9) [77.3, 88.8]
ORR+PRL (CR+CRi+nPR+PR+PRL), no. (%) [95% CI][k]	142 (91.6) [86.2, 95.0]	136 (87.7) [81.6, 92.0]
Complete Response (CR), no. (%)	5 (3.2)	6 (3.9)
Partial Response (PR), no. (%)	114 (73.5)	122 (78.7)
Partial Response with lymphocytosis (PRL), no. (%)	18 (11.6)	6 (3.9)
Overall survival (OS)[l]		
Events,[m] no. (%)	21 (13.5)	26 (16.8)
Death	21 (13.5)	26 (16.8)
Median overall survival in months [95% CI]	NE [NE, NE]	NE [NE, NE]
Stratified analysis, versus Arm B		
Hazard ratio (95% CI)[h]	0.78 (0.44, 1.40)	—
p-value[i]	0.4094	—
Investigator Assessed Duration of Response (DOR)[n]		
Median DOR in months [95% CI]	NE [NE, NE]	18.0 [11.9, 19.8]
Stratified analysis, versus Arm B		
Hazard ratio (95% CI)[h]	0.19 (0.11, 0.33)	—
p-value[i]	<0.0001	—
Time to Next Treatment (TTNT)[o]		
Median TTNT in months [95% CI]	NE [NE, NE]	22.6 [17.5, 25.3]
Stratified analysis, versus Arm B		
Hazard ratio (95% CI)[h]	0.30 (0.20, 0.46)	—
p-value[i]	<0.0001	—

BR=bendamustine/rituximab; CI=confidence interval; CR=complete response; CRi=complete response with incomplete blood count recovery; DOR=duration of response; IR=idelalisib/rituximab; IXRS=interactive voice/web response system; NE=not estimable; no.=number; nPR=nodular partial response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; PRL=partial response with lymphocytosis; SD=standard deviation; TTNT=time to next treatment.

a. Data have not changed since the ACE-CL-309 CSR dated 17 July 2019 (with a data cutoff date of 15 January 2019).
b. 3 subjects (1 in the acalabrutinib arm and 2 in the IR/BR arm) withdrew consent before receiving any study treatment.
c. Discontinued all study treatment per randomization assignment. Arm B subjects who crossed over are summarized separately.
d. Study exit and time on study based on the whole study period—that is, main study period + crossover period.
e. Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.
f. PFS, defined as the time from date of randomization to the date of first investigator-assessed disease progression or death due to any cause, whichever came first.
g. Based on the earliest contributing assessment.
h. Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS.
i. Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS.
j. Best overall response was defined as the best response as assessed by the investigator on or before the initiation of subsequent anticancer therapy.
k. 95% CI based on Normal approximation (with use of Wilson's score).
l. OS was defined as the time from date of randomization to death due to any cause.
m. Death of any cause.
n. DOR was defined as the time from the first documentation of objective response to the earlier time of disease progression or death from any cause.
o. TTNT was defined as the time from randomization to institution of nonprotocol-specified treatment for CLL.

Data cutoff date for this ACE-CL-309 Efficacy Addendum is 01 August 2019.

Figure 1 **Kaplan-Meier Plot for Progression-Free Survival by Investigator Assessment: Censoring at Subsequent Anticancer Therapy (ITT Population)**



- Secondary endpoint: IRC-assessed ORR

In terms of ORR, and ORR including partial response with lymphocytosis, no statistically significant difference between study arms was noted, neither per IRC nor per investigator. The ORR per IRC was 81% in the experimental arm, with no subject reaching CR or CRi. As expected for a BTK inhibitor the activity was retained, and numerically higher than for the control, in subjects with del 17p or TP53 mutation.

As the ORR by IRC did not reach statistical significance the downstream outcomes are only nominally reported.

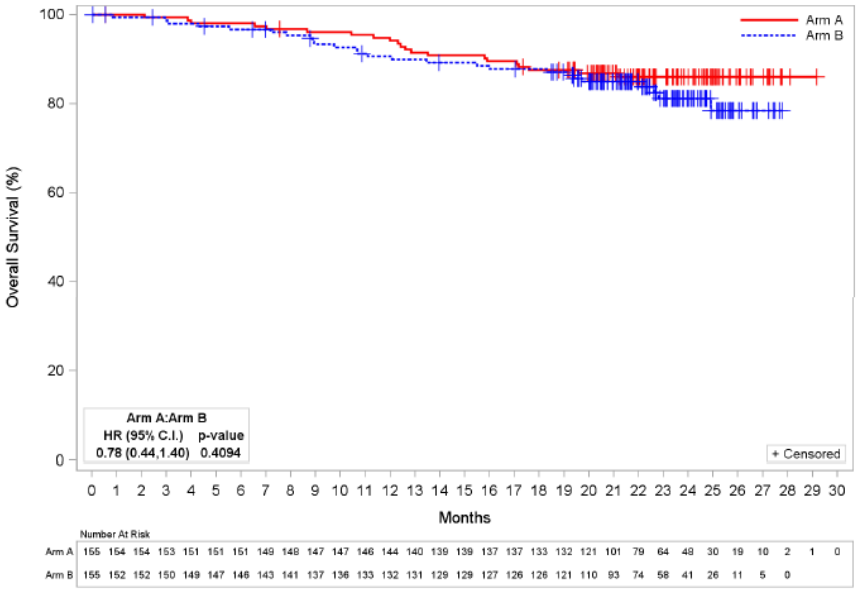
- Secondary endpoint: Time to next treatment

Based on event fractions of 34% in the control arm, including cross-over (23%), and 14% in the experimental arm, the median time to next treatment was not reached for any of the study arms. The HR was 0.35 (0.21, 0.58). The median time from first dose to subsequent anticancer therapy was 10 months in the experimental arm.

- Secondary endpoint: OS

With a median follow-up of around 16 months event rates were low, 12% in the control arm and 10% in the experimental arm. Updated information is presented above.

Figure 22 Kaplan Meier plot for Overall Survival (ITT population)



Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Ancillary analyses

Table 6 Sensitivity Analysis of Progress-Free Survival (PFS) by Investigator Assessment (ITT Population: Including PFS Events Without Censoring for Subsequent Anticancer Therapy)

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subject Status		
Events,[a] no. (%)	37 (23.9)	91 (58.7)
Death	13 (8.4)	12 (7.7)
Disease progression	24 (15.5)	79 (51.0)
Censored,[b] no. (%)	118 (76.1)	64 (41.3)
Randomization	0	2 (1.3)
Last adequate assessment before data cutoff	118 (76.1)	62 (40.0)
Progression-free survival, months		
Median (95% CI)	NE (NE, NE)	16.7 (14.1, 22.3)
Min, Max	0.5+, 28.0+	0.0+, 26.7+
Stratified analysis, versus Arm B		
Hazard ratio (95% CI)[c]	0.28 (0.19, 0.42)	—
p-value[d]	<0.0001	—
KM estimates of PFS rate by timepoint, % (95% CI)		
6 Months	94.1 (89.0, 96.9)	92.1 (86.5, 95.4)
9 Months	92.2 (86.6, 95.5)	81.9 (74.7, 87.2)
12 Months	88.9 (82.7, 92.9)	66.6 (58.3, 73.6)
15 Months	85.6 (78.9, 90.3)	53.3 (44.8, 61.0)
18 Months	81.6 (74.4, 86.9)	47.6 (39.3, 55.5)
21 Months	78.0 (70.4, 83.8)	45.0 (36.7, 53.0)
24 Months	73.2 (64.5, 80.1)	33.5 (23.8, 43.5)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; no.=number; PFS=progression-free survival.

Note: Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS.

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS.

Table 7 **Sensitivity Analysis of Progress-Free Survival (PFS) by Investigator Assessment (ITT Population: Excluding Subjects With Important Protocol Deviations)**

	Arm A Acalabrutinib (N=155)	Arm B IR or BR (N=155)
Subject Status		
Events,[a] no (%)	30 (21.0)	73 (56.2)
Death	9 (6.3)	8 (6.2)
Disease progression	21 (14.7)	65 (50.0)
Censored,[b] no (%)	113 (79.0)	57 (43.8)
Randomization	0	2 (1.5)
Last adequate assessment before data cutoff	109 (76.2)	55 (42.3)
Last adequate assessment before subsequent anticancer therapy	4 (2.8)	0
Progression-free survival, months		
Median (95% CI)	NE (NE, NE)	16.8 (14.1, 22.6)
Min, Max	0.5+, 28.0+	0.0+, 26.7+
Stratified analysis, versus Arm B		
Hazard ratio (95% CI)[c]	0.25 (0.16, 0.38)	—
p-value[d]	<0.0001	—
KM estimates of PFS rate by timepoint, % (95% CI)		
6 Months	95.0 (89.8, 97.6)	92.1 (85.8, 95.7)
9 Months	92.9 (87.1, 96.1)	82.3 (74.3, 88.0)
12 Months	89.3 (82.8, 93.4)	68.1 (59.1, 75.6)
15 Months	86.4 (79.4, 91.1)	53.8 (44.5, 62.2)
18 Months	84.2 (77.0, 89.3)	48.7 (39.5, 57.3)
21 Months	80.9 (73.2, 86.6)	45.6 (36.4, 54.3)
24 Months	75.8 (66.8, 82.7)	35.5 (24.9, 46.3)

BR=bendamustine/rituximab; CI=confidence interval; IR=idelalisib/rituximab; ITT=intent-to-treat; IXRS=interactive voice/web response system; KM=Kaplan-Meier; Max=maximum; Min=minimum; NE=not estimable; no.=number; PFS=progression-free survival.

Note: Time to event (or time to censor for censored subjects) is calculated as date of disease progression or death (censoring date for censored subjects) - randomization date + 1. Months are derived as days/30.4375.

[a] Based on the earliest contributing assessment.

[b] Based on the latest contributing assessment.

[c] Based on stratified Cox proportional hazards model, stratified by randomization stratification factors as recorded in IXRS.

[d] Based on stratified log-rank test, stratified by randomization stratification factors as recorded in IXRS.

Summary of main study ASCEND (ACE-CL-309)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2. Summary of Efficacy for Acalabrutinib

Title: A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia		
Study identifier	**EUDRACT 2015-004454-17 (ACE-CL-309)**	
Design	This randomized, global, multicenter, open-label, Phase 3 study will evaluate the efficacy and safety of acalabrutinib monotherapy versus Investigator's choice of either idelalisib/rituximab or bendamustine/rituximab in subjects with R/R CLL.	
	Duration of run-in phase:	Not applicable

	Duration of main phase:		The maximum duration of the study is approximately 48 months from the first subject randomized. Therefore, the end of study will occur approximately 48 months after the first subject is randomized. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may be eligible to enroll in a separate rollover study.
	Duration of Extension phase:		Not applicable
Hypothesis	Under the model assumption of a median PFS of 31 months for subjects in Arm A versus 17 months for subjects in Arm B, the study is sized to achieve approximately 90% power to detect a hazard ratio (HR; Arm A/Arm B) of 0.55 for PFS. The study is expected to enroll approximately 306 subjects with a 1:1 randomization ratio between Arm A and B. With an event-driven design, the final analysis of PFS is planned when a total of 119 IRC-assessed PFS events have been observed which is anticipated to occur approximately 27 months after the first subject is randomized. The interim analysis of PFS will be conducted when approximately two-thirds of the IRC-assessed PFS events for the final analysis (i.e., 79 events) have been observed.		
Treatments groups	Arm A: Acalabrutinib 100 mg orally (PO) twice per day (BID)		Acalabrutinib 100 mg orally (PO) twice per day (BID) administered until an unacceptable drug-related toxicity occurs or until disease progression (n=155)
	Arm B: Investigator's choice of: • Idelalisib 150 mg PO BID in combination rituximab or • Bendamustine in combination with rituximab		• Idelalisib 150 mg PO BID administered in combination with ≤ 8 doses of intravenous (IV) rituximab (first dose at 375 mg/m2, subsequent doses at 500 mg/m2 IV every 2 weeks for 4 infusions, then every 4 weeks for an additional 3 infusions) until disease progression or unacceptable toxicity. • Bendamustine 70 mg/m2 IV (Day 1 and 2 of each cycle) in combination with rituximab IV (375 mg/m2/500 mg/m2) on Day 1 of each cycle for up to 6 cycles. (n=155)
Endpoints and definitions	Primary endpoint	Treatment of adult patients with previously treated CLL/SLL	To evaluate the efficacy of acalabrutinib monotherapy (Arm A) compared with idelalisib/rituximab or bendamustine/rituximab (Arm B) based on IRC assessment of PFS per IWCLL 2008 criteria in subjects with R/R CLL.
	Secondary endpoints	Treatment of adult patients with previously treated CLL/SLL	To evaluate Arm A compared with Arm B in terms of: • Investigator (INV)-assessed PFS per IWCLL 2008 criteria. • INV- and IRC-assessed overall response rate (ORR) per IWCLL 2008 criteria. • Overall survival (OS). • Patient-reported outcomes (PROs) by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue). • INV- and IRC-assessed duration of response (DOR). • Time to next treatment (TTNT).

	Safety and exploratory endpoints	Treatment of adult patients with previously treated CLL/SLL	Safety: Incidence of adverse events (AEs) and serious adverse events (SAEs) and changes in laboratory measurements and vital signs from baseline. Exploratory: Evaluate Arm A compared with Arm B in terms of: • Improvement and/or resolution of disease-related symptoms. • Hematologic improvement in the subset of subjects with cytopenia(s) at baseline. • PROs by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires Core 30 (QLQ-C30) and EuroQoL Five-Dimension (EQ-5D-5L). • Medical resource utilization (MRU). • Potential predictive biomarkers and mechanisms of resistance for the disease.
Database lock	15JAN2019 data cutoff; 11MAR2019 data extract		

Results and Analysis

Analysis description	**Primary Analysis**
One interim analysis to be performed when approximately 79 IRC-assessed PFS events have occurred	To evaluate the efficacy of acalabrutinib monotherapy (Arm A) compared with idelalisib/rituximab or bendamustine/rituximab (Arm B) based on IRC assessment of progression-free survival (PFS) PFS, defined as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first. Intent-to-treat population is the primary analysis population.

Analysis description	**Secondary Analysis**
One interim analysis to be performed when approximately 79 IRC-assessed PFS events have occurred	IRC-assessed ORR OS To control the overall Type I error α at 0.05 level, the Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundary were used to split α into α1 and α2 for interim and final analyses, respectively. The nominal α1 and α2 levels would be determined based on the actual information fraction at the time of the interim analysis. Within each analysis, the fixed sequence procedure would be utilized to adjust for multiple comparisons. The secondary endpoint would be tested in the order as specified above. Intent-to-treat population is the primary analysis population.

	CALQUENCE Monotherapy N=155	**Investigator's Choice of Idelalisib + Rituximab Product or Bendamustine + Rituximab Product N=155**
Progression-Free Survival [a]		
Number of events, n (%)	27 (17)	68 (44)
Disease progression, n	19	59
Death, n	8	9
Median (95% CI), months [b]	NE (NE, NE)	16.5 (14.0, 17.1)
HR (95% CI) [c]	0.31 (0.20, 0.49)	
P-value [d]	< 0.0001	
Overall Response Rate (CR + CRi + nPR + PR) [a, e]		
ORR, n (%) [e]	126 (81)	117 (75)
(95% CI)	(74, 87)	(68, 82)

CR, n (%)	0	2 (1)
CRi, n (%)	0	0
nPR, n (%)	0	0
PR, n (%)	126 (81)	115 (74)

ITT=intent-to-treat; CI=confidence interval; HR=hazard ratio; NE=not estimable; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response
[a] Per 2008 IWCLL criteria.
[b] Kaplan-Meier estimate
[c] Based on a stratified Cox-Proportional-Hazards model
[d] Based on a stratified Log-rank test. The pre-specified type I error rate (α) for this interim analysis is 0.012 derived from a Lan-DeMets alpha spending function with O'Brien-Fleming boundary
[e] Through a hierarchical testing procedure, the difference in ORR was not statistically significant, based on a Cochran-Mantel Haenzel test with adjustment for randomization stratification factors.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Supportive study ACE-CL-001

Title: A Phase 1/2, Multicentre, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia, Richter's Syndrome or Prolymphocytic Leukemia.

This is an ongoing Phase1/2, multicentre, open-label, nonrandomized, sequential group, dose-escalation study designed to evaluate the safety, PK, and pharmacodynamics of acalabrutinib in subjects with CLL/SLL, Richter's syndrome, or PLL. The study enrolled 306 subjects at 12 centres in the US, UK, and Italy; 301 subjects received study treatment. The primary objectives were to establish the safety and the maximum tolerated dose of orally administered acalabrutinib in subjects with CLL/SLL, and to determine the PK of orally administered acalabrutinib and identify its major metabolite. The secondary objective was to evaluate tumour response by ORR, DOR, and PFS. In the Phase 1 portion of the study, subjects with CLL and SLL received acalabrutinib at once daily (QD) doses of 100 mg, 175 mg, 250 mg and 400 mg, and BID doses of 100 mg and 200 mg, for 28 days (1 cycle).

Radiologic tumour assessment was done at screening and at the end of Cycles 2, 4, and 6; then every 6 cycles until Cycle 36; and then every 12 cycles thereafter. Tumour response was assessed by the investigator based on IWCLL 2008 criteria per Hallek et al. 2008 with incorporation of the clarification for treatment-related lymphocytosis per Cheson et al. 2012. Confirmation of CR required bone marrow analysis and radiologic tumour assessment.

No dose-limiting toxicities were observed in the Phase 1 dose escalation portion of the study, and the maximum tolerated dose was not reached at doses up to 400 mg QD.

In R/R subjects, ORR for the Efficacy Evaluable Population (N=130) was 90.8% (95% CI: 84.4, 95.1), including 6 subjects (4.6%) with CR and 112 subjects (86.2%) with PR. For subjects with 17p deletion, ORR was 92.3% (95% CI: 74.9, 99.1).

In previously untreated subjects, ORR for the Efficacy Evaluable Population (N=97) was 99.0% (95% CI: 94.4, 100), including 5 subjects (5.2%) with CR and 91 subjects (93.8%) with PR. For subjects with 17p deletion, the ORR was 100% (95% CI: 66.4, 100).

The median time to initial response for the responders was 4.7 months (range: 1.6–43.7 months) in R/R subjects and 3.7 months (range: 1.7-22.1 months) in previously untreated subjects.

With a median follow-up of 41.7 months (range: 0.56-58.48 months) in the R/R subjects and 45.6 months (range: 0.92-52.34 months) in the previously untreated subjects, the median DOR for the Efficacy Evaluable Population in both the R/R and previously untreated subgroups was not reached.

Using KM point estimates, 58.1% (R/R) and 92.3% (previously untreated) of subjects were event-free at 48 months.

These single-arm data with long follow-up support retained activity in del 17p disease, although number of subjects are limited; 9 in the previously untreated group and 24 in the r/r group. Regarding duration of response no medians (overall or for the del 17p subgroup) were reached for the previously untreated group or overall for the r/r group but was 31 months in the del 17p subgroup of the latter. Thus, del 17p disease may be associated with shorter DOR also when treated with acalabrutinib but longer follow-up is needed.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application rests on two pivotal trials in two different populations. In previously untreated CLL trial ACE-CL-007 was a Randomized, Multicentre, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP- 196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia. The study enrolled previously untreated subjects who were unfit based on the inclusion criterion of age ≥65 years or age <65 years with a Cumulative Illness Rating Score Geriatric (CIRS-G) score of >6 or a creatinine clearance of 30-69 mL/min (using the Cockcroft-Gault equation).

In Relapsed or refractory CLL trial ACE-CL-309 was a Randomized, Multicentre, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia.

Subjects were required to have received ≥1 prior systemic therapy for CLL to be eligible to enrol. Prior exposure to a B-cell lymphoma (BCL)-2 inhibitor (e.g., venetoclax/ABT-199) or a B-cell receptor (BCR) inhibitor (e.g., BTK inhibitors or PI3K inhibitors) was not allowed.

An active comparator has been chosen for each study. In ACE-CL-007 in subjects with previously untreated CLL, acalabrutinib+obinutuzumab as well as acalabrutinib monotherapy were compared with obinutuzumab+chlorambucil. Obinutuzumab+Chlorambucil is one of the standard treatments for low risk patients or patient with comorbidities, thus the chosen comparator is supported for unfit patients. Other options as for first line treatment are ibrutinib, FCR (Rituximab-Fludarabine and cyclophosphamide) for patients < 65 years or Rituximab–Bendamustine (R-B) for patients ≥65 years. However, in presence of TP53 mutation or del(17p) ibrutinib had been the preferred choice.

In ACE-CL-309 in subjects with R/R CLL, acalabrutinib monotherapy was compared with investigator's choice of idelalisib+rituximab (IR) or bendamustine+rituximab (BR), as BR is mostly used as first line, idelalisib –Rituximab or ibrutinitb are mostly used in R/R CLL. Even when the proposed active comparators are supported, it would be ideally preferred a direct comparison to the standard BTK inhibitor ibrutinib. Additionally, for the indication in R/R CLL the main drawback of the control arm being the doctor's choice makes the results of this group more heterogeneous than desirable.

At both studies, a crossover period has been proposed at investigator discretion for those patients not receiving acalabrutinib, once progression has been confirmed by IRC, to receive treatment with single-agent acalabrutinib at 100 mg BID until next disease progression or unacceptable toxicity. This cross-over will have an impact on the survival outcomes comparison.

For both studies primary efficacy endpoint was based on IRC assessment of PFS per IWCLL criteria (Hallek et al. 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson

et al. 2012). Even when the choice of primary endpoint seems adequate, a clarification by the applicant about the applied "IWCLL criteria (Hallek et al. 2008) with incorporation of the clarification for treatment-related lymphocytosis (Cheson et al. 2012)" would be acknowledged. From the statistical assessment point of view the applicant split α into α1 and α2 for interim and final analyses. Secondary endpoints were tested in a hierarchical order separately for interim and final analyses. It is however noting that since the test of ORR between acalabrutinib monotherapy and obinutuzumab+chlorambucil was not statistically significant (p=0.0763), it will not be possible to formally test OS in the final analysis.

Sensitivity analysis for PFS as assessed by IRC without censoring for subsequent anticancer therapy were performed. The performed sensitivity analysis for subsequent anticancer therapy differed from what was specified in the SAP. An additional analysis for PFS without censoring for subsequent anticancer and without censoring of events after 2 or more consecutively missed visits (i.e. combining sensitivity analyses with numbers 2 and 3 in the company's documentation) has been provided and supports the robustness of the primary outcome.

The number of patients that were randomised but not treated were more frequent in the control arm, Arm A (8/177, 4.5%) than in acalabrutinib combination arm, Arm B (0/179, 0%) and in acalabrutinib monotherapy Arm C (1/179, 0.6%). In the control arm one patient did not fulfil the inclusion criteria and two died before treatment start. The other 5 dropped out of other reasons. The study was open label, and knowledge of the allocated treatment may have affected the dropout rate. The applicant has provided a sensitivity analysis for PFS, arm A vs B, where the patients that did not fulfil the inclusion criteria and the two that died before treatment start were excluded, and where the 5 other patients who dropped out were analysed as if they were followed without event until end of study. The results of this analysis were generally consistent with what was observed in the primary analysis.

Updated results reported for both pivotal studies are based on pre-specified interim analyses and data cutoff date of 08 February 2019 for study 007 and 15 January 2019 for study 309.

Efficacy data and additional analyses

In ***previously untreated CLL (study 007),*** with a median-follow up of 28 months and an event rate of 52% in the control arm IRC-assessed PFS for Acala+Obin *vs* clb+obi, the primary outcome, showed a HR of 0.10 [95% CI: 0.06, 0.17]; p<0.0001, in favour of the Acala+Obin arm. The sensitivity analyses are supportive of this outcome. The median estimated PFS for the experimental arm was not reached; the median estimated PFS for the control arm was 22.6 months (95%CI: 20.2, 27.6). In terms of HR for PFS, the subgroup analyses consistently favour the experimental arm.

With a median-follow up and event rate for the control arm as above, IRC-assessed PFS for acalabrutinib monotherapy *vs* clb+obi, the key alpha-controlled secondary outcome, showed a HR of 0.20 [95% CI: 0.13, 0.30]; p<0.0001 in favour of the experimental arm. The sensitivity analyses are supportive of this outcome. The median estimated PFS for acalabrutinib monotherapy was not reached; the median estimated PFS for the control arm was 22.6 months (95%CI: 20.2, 27.6). In terms of HR for PFS, the point estimates for the subgroup analyses consistently numerically favour the acalabrutinib monotherapy arm.

The IRC-assessed ORR for Acala+Obin, acalabrutinib monotherapy, and the control arm was 93.9% (95% CI: 89.3–96.5), 85.5% (95% CI: 79.6–89.9), and 78.5% (95% CI: 71.9–83.9), respectively. As expected for a BTK inhibitor, the fraction of subjects reaching CR was less than 1% in the acalabrutinib monotherapy arm and not higher than 13% in the Acala+Obin combination arm. The ORR difference between Acala+Obin and the control arm was 15.3% (95% CI: 8.3–22.3), p<0.0001; the difference

between the acalabrutinib monotherapy arm and the control arm was not statistically significant, meaning that the downstream secondary endpoints in the hierarchy are only nominally reported.

Although the subgroup analyses generally are consistent with the overall outcome, some analyses are of special interest, particularly regarding del 17p/TP53 mutation y/n: The activity of the acalabrutinib combination is slightly higher in the del17p/TP53 mutation-negative subgroup (95% vs 84% in the positive subgroup), while similar for the subgroups with acalabrutinib monotherapy where the activity corresponds to the activity of the acalabrutinib combination in the del17p/TP53 mutation-positive subgroup. The ORR of the control regimen is roughly similar to what is noted with acalabrutinib monotherapy in the negative subgroup but considerably lower than both experimental arms in positive disease, 56%.

The time to next treatment was numerically prolonged compared with control for both Acala+Obin (HR=0.14 [95% CI: 0.08–0.26]) and acalabrutinib monotherapy (HR=0.24 [95% CI: 0.15–0.40]). The median time to next treatment was not reached for any treatment arm.

With an event rate of only 10% in the control arm, and 5% in the Acala+Obin arm and 6% in the monotherapy arm, data on OS is, as expected for a first-line treatment of CLL with a median of 28 months of follow-up, immature. In addition, the massive cross-over from the control arm to acalabrutinib monotherapy makes relative OS data practically non-interpretable. Nevertheless, a HR of 0.47 (0.21, 1.06) is reported for the acalabrutinib combination *vs* control, and a HR of 0.60 (0.28, 1.27) for acalabrutinib monotherapy *vs* control, both in favour of the experimental regimens.

Study enrolment in the 007 study (previously untreated patients) was restricted to subjects ≥65 years of age or younger with comorbidity. As an indication encompassing the whole population is sought extrapolation was discussed and considered acceptable (see also discussion on Benefit / risk).

With the possible exception of biased early censoring of limited size in the control arm (6% vs 0.6% in the Acala+Obin arm and 3% in the acalabrutinib monotherapy arm) in this open study, no worrisome censoring is noted.

Inspection of the KM curves shows that the down-flection of the control arm starts some months after cessation of therapy. This is not surprising and emphasises the need for data on OS/PFS2. Given the massive cross-over from the control arm robust data on OS will never be achieved.

Comparing Acala+Obin *vs* Clb+Obin, notably, the point estimate for PFS HR is similar (0.1) for subjects with (25 subjects in each arm) or without (154 in the experimental arm and 152 in the control arm) del 17p or TP53 mutation. This might be surprising considering the suboptimal control regimen Clb+Obin for subjects with these genomic aberrations, but numbers are low. Expanding the analysis to encompass subjects with all genetic high-risk features (del 17p, TP53 mutation, del 11q and/or unmutated IGHV; n=117 in the experimental arm and 129 in the control arm) the corresponding point estimate is 0.08 *vs* 0.22 in the complementary group.

When comparing acalabrutinib monotherapy *vs* Clb+Obin, as noted for the primary analysis comparing Acala+Obin *vs* Clb+Obin, the PFS HR for subjects with del 17p or TP53 mutated disease (n=23 subjects in the experimental arm and 25 in the control arm) is approximately the same as for the complementary group. A numerically substantial difference between the groups is however noted when mutational status of IGHV and all genetic high-risk features together (as defined above) are considered.

In ***Relapsed or refractory CLL (study 309)*** with a median-follow up of 16 months and an event rate of only 44% in the control arm IRC-assessed PFS showed a HR of 0.31 [95% CI: 0.20, 0.49]; p<0.0001, in favour of the experimental arm. The median estimated PFS for the experimental arm was not reached; the median estimated PFS for the control arm was 16.5 months (95%CI: 14.0, 17.1).

The performed sensitivity analyses are supportive of the primary outcome. The subgroup analyses consistently favour the experimental arm. It is noted that the point estimate for PFS HR is 0.21 for the subgroup of subjects with del 17p or TP53 mutation (n=87) while 0.36 in the complementary group. With an event rate of 44% in the control arm, similar as for the primary analysis, the HR for investigator-assesses PFS, a secondary endpoint, was 0.28 (0.18, 0.45), p <0.0001, and thus consistent with the primary analysis.

With the possible exception of biased early censoring of limited size in the control arm (6% vs 0.6% in the Acala+Obin arm and 3% in the acalabrutinib monotherapy arm) in this open study, no worrisome censoring is noted. A sensitivity analysis showed results generally consistent with was observed in the primary analysis.

Inspection of the KM curves shows that the down-flection of the control arm starts some months after cessation of therapy. This is not surprising and emphasises the need for data on OS/PFS2. Given the massive cross-over from the control arm robust data on OS will never be achieved.

In terms of ORR, and ORR including partial response with lymphocytosis, no statistically significant difference between study arms was noted, neither per IRC nor per investigator. The ORR per IRC was 81% in the experimental arm, with no subject reaching CR or CRi. As expected for a BTK inhibitor the activity was retained, and numerically higher than for the control, in subjects with del 17p or TP53 mutation. As the ORR by IRC did not reach statistical significance the downstream outcomes are only nominally reported.

With a median follow-up of around 16 months event rates for OS were low, 12% in the control arm and 10% in the experimental arm. HR was 0.84 (0.42, 1.66).

Given the low maturity at the time of this interim analysis in study 309, performed in January 2019, an update of the primary and the time-dependent analyses was requested and with 6 months longer follow-up, and an acceptable PFS maturity of 58% in the control arm, outcomes remain essentially stable.

Patients previously treated with ibrutinib or venetoclax were excluded from the r/r CLL study. While treatment with acalabrutinib would be considered irrational after progression under or after ibrutinib drug pressure, it is unknown whether prior exposure to venetoclax might impact response to acalabrutinib. The applicant presented external data reasonably supporting the use of BTK inhibitors in subjects previously treated with venetoclax, and the use of acalabrutinib in subjects intolerant, but not resistant, to ibrutinib. This is in line with what could mechanistically be expected.

Updated results (cut-off 1 August 2019) based on investigator's assessment: With a median follow-up of 22.1 months (range: 0.53-29.11) in the acalabrutinib arm and 21.9 months (range: 0.03-27.73) in the IR/BR arm, and event rates of 58% in the control arm and 23% in the experimental arm, the PFS HR was 0.27 [95% CI: 0.18, 0.40]; p<0.0001. The outcome is supported by the performed sensitivity analyses. The median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.8 months (95% CI: 14.1, 22.4).

With 6 months longer follow-up, and an acceptable PFS maturity of 58% in the control arm, outcomes remain essentially stable.

With a median follow-up of around 16 months event rates for OS were low, 12% in the control arm and 10% in the experimental arm. HR was 0.84 (0.42, 1.66). At the updated analysis, with a median follow-up of 22 months and 21 events in the acalabrutinib arm and 26 events in the control arm, HR was 0.78 (0.44, 1.40).

Per IRC assessment, the median duration of response was 13.6 months in the control arm and not reached in the experimental arm; HR 0.33 (0.19, 0.59); at the updated analysis using investigator-assessed DOR, the corresponding figures were 18 months, not reached, 0.19 (0.11, 0.33)

Based on event fractions of 34% in the control arm, including cross-over (23%), and 14% in the experimental arm, the median time to next treatment was not reached for any of the study arms. The HR was 0.35 (0.21, 0.58). The median time from first dose to subsequent anticancer therapy was 10 months in the experimental arm. At the updated analysis, the HR was 0.30 (0.20, 0.46).

Further, in terms of HR for PFS, the subgroup analyses consistently favour the experimental arm. Notably, the point estimate for PFS HR is similar (0.1) for subjects with (25 subjects in each arm) or without (154 in the experimental arm and 152 in the control arm) del 17p or TP53 mutation. This might be surprising considering the suboptimal control regimen for subjects with these genomic aberrations, but numbers are low. Expanding the analysis to encompass subjects with all genetic high-risk features (del 17p, TP53 mutation, del 11q and/or unmutated IGHV; n=117 in the experimental arm and 129 in the control arm) the corresponding point estimate is 0.08 *vs* 0.22 in the complementary group. The control regimen, Clb+Obin, is deemed suboptimal for subjects with del 17p/TP53 mutation, even at the time of study initiation (September 2015).

The applicant has provided compiled absolute data on PFS and ORR with DOR per treatment arm and genetic risk status (del 17p or TP53-mutation *vs* the complementary group). These data suggest that also the acalabrutinib-containing study arms performed numerically inferior in subjects with del 17p or TP53 mutation-positive disease. The applicant's justification for the use of chl+obi in the control arm, alluding to historical reasons, is acknowledged and accepted.

In study 309 censoring is higher in the control arm during the first 9 months, it was argued that the higher frequency of study treatment discontinuation in the control arm contributed to the observed unevenly distributed censoring time the differing censoring pattern between study arms beyond 9 months. Bias in terms of informative censoring beyond the first 9 months of the study does not seem to confound the outcomes. With the possible exception of biased early censoring of limited size, as discussed above, possibly also influencing the higher fraction of "no post-baseline assessment" in the control arm (6 vs 0.6%), no worrisome censoring is noted. Inspection of the KM curves shows that the down-flection of the control arm starts some months after cessation of therapy. This is not surprising and emphasises the need for data on OS/PFS2.

2.5.4. Conclusions on the clinical efficacy

Calquence (acalabrutinib) has demonstrated efficacy in terms of PFS and supportive secondary endpoints both as monotherapy and in combination with obinutuzumab in patients with previously untreated or having received at least 1 prior treatment for CLL.

The final Clinical study reports for studies ACE-CL-007 (including data on time to second subsequent therapy) and ACE-CL-309 are expected to be submitted by Q3 2022 (see RMP) as post approval data.

2.6. Clinical safety

The assessment of safety of acalabrutinib is based two pivotal studies presented separately, ACE-CL-007 performed in treatment naïve CLL subjects (elderly or patients with comorbidities) and ACE CL-309, in R/R CLL subjects (subjects were required to have received ≥1 prior systemic therapy for CLL). The MAH also presents safety data as integrated analysis of pooled safety data from, in total, 10 open-

label efficacy and safety studies, (phase 1 to phase 3) in subjects with hematologic malignancies treated with acalabrutinib, including the two pivotal studies.

Both studies are ongoing, and the present application presents pre planned interim analyses for the respective pivotal study.

The safety population consists of all subjects who received any amount of study drug.

The 10 studies include the following:

- Two Phase 3 pivotal studies in R/R CLL (ACE-CL-309) and previously untreated CLL (ACE-CL-007)
- Three supportive CLL studies evaluating acalabrutinib monotherapy (15-H-0016 and ACE-CL-001) and acalabrutinib+obinutuzumab (ACE CL 003)
- Five supportive studies evaluating acalabrutinib monotherapy in other hematologic malignancies (ACE-LY-002 [activated B-cell diffuse large B-cell lymphoma], ACE LY 003 [follicular lymphoma], ACE-LY-004 [mantle cell lymphoma], ACE MY 001 [multiple myeloma] and ACE WM 001 [Waldenström macroglobulinemia])

The data from these 10 studies were analysed in 5 analysis pools as follows:

- Mono Pivotals (N=333): This population consists of all subjects from CLL pivotal studies (ACE-CL-007 and ACE-CL-309) who received at least 1 dose of acalabrutinib monotherapy.
- Mono CLL (N=762): This population consists of subjects from CLL pivotal studies (ACE CL-007 and ACE-CL-309) and CLL supportive studies (ACE-CL-001 and 15 H 0016) who received at least 1 dose of acalabrutinib monotherapy including subjects who crossed over from any control arm.
- Combo CLL (N=223): This population consists of subjects from Studies ACE CL 007 and ACE-CL-003 who received at least 1 dose of combination therapy of acalabrutinib and obinutuzumab.
- Total CLL (N=985): This population consists of subjects from Mono CLL and Combo CLL populations described above.
- Mono HemMalig (N=1040): This population consists of subjects from all hematologic malignancy studies in which subjects received at least 1 dose of acalabrutinib monotherapy including subjects who crossed over from any control arm.

Patient exposure

Pivotal study ACE-CL-007

The median duration of exposure to acalabrutinib was 27.7 months (range: 0.7–40.3 months) in the acalabrutinib+obinutuzumab (Acala+Obin) arm and 27.7 months (range 0.3–40.2 months) in the acalabrutinib monotherapy (Acala-mono) arm, with 83.1% and 81.0% of subjects in the 2 arms, respectively, receiving ≥2 years of acalabrutinib therapy. The median duration of obinutuzumab treatment was 5.5 months (range: 0.9-7.1 months) in the Acala+Obin arm and 5.6 months (range: 0.9-7.4 months) in the chlorambucil+obinutuzumab (Clb+Obin) arm. The median duration of chlorambucil treatment was 5.5 months (range: 0.5–7.2 months) in the Clb+Obin arm.

The median relative dose intensity was in the two Acala containing arms >98 %.

Pivotal study ACE-CL-309

The median duration of monotherapy acalabrutinib treatment was 15.7 months (range: 1.1-22.4 months) with 85.7% of subjects receiving ≥1 year of therapy. In the idelalisib+rituximab (IR) group,

the median duration of idelalisib treatment was 11.5 months (range: 0.1-21.1 months) and the median duration of rituximab was 5.5 months (range: 0.9-8.5 months). In the bendamustine+rituximab (BR) group, the median duration of bendamustine treatment was 5.6 months (range: 1.0-7.1 months) and the median duration of rituximab treatment was 5.5 months (range: 0.9-7.1 months).

The median dose intensity of acalabrutinib was 99.5%.

Pooled populations

Median durations of exposure for the different pools ranged from 19.3 to 29.8 months. Median duration of exposure to acalabrutinib in Mono HemMalig population was 24.6 months and in ComboCLL (combination with obinutuzumab) 29.8 month.

In summary, the acalabrutinib exposure presents altogether sufficient data for safety assessment. Data on exposure has been presented for several time intervals and most patients in all five pools were exposed to acalabrutinib for >12 months. Together with the high relative dose intensity, i.e. > 98%, this indicates an acceptable tolerability.

The safety database includes CLL subjects covering the proposed target population, possibly with a retrenchment in a younger, treatment naïve, fit population. However, there is little diffidence of worse outcome, with respect to safety, in this subgroup.

At the time of data cut-off, >88% of the subjects in Mono Pivotal and Combo CLL, were still on treatment.

From here on, pooled data reported will only be those collected from the Mono Pivotal and Combo CLL populations.

Adverse events

ACE-CL-007

In the Acala-Obin arm the most frequent (>20%) TEAEs were (by PT) headache (39.9%), diarrhea (38.8%), neutropenia (31.5%), fatigue (28.1%), contusion (23.6%), arthralgia (21.9%), cough (21.9%), upper respiratory tract infection (21.3%), and nausea (20.2%). All of these frequent AEs were Grade 1 or 2, with the exception of neutropenia.

In the Acala-mono arm the most frequent TEAEs were headache (36.9%), diarrhea (34.6%), and nausea (22.3%). Almost all of these frequent TEAEs were Grade 1 or 2, with the exception of 2 subjects (1.1%) with Grade 3 TEAEs of headache and 1 subject (0.6%) with a Grade 3 TEAE of diarrhea. None of these frequent TEAEs were Grade 4.

In the Clb+Obin arm the most frequent TEAEs were neutropenia (45.0%), infusion related reaction (39.6%), nausea (31.4%), diarrhea (21.3%), and pyrexia (20.7%). Most of these frequent TEAEs were Grade 1 or 2, with the exception of neutropenia (Grade ≥3, 41%).

Treatment-Emergent CTCAE Grade ≥3 Adverse Events Reported in ≥2% of Subjects in Any Treatment Arm (Safety Population, ACE-CL-007)

Preferred Term	No. (%) of Subjects		
	Arm B Acalabrutinib+ Obinutuzumab (N=178)	Arm C Acalabrutinib Monotherapy (N=179)	Arm A Obinutuzumab+ Chlorambucil (N=169)
Subjects with ≥1 Grade ≥3 TEAE	125 (70.2)	89 (49.7)	118 (69.8)
Neutropenia	53 (29.8)	17 (9.5)	70 (41.4)
Thrombocytopenia	15 (8.4)	5 (2.8)	20 (11.8)
Anaemia	10 (5.6)	12 (6.7)	12 (7.1)
Febrile neutropenia	3 (1.7)	2 (1.1)	9 (5.3)
Diarrhoea	8 (4.5)	1 (0.6)	3 (1.8)
Upper respiratory tract infection	4 (2.2)	0	1 (0.6)
Pneumonia	10 (5.6)	4 (2.2)	3 (1.8)
Infusion related reaction	4 (2.2)	0	9 (5.3)
Alanine aminotransferase increased	5 (2.8)	1 (0.6)	3 (1.8)
Neutrophil count decreased	2 (1.1)	0	5 (3.0)
Tumour lysis syndrome	2 (1.1)	0	13 (7.7)
Syncope	4 (2.2)	2 (1.1)	1 (0.6)
Hypertension	5 (2.8)	4 (2.2)	5 (3.0)

CTCAE=Common Terminology Criteria for Adverse Events; TEAE=treatment-emergent adverse event.
TEAEs coded with MedDRA Version 21.1.
A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Source: Table 14.3.2.2.

ACE-CL-309

The treatment in the Acala arm in ACE-CL-309 was continued until PD or unacceptable toxicity while the IR received idelalisib until PD or unacceptable toxicity but rituximab for 6 cycles. The BR group received maximum 6 cycles of both drugs. The actual median time on treatment at DCO for Acala was (15.7 months), for idelalisib treatment was 11.5 months and for Clb+Obin 5.6 months.

The most common TEAEs among subjects treated with monotherapy acalabrutinib, (≥10% of subjects) were: headache (22.1%), neutropenia (19.5%), diarrhoea (18.2%), anaemia and cough (14.9% each), upper respiratory tract infection (14.3%), pyrexia (12.3%), thrombocytopenia (11.0%) and pneumonia and respiratory tract infection (10.4% each). The majority of these TEAEs were Grade 1 or 2. One subject in the acalabrutinib group had febrile neutropenia Grade ≥3.

In the IR group, the most common TEAEs (≥10% of subjects) were: diarrhoea (46.6%), neutropenia (44.9%), pyrexia (17.8%), cough (15.3%), upper respiratory tract infection (14.4%), thrombocytopenia and rash (13.6% each), nausea (12.7%), and pneumonia and increased alanine aminotransferase (11.9% each). Most of these AEs were Grade 1 or 2.

In the BR group, the most common TEAEs (≥10% of subjects) were: neutropenia (34.3%), fatigue, and infusion-related reaction (22.9% each), nausea (20.0%), pyrexia (17.1%), constipation, diarrhoea, and thrombocytopenia (14.3% each), and anaemia and upper respiratory tract infection (11.4% each). Most of these AEs were Grade 1 or 2.

Treatment-Emergent Adverse Events with CTCAE Grade ≥3 Reported in ≥2% of Subjects in Either Arm A or Arm B (Safety Population)

	No. (%) of Subjects		
	Arm A	Arm B	
	Acalabrutinib (N=154)	IR (N=118)	BR N=35)
Subjects with at least 1 Grade ≥3 TEAE	76 (49.4%)	106 (89.8%)	17 (48.6%)
Neutropenia	24 (15.6%)	47 (39.8%)	11 (31.4%)
Anaemia	18 (11.7%)	8 (6.8%)	3 (8.6%)
Pneumonia	8 (5.2%)	10 (8.5%)	1 (2.9%)
Thrombocytopenia	6 (3.9%)	9 (7.6%)	1 (2.9%)
Upper respiratory tract infection	3 (1.9%)	4 (3.4%)	1 (2.9%)
Alanine aminotransferase increased	2 (1.3%)	10 (8.5%)	1 (2.9%)
Diarrhoea	2 (1.3%)	28 (23.7%)	0
Neutrophil count decreased	2 (1.3%)	9 (7.6%)	1 (2.9%)
Aspartate aminotransferase increased	1 (0.6%)	6 (5.1%)	1 (2.9%)
Febrile neutropenia	1 (0.6%)	3 (2.5%)	1 (2.9%)
Influenza	1 (0.6%)	2 (1.7%)	1 (2.9%)
Pyrexia	1 (0.6%)	8 (6.8%)	1 (2.9%)

Serious adverse event/deaths/other significant events

ACE-CL-007

Out of the 33 deaths (6.3%) recorded in the ACE-CL-007 study until DCO, there were 4, 6 and 10 death due to AE in the Acala+Obin, Acala-mono and Clb+Obin arm, respectively. No Grade 5 TEAE/fatal by PT occurred in more than 1 subject, except for Grade 5 events of sepsis (2 [(1.1%]) in the Acala+Obin arm, however, not considered related to treatment. AE Grade 5/fatal outcome that occurred beyond the treatment-emergent period (>30 days after the last study treatment) occurred at the highest rate in the Clb+Obin arm and a higher rate in the Acala mono arm than in the Acala+Obin arm. Two deaths occurred in the crossover population, 1 death due to Richter's transformation (>30 days of last acalabrutinib dose) and the other was due to the TEAE of acute myocardial infarction (within 30 days of last acalabrutinib dose).

The frequency of patients with ≥ 1 SAE any grade was highest in the Acala+Obin combination arm, with focus on SOC infection and infestations. However, SAE Grade ≥3 was in the same range in the 2 acalabrutinib containing arms, 32% and 29%, compared to 19% in the Clb+Obin arm. PT Grade ≥3 Febrile neutropenia (4.1%), was most notable in the Clb+Obin arm, as were tumor lysis syndrome (TLS, 4.7%). SAE TLS occurred in ≤1% in the 2 acalabrutinib containing arms, which is in the same range as for the approved BTK inhibitor (Imbruvica SmPC).

ACE-CL-309

Fifteen (9.7%) subjects who received acalabrutinib and 18 (11.8%) subjects who received IR or BR had died as of the DCO, including 3 subjects in the IR group who died after crossover to acalabrutinib treatment. The most common primary cause of death in all treatment groups was AEs, however, AEs as primary cause of death was less frequent in the Acala-mono arm. PD as primary cause of death was more common in the Acala-mono group; 5 (3.2%), whereof 4/5 (2.6%) during the period beyond 30 days after last dose of study drug, which contrasted with the IR/BR arm, where no deaths due to PD

occurred during the studied period. However, deaths due to Richter's transformation occurred > 30 days after last dose of study drug in the IR/BR arm in 3/1 subjects.

SAEs occurred in 28.6%, 55.9%, and 25.7% of subjects who received Acala, IR, and BR, respectively, and most SAEs were Grade ≥3. The rate of SAEs resolved/unresolved in the different study arms, needs to be clarified. Among subjects treated with Acala, the most common SAE was pneumonia (8 subjects [5.2%]). Among subjects treated with IR, the most common SAEs were diarrhoea (16 [13.6%] subjects), pneumonia (10 [8.5%] subjects), pyrexia (8 [6.8%] subjects), anaemia (4 [3.4%]), and colitis and pneumococcal pneumonia (3 [2.5%] each). Among subjects treated with BR, no SAE occurred in ≥1 subject.

Adverse Events of Special Interest

The following Events of Clinical Interest (ECIs) have been identified based on nonclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitor. The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by SOC, or by sponsor-defined baskets of MedDRA Adverse Event Grouped Terms. The definition of ECIs are identical for study ACE-CL-007 and study ACE-CL-309 and therefor also used for the pooled populations.

Patients with significant cardiovascular disease were excluded from the pivotal studies.

ACE-CL-007

Cardiac events (any grade) were reported in the same fequency,14.0%, in both the Acala+Obin arm and the Acala-mono arm. Cardiac events (any grade) in the Clb+Obin arm were reported at a lower frequency than in either of the Acala arms, 7.7%.

TEAE Atrial fibrillation (any grade) was recorded in 3.4% and 3.9% of the patients in the Acala+Obin and the Acala-mono arm, respectively. In the Clb+Obin arm, atrial fibrillation was recorded only in 1 patient (0.6%).

Other cardiac events occurred in 11.8%, 12.8% and 7.7% in the Acala+Obin, Acala-mono and Clb+Obin treatment arms, respectively. PT Myocardial infarction (inclusive PT acute myocardial infarction) Grade ≥3 occurred in 3 subjects in the Acala+Obin arm, 4 subjects in the Acala-mono arm and 1 subject in the Clb+Obin arm. Except for cardiac failure in 2 patients in the Acala-mono arm, no other cardiac event occurred more than in 1 patient in any treatment arm.

ACE-CL-309

Cardiac events were reported more often in the Acala arm, 13.0%, compared to IR 7.6% or BR 8.6%. Grade ≥3 cardiac events were reported with similar frequency in the Acala and the IR groups, 3.2% and 3.8%, respectively. All cardiac events in the BR group, 8.6%, were of Grade ≥3.

The most common cardiac event by PT was atrial fibrillation, reported in 8 (5.2%, 2 were Grade 3), 3 (2.5%) and 1 (2.9%; Grade 3) subjects in the Acala, IR, and BR treatment groups, respectively. None of the atrial fibrillation events lead to study drug discontinuation.

Other cardiac events occurred in 9.7%, 5.9% and 5.7% in the acalabrutinib, IR, and BR treatment groups, respectively.

In the Acala treatment arm, 6 subjects had SAEs of cardiac events. Three SAEs of atrial fibrillation, one a Grade 3 angina unstable and one Grade 3 acute coronary syndrome, both reported as related to acalabrutinib and the sixth patients had a SAE of Grade 4 cardiac arrest (reported as not related).

Among subjects who received IR, 4 subjects had SAEs of cardiac events and among subjects who received BR, 3 subjects had SAEs of cardiac events.

Pooled populations: The rate of any grade cardiac events (SOC cardiac disorders) occurred at a slightly increased in Mono HemMalig, 15.6% and Combo CLL 19.7%, possibly due to, in part, inclusion of a different study population in the added studies. However, atrial fibrillation occurred at the same level as reported for the pivotal Acala arms, Mono HemMalig (4.5%) and Combo CLL (4.5%). The time from first acalabrutinib dose to onset of atrial fibrillation event ranged from 8 to 1280 days, with a median onset of 521.5 days for subjects in Mono HemMalig.

Regarding other BTK inhibitors, a risk of cardiac arrhythmia, including atrial fibrillation, atrial flutter and cases of ventricular tachyarrhytmia have been reported in patients treated with ibrutinib. However, no causal relationship between acalabrutinib and cardiac arythmias, other than atrial fibrillation/flutter, can be established and since no significant effects were observed in ECG with acalabrutinib in a QT/QTc study, ventricular fibrillation can be monitored with routine pharmacovigilance activities.–

Hypertension

ACE-CL-007

Hypertension events (any grade) were infrequent and occurred in 7.3% in the Acala+Obin arm, 4.5% in the Acala-mono arm and 6 subjects 3.6% in the Clb+Obin arm. Grade 3 hypertension was seen in 2.8%, 2.2% and 3.9% subjects in the Acala+Obin, Acala-mono and Clb+Obin treatment arms, respectively and no Grade 4 or 5 events occurred.

ACE-CL-309

Hypertension events were equally infrequent in the pivotal study ACE-CL-309. Hypertension (all grades) occurred in 3.2%, 4.2% and 0 subjects treated with Acala, IR or BR, respectively. Three subjects treated with acalabrutinib and 1 subject treated with IR had Grade 3 hypertension.

Pooled populations: In the Mono HemMalig pool frequency of hypertension 7.1% of the patients reported with hypertension any grade, Grade ≥3, 3.5%. A higher frequency was reported in the Combo CLL pool, 12.6% and Grade ≥3, 3.6%. For the presently only approved BTK where hypertension is reported (Imbruvica SmPC) with a prevalence increasing for every year of exposure.– Presented data on hypertension from the large pool of patients treated with acalabrutinib monotherapy (MonoHemMalig pool), does not indicate, so far, that continuous exposure (<12 months, >12 months < 24 months or >24 months <36 months) to acalabrutinib is accompanied with an increased risk for hypertension.

Haematology/cytopenia

ACE-CL-007

The acalabrutinib containing arms, in general, had less events of cytopenia compared to the Clb+Obin arm. However, the addition of Obin to Acala increased the frequency of cytopenia compared to Acala alone. Neutropenia all grades occurred at the highest rate in the Clb+Obin arm (49.1%) and the rates were 33.1% and 11.7% the Acala+Obin arm and Acala-mono arm respectively. Almost all events were Grade ≥3.

ACE-CL-309

Leukopenia was the most frequently reported category of cytopenia in all 3 treatment groups, with a lower occurrence in subjects treated with acalabrutinib (21.4%) than IR (53.4%) or BR (37.1%). Neutropenia events (including PTs neutropenia, decreased neutrophil count, and febrile neutropenia) stood for almost all reported Leukopenia events. The almost double rate of neutropenia in the acalabrutinib arm in ACE-CL-307, compared to the Acala-mono of ACE-CL-007, can be explained by the study population, i.e. previously treated CLL patients.

In the acalabrutinib arm 17.5% was Grade ≥3 neutropenia events including 11 subjects with Grade 4 events. There was no Grade 5 neutropenia event, and no neutropenia events led to discontinuation of acalabrutinib.

In subjects treated with IR, Grade ≥3 neutropenia events occurred in 55 (46.6% plus 3 subjects with PT granulocytopenia) and in the BR group 12 (34.3%) subjects. Among subjects in the IR/BR arm, 3 subjects had SAEs of neutropenia or febrile neutropenia.

According to information provided by the applicant, in both pivotal trials, almost all patients with TEAEs Grade≥3 of anaemia (5.6%, 6.7% in the Acala+Obin and Acala mono arm in 007 and 11.7% in the Acala mono arm in 309) received transfusions and/or EPO for the management of the AE anemia.

Pooled populations: In the Mono HemMalig population the rates of anemia, neutropenia and thrombocytopenia were reported in 13.8%, 15.7%, and 8.9%, respectively. Out of these, 7.8%, 14.2%, and 4.8% were Grade ≥3. Of note, the rates of neutropenia and thrombocytopenia in the ComboCLL population were notably higher. The applicant has clarified that also the recurrence rate of neutropenia grade ≥3 TEAE, was higher in the acalabrutinib + obinutuzumab combination arm compared to the acalabrutinib monotherapy arm (ACE-CL-007). The rate of G-CSF usage in subjects in with at least 1 Grade ≥3 TEAE was 46% and 37% respectively (combination vs monotherapy).

The rate, of at least 1 Grade ≥3 TEAE of neutropenia in ACE-CL-309, in the acalabrutinib monotherapy arm (16%) and the rate of G-CSF usage in subjects in Study ACE-CL-309 with at least 1 Grade ≥3 TEAE of neutropenia was 52.0%.

Haemorrhage

ACE-CL-007

Haemorrhage (SMQ term) occurred in 42.7%, 39.1% and 11.8% in the Acala+Obin arm, Acala-mono arm and the Clb+Obin arm, respectively. The most frequent haemorrhage event was contusion (PT) 23.5%, 15.1% and 4.1% in the three treatment arms respectively. The majority of haemorrhage event in Acala containing arms and all events in the Clb+Obin arm, were of Grade 1-2 and. Major haemorrhage Grade ≥3 occurred in 3 patients in each of the two acalabrutinib containing arms and no patient in the Clb+Obin arm.

With respect to reported ischemic cerebrovascular event in study 007 (4 events) it has been difficult to reach a conclusion on the potential relationship with acalabrutinib treatment due to confounding factors. It is, therefore, proposed to include ischemic cerebrovascular events as an important potential risk in the RMP, to further characterise it.

ACE-CL-309

Haemorrhage events occurred more frequently in subjects who received acalabrutinib (26.0%) than in subjects who received IR (7.6%) or BR (5.7%). Grade ≥3 haemorrhage events occurred with similar frequency in subjects treated with acalabrutinib (1.9%), IR (2.5%), and BR (2.9%). Major

haemorrhage events also occurred with similar frequency in the acalabrutinib, IR and BR treatment groups (1.9%, 2.5%, and 2.9%, respectively).

The most common haemorrhage event by PT was contusion, reported in 13 subjects (8.4%) in the acalabrutinib treatment arm and 3 (2.5%) in IR treated subjects and none in the BR group. This was followed by PT haematoma in 5.8%, 1.7% and 2.9% in the acalabrutinib, IR and BR group respectively.

The pattern of haemorrhage events in ACE-CL-007 is the same as in ACE-CL-309 but occurring at a clearly higher frequency in ACE-CL-007. The Acala median exposure time differs in the two pivotal studies (27.7 months vs 15.7 months). The question on incidence over time arises and data has been provided during the present round.

Pooled populations: The frequency of haemorrhage events in Mono HemMalig was 46.3% and Combo CLL, 48.4%. In the Mono HemMalig population, the median time to onset for Grade ≥3 haemorrhage event was 174.0 days (range:4 to 1327 days). Major haemorrhage events were reported for Mono HemMalig in 3.6% and Combo CLL in 3.6%. Four (4) subjects had their study treatment permanently discontinued due to a haemorrhage event. All were assessed as related to acalabrutinib (3) or acalabrutinib and obinutuzumab (1), three were reported resolved and one continuous (ITP). The most frequently reported major haemorrhage was haematoma (n=5), followed by epistaxis and retinal haemorrhage (n=4 each), gastrointestinal haemorrhage (n=3), and gastric haemorrhage, haematuria, and intracranial haemorrhage (n=2 each). Other major haemorrhage events occurred in 1 subject each, including 4 events in the CNS (cerebral microhaemorrhage, intracranial haematoma, subarachnoid haemorrhage, and traumatic intracranial haemorrhage).

Hepatotoxicity

ACE-CL-007

Since patients with AST/ALT >3.0 x ULN and total bilirubin >1.5 x ULN were excluded from study ACE-CL-007 no subject entered the study with significant hepatic impairment, no analysis on TEAEs by baseline hepatic function is feasible.

With respect to ALT and AST, no temporal trend is noted. A slight increase over time, in mean bilirubin is noted. Judging by the total level of bilirubin, this is presently of no clinical concern.

The Acala-mono arm had a lower frequency of hepatotoxicity events than subjects in the other 2 treatment arms. Subjects in the Acala+Obin treatment arm had the highest frequency of hepatotoxicity events across the 3 treatment arms. Grade ≥3 hepatotoxicity events occurred in 5.1% in the Acala+Obin arm, compared to 0.6% in the Acala mono arm.

A total of 6 subjects (2 subjects in each treatment arm) fulfilled the biochemical criteria for Hy's law (elevations ≥3×ULN in ALT or AST concurrent with total bilirubin ≥2×ULN). In four subjects no action was taken with study medication, in 1 subject, acalabrutinib therapy was interrupted but restarted and in 1 patient acalabrutinib was discontinued. The applicant conducted a review of the laboratory and clinical data for each case described above and determined that these were not true Hy's law cases. This conclusion is agreed.

ACE-CL-309

Hepatotoxicity was much less common in the Acala arm compared to the IR/BR arm. Hepatic toxicity is however, a known ADR with the frequency very common, with respect to idelalisib, and for bendamustin with the frequency common.

No SAEs of hepatotoxicity events or Grade 4 or Grade 5 hepatotoxicity events occurred in the acalabrutinib arm in ACE-CL 309, while three subjects treated with IR had serious hepatotoxicity events and four additional subjects had non-serious Grade 4 hepatotoxicity.

Pooled populations: In the Mono HemMalig population, hepatotoxicity events were reported in 3.7% of subjects. Grade ≥3 TEAEs of hepatotoxicity occurred in 1.7% of subjects. In the Mono HemMalig population, the most common hepatic AE (all grades) was ALT increased (2.0%). The frequency of all grades and Grade ≥3 hepatic AEs higher in the Combo CLL (7.2%, 4.0%) population.

Infections

ACE-CL-007

Infections occurred more frequently in the two acalabrutinib containing arms, 69.1% in the Acala+Obin arm and 65.4% in the Acala-mono arm. The most frequent infection events, in both arms, were upper respiratory infections, and second in order, urinary tract infections. Grade ≥3 events occurred in 20.8% and 14.0%, respectively.

One case of PML (Grade 3 SAE) was reported in a patient in the Acala+Obin arm, who earlier had discontinued obinutuzumab after just one dose, due to neutropenia. The event was reported as related to acalabrutinib. The event led to discontinuation of study drug.

Hepatitis B reactivation (Grade 2) was reported in 2 cases in the Acala+Obin arm and considered related to obinutuzumab and acalabrutinib. This led to discontinuation of study drug in both subjects.

Subjects in the Clb+Obin arm had infection events at lower rates than subjects in the other 2 treatment arms. The most frequent infection events were upper respiratory infections in 8.3% and urinary tract infections in 4.7%. Grade ≥3 events occurred in 8.3%.

ACE-CL-309

Infections occurred in 56.5%, 65.3%, and 48.6% of subjects treated with Acala, IR, or BR, respectively, and Grade ≥3 infections occurred in 14.9%, 28.0%, and 11.4% of subjects in the 3 treatment groups, respectively. The most common infections in all treatment groups were upper respiratory tract infection, reported in 22 (14.3%), 17 (14.4%), and 4 (11.4%) subjects in the 3 treatment groups, respectively.

Twenty subjects who received acalabrutinib had SAEs of infection, of which the most common of which was pneumonia (8 subjects).

Hepatitis B reactivation was reported for 2 patients in the acalabrutinib arm. One was of Grade 3 Hepatitis B reactivation and 1 of Grade 1. None were reported as SAEs.

Pooled populations: In the Mono HemMalig population infections occurred in 66.7% with the most common event upper respiratory tract infection (22%). In the Combo CLL infections occurred in 74% with the most common event upper respiratory tract infection (31.4%).

Herpes zoster reactivation was reported in all pooled populations but with a higher frequency in the Combo CLL pool (4.9%). In Mono HemMalig and ComboCLL populations, there were also Grade ≥3 HZV/HSV infections reported. Since both HBV and HSV/ Herpes zoster reactivations have been

reported in acalabrutinib combination treatment and acalabrutinib mono treatment this should be clarified in the SmPC.

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis in Acala-mono and Acala+Obin treatment, was reported ~1%, The IR group had a significantly higher ILD frequency, 6.8%, Grade ≥3 events in 3.4%. The data does not support inclusion of ILD in the SmPC, however, the applicant presented arguments against including ILD as an important potential risk in the RMP. The arguments are accepted. Routine pharmacovigilance activities are expected to suffice.

Second Primary Malignancies (Including and Excluding Skin)

ACE-CL-007

Second primary malignancies (any grade) occurred in 19 (10.7%), 15 (8.4%) and 6 (3.6%) subjects in the Acala+Obin arm, Acala-mono arm, and Clb+Obin arm, respectively. Basal cell carcinoma was the most frequent second primary malignancy (any grade) in the Acala+Obin and Acala-mono treatment arms (7 subjects [3.9%] and 8 subjects [4.5%], respectively). All Grade ≥3 events of second primary malignancies (by PT) occurred in ≤2 subjects with the exception of basal cell carcinoma. The median time to first onset of SPMs was in the Acala+Obin arm 226 d, in the Acala-mono arm 136 d and in the Clb+Obin arm 41 d.

Treatment-Emergent Events of Clinical Interest: Second Primary Malignancies, excluding non-melanoma skin (Safety Population)

ECI Category ECI Subcategory Preferred Term	No. (%) of Subjects					
	Arm B Acalabrutinib+ Obinutuzumab (N=178)		Arm C Acalabrutinib Monotherapy (N=179)		Arm A Obinutuzumab+ Chlorambucil (N=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Second primary malignancie excluding non-melanoma skin	6)	6 (3.4)	5 (2.8)	2 (1	3 (1.8)	2 (1.2)
Non-small cell lung cancer	2 (1.1)	1.1)	0	0		
Squamous cell carcinoma	1)	0.6)	0	0		
Basosquamous carcinoma	.6)	0	0	0	0	0
Bladder transitional cell carcinoma	1 (0.6)	0	0	0	0	0
Breast cancer	1 (0.6)	1 (0.6)	0	0	0	0
Gastric cancer stage IV	1 (0.6)	1 (0.6)	0	0	0	0
Metastases to bone	1 (0.6)	1 (0.6)	0	0	0	0
Prostate cancer	1 (0.6)	0	2 (1.1)	0	1 (0.6)	0
Renal cell carcinoma	1 (0.6)	0	0	0	0	0
Acute myelomonocytic leukaemia	0	0	0	0	1 (0.6)	1 (0.6)
Glioblastoma	0	0	1 (0.6)	1 (0.6)	0	0
Lung adenocarcinoma	0	0	0	0	1 (0.6)	1 (0.6)
Malignant melanoma in situ	0	0	1 (0.6)	0	0	0
Transitional cell carcinoma	0	0	1 (0.6)	1 (0.6)	0	0

ECI=event of clinical interest; IV=4.

[a] Subject [redacted] had a Grade 1 SAE of squamous cell carcinoma of the left cheek on Day 349 that resolved on Day 414 with a medical procedure. The event was related to acalabrutinib. Study medication was not changed. Subject [redacted] had a Grade 3 SAE of squamous cell carcinoma (epidermoid) on Day 72 that was ongoing; acalabrutinib and obinutuzumab were discontinued due to the event. The subject was subsequently treated with radiotherapy. The event was not related to study medication (Listing 16.2.7.4).

[b] Subject [redacted] had a Grade 2 nonserious AE of basosquamous cell carcinoma of the nose on Day 194 that resolved that same day with a medical procedure. The event was related to acalabrutinib and obinutuzumab; study medication was not changed (Listing 16.2.7.4).

[c] Subject [redacted] had a Grade 5 SAE on Day 952 of metastases to bone (multiple bone metastases) from recurrence of prostate cancer that was fatal on Day 1068. The event was not related to study medication (Listing 16.2.7.4).

A subject with multiple severity grades for a given TEAE was counted only once under the maximum severity.
MedDRA version 21.1.

Further, 13 events of SPMs were identified outside the treatment-emergent period or were preferred terms of second primary malignancy not captured by the ECI definition criteria. Eleven of these occurred in the Clb+Obin arm, (not counting patients the cross-over cohort) and 2 in the Acala-mono arm. Out of these eleven cases in the Clb+Obin arm, only two were SPMs not counting non-melanomas skin cancer.

ACE-CL-309

Treatment-emergent second primary malignancies occurred in 11.7%, 2.5% and 1 (2.9%) subjects in the acalabrutinib, IR, and BR treatment groups, respectively. Grade ≥3 events occurred in 6 (3.9%) subjects treated with acalabrutinib and 1 (2.9%) subject treated with BR. Seven Acala-treated subjects had SAEs of second primary malignancies, including 2 subjects with Grade 5 events (lung neoplasm malignant [1] and neuroendocrine carcinoma [1]). One subject had a non-serious event of Grade 3 bladder transitional cell carcinoma, that was reported as related to acalabrutinib treatment.

In the pooled populations the frequency of SPMs (nonmelanoma skin only) increased every year from initiation of study treatment. Likewise, the frequency of second primary malignancy (excluding nonmelanoma skin) increased every year from initiation of study treatment.

Tumour Lysis Syndrome

In the Acala mono arms, TLS occurred in either 0% or ≤1%. In the Acala+Obin groups, TLS occurred with a slightly higher frequency. Of the both pivotal studies all treatment arms, subjects receiving the combination of Clb+Obin were at the highest risk of experiencing TLS.

Laboratory findings

Among subjects treated with acalabrutinib, there were no clinically meaningful trends in haematology or clinical laboratory values, serum immunoglobulin values, or vital sign values. In the acalabrutinib-containing treatment arms, the trend toward worsening of baseline toxicity grade was limited to decreased neutrophils and platelets, and increased leukocytes. In the obinutuzumab-containing treatment arms, a trend toward worsening of baseline toxicity grade for the haematology parameters of decreased neutrophils, haemoglobin and platelets. With respect to baseline level of $CD4^+$, $CD8^+$ lymphocytes (T-lymphocytes) and NK cells, a slight decrease was seen in the Acala+Obin and Acala-mono arm. A more obvious decrease was, however, seen in the Clb+Obin arm. $CD19^+$ (B-cells) cells decreased in all three treatment arms but was most pronounced in the Clb+Obin arm.

The most common Grade 3 or 4 laboratory abnormality was increased urate, reported in 29.2%, 22.3% and 37.3% of subjects in the Acala+Obin, Acala-mono, and Clb+Obin treatment arms, respectively. This was sees without any change in S-Creatinine. In Study ACE-CL-007, the median time to maximum increase in urate varies between the three treatment groups but seems to be more related to study treatment initiation in the two obinutuzumab containing arms, rather than related to acalabrutinib. Surprisingly, no clear conclusion can be drawn, with respect to relationship between TLS and urate increased, from study ACE-CL-007.

Abnormalities in ALT, alkaline phosphatase and AST occurred notably less frequently the acalabrutinib arm compared to the IR and BR groups. In addition, albumin was decreased in a higher rate, in the latter two groups. Laboratory shifts ≥3 were significantly more frequent in the IR/BR arm.

Compared to the Mono HemMalig pool, the ComboCLL pool had higher rates of shifts in laboratory parameters. However, the clinical importance concerning shifts in laboratory levels, without knowledge of concurrent clinical events cannot be concluded.

In the pivotal study ACE-CL-007, treatment induced lymphocytosis only occurred in the two acalabrutinib containing arms, slightly more in the monotherapy arm, compared to the combination arm. The onset and duration of lymphocytosis in Acala-mono arms are in concordance between the two pivotal studies and repeated in the pooled populations. However, duration of lymphocytosis was shorter when acalabrutinib and obinutuzumab was combined. Lymphocytosis was less marked and with shorter duration, in the IR treated group in pivotal study ACE-CL-309 and more or less absent in Clb+Obin and BR treatment. The were no reports of leukostasis.

Vital signs, ECG, blood pressure and related observations

Based on the findings of a Phase 1 thorough QT/QTc study, conducted in 48 healthy adult subjects (Study ACE-HV-005), therapeutic or supratherapeutic plasma acalabrutinib concentrations in healthy subjects and previously treated CLL subjects, did not prolong the QTc interval in a thorough QT study, nor cause any shift in relevant electrocardiographic measurements.

ECGs were performed at Screening only, in two pivotal studies. During screening for the study ACE-CL-007, 4 patients in the Acala+Obin arm, 3 subjects in the Acala-mono arm and 2 subjects in the Clb+Obin arm met the criteria of QTcF or QTcB >480 msec. All these 9 subjects were enrolled under Protocol Amendment 2.0 which did not have an exclusion for QTcF or QTcB >480 msec, hence these were not considered to be important protocol deviations. However, no ventricular tachyarrhythmias were reported in any of the study arms during the treatment period.

In the study ACE-CL-309, no patients met the criteria of QTcF >480 ms. One patient had a significant abnormal ECG at baseline. No ventricular tachyarrhythmias were reported in study ACE-CL-309.

Safety in special populations

Renal impairment

Patients with severe renal impairment (creatinine >2.5×ULN, estimated CrCl <30 (using Cockcroft-Gault formula i.e. Grade ≥3 renal impairment), were not included in the clinical development program. In the Mono HemMalig population, 33.3% of the subjects had normal renal function, 40.9% of the subjects had mild renal dysfunction and 24.1% of the subjects had moderate renal dysfunction. Anemia, neutropenia, decreased appetite, and pneumonia were Grade ≥3 AEs reported in ≥2 percentage points more subjects with moderate renal dysfunction than subjects with normal renal function.

Hepatic impairment

The two pivotal studies included only patients with a baseline hepatic impairment Grade ≤1. This was also the case with the supportive studies included in the pooled populations. 12 subjects with mild to moderate hepatic impairment, received acalabrutinib in PK/pharmacodynamics studies.

In Mono HemMalig population 858 (82.0%) subjects with normal hepatic function, 160 (15.3%) subjects with mild hepatic function, and 9 (0.9%) subjects with moderate hepatic function were enrolled. The incidence in subjects with normal hepatic function, mild hepatic function and moderate hepatic function (n=1), experiencing any AE, and the proportions of subjects with specific AEs, were generally similar between the hepatic function subgroups.

Sex

Male subjects were 67.9% in the Mono HemMalig population. Most of male and female subjects experienced any AE, and the proportions of subjects with specific AEs were generally similar between the sexes. The most common AEs (all grades), that were reported in ≥ 5 % more in female than male subjects were anaemia (16.7% vs 11.6%), neutropenia (16.4% vs 10.4%), petechiae (14.3% vs 8.9%), and urinary tract infection (14.9% vs 5.4%). In addition, Grade ≥3 AEs reported in ≥2 % more in female than male subjects were anaemia and neutropenia.

Age

In the Mono HemMalig population, 37.5% of the subjects were ≤65 years old, 41.1% of the subjects ≥65 years but ≤75 years and 22.0% were≥75 years.

The proportion of patients experiencing any AE were generally similar between the age groups, as were the proportions of subjects with specific AEs. Headache and sinusitis were reported in more subjects (≥10 %) in the younger category. Grade ≥3 anaemia was reported in more subjects in the oldest category, compared to subjects in the younger categories.

	Mono HemMalig (N=1040)			
MedDRA Terms	Age <65 (n=388)	Age ≥ 65 and < 75 (n=424)	Age ≥ 75 and < 85 (n=207)	Age ≥ 85 (n=21)
Total AEs	368 (94.8%)	411 (96.9%)	201 (97.1%)	21 (100.0%)
Serious AEs – Total	124 (32.0%)	170 (40.1%)	99 (47.8%)	12 (57.1%)
Fatal	8 (2.1%)	23 (5.4%)	12 (5.8%)	4 (19.0%)
Hospitalization/prolong existing hospitalization	118 (30.4%)	157 (37.0%)	95 (45.9%)	12 (57.1%)
Disability/incapacity	2 (0.5%)	1 (0.2%)	4 (1.9%)	0
Other (medically significant)	9 (2.3%)	9 (2.1%)	6 (2.9%)	0
AE leading to drop-out	24 (6.2%)	42 (9.9%)	24 (11.6%)	4 (19.0%)
Psychiatric disorders	73 (18.8%)	75 (17.7%)	37 (17.9%)	6 (28.6%)
Nervous system disorders	236 (60.8%)	222 (52.4%)	112 (54.1%)	8 (38.1%)
Accidents and injuries	0	0	0	0
Cardiac disorders	51 (13.1%)	70 (16.5%)	39 (18.8%)	2 (9.5%)
Vascular disorders	91 (23.5%)	91 (21.5%)	51 (24.6%)	4 (19.0%)
Cerebrovascular disorders	0	0	0	0
Infections and infestations	253 (65.2%)	284 (67.0%)	141 (68.1%)	16 (76.2%)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	67 (17.3%)	82 (19.3%)	61 (29.5%)	6 (28.6%)

Abbreviations: AE=adverse event; Mono HemMalig=acalabrutinib monotherapy hematologic malignancies.
Note: The Mono HemMalig population consists of subjects from all hematological malignancies studies.

Immunological events

No relevant findings were seen, immunological events were not specifically studied.

Safety related to drug-drug interactions and other interactions

See clinical pharmacology section.

Discontinuation due to adverse events

In the Acala mono arms in the two pivotal studies, dose interruptions occurred due to AEs in 15.6%, 18.8%, in ACE-CL-007 and ACE-CL-309, respectively. The events of infusion related interruptions

occurred to a notably lesser extent in the Acala+Obin combination compared to Clb+Obin combination (21.3% versus 49,1%). Similar data was shown in the pooled populations.

The rate of study drug discontinuations in the acalabrutinib arms in the pivotal studies as well as the pooled populations was at the range of 9-10%. In addition, the discontinuation rate due to AEs in the crossover group in study ACE-CL-007 was 6.7% and the crossover group in study ACE-CL-309 was 8.6%. Chlorambucil was discontinued in 14% of the patients while any discontinuation in the IR/BR arm (combined), was 44.4%. Discontinuation of obinutuzumab in the 2 obinutuzumab-containing arms was 6% and the most common reasons were infusion related reactions and neutropenia.

Post marketing experience

No further safety findings were identified from marketing experience.

2.6.1. Discussion on clinical safety

The application is based on interim analyses of 2 pivotal studies, relevant to the claimed indication, i.e. CLL and additional 8 supportive studies, together making up the different pooled populations. The largest pool, Mono HemMalig consists of 1040 subjects, from all hematologic malignancy studies in which subjects received at least 1 dose of acalabrutinib monotherapy including subjects who crossed over from any control arm in the pivotal trials. The majority in the pool was CLL patients. The size of the safety data base is deemed adequate to assess the tolerability of acalabrutinib.

The mean duration of acalabrutinib exposure, combined for the two monotherapy arms was, as of the primary analysis, in the pivotal studies 19.3 months and in the Mono HemMalig pool, 24.6 months. In the Mono HemMalig pool, 72% were exposed >12 months and 51% more than 24 months. The time of exposure is considered adequate to assess TEAEs during short and medium time of exposure. The final reports and outstanding data on long-term safety, should be part of post-authorisation measures.

In the pivotal study ACE-CL-007 (previously untreated), the substantially longer duration of treatment in the two acalabrutinib containing arms vs the Clb-Obin arm, should be noted when comparing AE rates. The same applies to the second pivotal study, ACE-CL-309 (relapsed/refractory) in which the BR group in arm B had a 6 months treatment period while the IR population received treatment until PD or unacceptable toxicity.

ACE-CL-007 (first line): In the Acala+Obin arm, fatal events occurred in the absence of disease progression in 6/178 (3.4%) of the patients and in the Acala-mono arm in 10/179 (5.6%) patients. In the Obin+Clb arm there were 12/169 (7.1%) deaths in the absence of disease progression. TEAEs leading to dose discontinuation of acalabrutinib were comparable in both acalabrutinib containing arms (Acala+Obin:10.7% and Acala-mono:9.5%) and the discontinuation rates for Obin were comparable in both obinutuzumab containing arms (Acala+Obin: 6.5% and Obin+Clb: 5.9%). TEAEs leading Clb discontinuation was 14.2%. TEAEs Grade ≥3 were reported in 70.2% in the Acala+Obin arm, with the most common AE neutropenia (29.8%) and infections (20.8%). In the Acala-mono arm, the TEAEs Grade ≥3 event rate was 49.7%, with the most common AEs infections (14%) and neutropenia (9.5%). For the Obin+Clb arm TEAEs Grade ≥3 was 69.8% with the most commonly reported AE Grade ≥3 neutropenia (41.1%) and thrombocytopenia (11.8%).

SAEs Grade ≥3 were reported in 38.8%, 29.6% and 19.5% in the Acala+Obin arm, Acala-mono arm and Obin+Clb arm, respectively. Infusion related reactions (Obin) occurred in 13.5% in the Acala+Obin arm (Grade ≥3, 2.2%) and in 39.6% in the Obin+Clb arm (Grade ≥3, 5.3%). SPMs were reported in 5.6% in the Acala+Obin arm, 2.8% in the Acala-mono arm and 1.8% in the Obin+Clb arm.

ACE-CL-309 (relapsed/refractory): In the Acala arm, fatal events occurred in the absence of disease progression in 9/154 (5.8%) patients and in the IR/BR arm in 10/4 (n=118/35; 8.4%/11.4%) patients. TEAEs leading to dose discontinuation occurred in 10.4% in the Acala arm and in 52.5% /17.1% in the IR/BR arm. TEAEs Grade ≥3 were reported in the Acala arm in 49.4%, the most common AEs neutropenia (15.6%) and anaemia (11.7%). In the IR group TEAE Grade ≥3 occurred in 89.8%, with the most common AEs neutropenia (39.8%) and diarrhoea (27%). In the BR group TEAEs Grade ≥3 were reported in 48.6% with the most common AEs neutropenia 31.4% and anaemia in 8.6%. SAEs Grade ≥3 were reported in the Acala arm in 26.6% and in IR/BR in 50.8% /25.7%.

The major safety issues noted with acalabrutinib as events of clinical interest in the Mono HemMalig population include: Atrial fibrillation/flutter, any grade, was reported in 4.4% of subjects. Grade ≥3 events were reported in 1.3% of subjects. Anaemia, neutropenia, and thrombocytopenia were reported in 13.8%, 15.7%, and 8.9% of subjects, respectively. Overall frequency of haemorrhage events; 46.3%. Major haemorrhage event was reported in 3.6%, with the most frequently reported sites; the GI tract, the CNS and epistaxis. SPMs were reported in 12.2% whereof the most frequent were skin malignancies (BCC 3.8% and SCCS 2.9%). SPMs, excluding nonmelanoma skin neoplasms, were reported in 6.5% of the subjects.

Overall, the size of the database suggest confidence with respect to most safety issues, further data will be provided with the submission of the final study reports (see RMP).

The nonclinical program has identified kidney, liver and heart as target organs of toxicity of acalabrutinib in rats and dogs. Macroscopic and microscopic findings in these organs were observed at doses above the maximum tolerated dose.

With respect to kidney and liver, the clinical relevance of the non-clinical findings is unclear. From the data submitted, no safety signals/ concerns have been evoked relevant to these findings. Subjects with severe renal impairment or end-stage renal disease have not been studied. Furthermore, it is not recommended to administer acalabrutinib in patients with severe hepatic impairment (see section 4.2 and 4.4 of the SmPC).

Cardiac events, beyond atrial fibrillation, occurred at a higher rate in acalabrutinib containing arms in both pivotal studies, compared to the comparator arms and must be further characterized. Use in patients with moderate to severe cardiac impairment is included in the safety specifications as missing information. Therefore, data from the final reports for the ongoing studies, will be informative for further characterisation of the safety profile of acalabrutinib. Hypertension is an Important Identified Risk, with an increasing prevalence over time exposed, for the approved BTK inhibitor, Ibrutinib. However, at this point, continuous exposure to acalabrutinib does not seem to increase the risk for hypertension.

The inherent risk, for CLL patients, to develop SPMs makes the true acalabrutinib related increase of SPM still not fully characterised and SPMs are presently included as Important identified risk in the safety specification. It has been identified that the applicant does not plan to follow the patients with respect to SPMs, for the duration of the in the pivotal study ACE-CL-007, after a PFS event. SPMs will be further characterized within the scope of clinical Study D8220C00008 (see RMP)

With respect to the updated safety analysis, with a data cut-off date of 01 August 2019, providing around 6 months of additional follow-up and an increase in median duration of treatment exposure of 6 months, the safety profile seems to be consistent with the primary analysis. With regards to the proposed extrapolation to more fit patients than those studied in first line, this does not present a problem from the safety point of view, as greater rather than lesser tolerability of AE's is assumed.

Overall, acalabrutinib presents with an acceptable safety profile, while the addition of obinutuzumab was associated with, in some respects, a substantial increase in toxicity. However, the higher

frequency and grade of severities of the TEAEs reported, in the combination group, did not translate into a corresponding high proportion of permanent discontinuations or a decreased relative dose intensity. Furthermore, the chosen comparators, in the pivotal studies did in many aspects appear to have a less favourable safety profile, also compared to the acalabrutinib+obinutuzumab combination group. Long term safety data will be provided (see RMP).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In the safety database assessed acalabrutinib presents with a manageable safety profile.

The CHMP considers the following measures necessary to address the missing information regarding long term safety and second primary malignancies:

- Submission of clinical Study D8220C00008; Submission of final CSRs of the pivotal studies 007 and 309 (see RMP).

2.7. Risk Management Plan

Safety concerns

Table 24: Summary of safety concerns

Important Identified Risks	Haemorrhage with or without association with thrombocytopenia Serious infections with or without association with neutropenia Second primary malignancy Atrial fibrillation/flutter
Important Potential Risks	Cerebrovascular events
Missing Information	Long-term safety Use in patients with moderate to severe cardiac impairment

Pharmacovigilance plan

Table 25: On-going and planned additional pharmacovigilance activities

Study & Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				

Study & Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study D8220C00008 is a Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with CLL Ongoing	The primary objective of this study is to evaluate the safety and tolerability of CALQUENCE monotherapy in approximately 600 subjects with TN or R/R CLL who may receive CALQUENCE for 48 cycles of study treatment (28 days per cycle).	Long term safety and SPM	Interim report	31/03/2021
			Final report	31/12/2025
Cohort to Study D8220C00008 is a Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with CLL Planned	The primary objective of the cohort is to evaluate the safety of CALQUENCE in patients with moderate to severe cardiac impairment	Moderate and severe cardiac impairment	Protocol amendment submission	30/09/2020
Study ACE-CL-007 and Study ACE-CL-309	The primary objective of these studies is to evaluate the efficacy and safety of CALQUENCE in treatment naive CLL patients (as monotherapy or combination therapy with obinutuzumab) and in relapsed/refractory CLL patients (as monotherapy)	Long Term Safety and SPM	Final reports	31/07/2022

Risk minimisation measures

Table Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures
Haemorrhage with or without association with thrombocytopenia	**Routine risk minimisation measures**: **Routine risk communication**: **SmPC section(s) 4.4 and 4.8** **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4

Table Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk Minimisation Measures**
Serious infections with or without association with neutropenia	**Routine risk minimisation measures**: **Routine risk communication**: SmPC section(s) 4.4 and 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4
Second primary Malignancy	**Routine risk minimisation measures**: **Routine risk communication**: SmPC section(s) 4.4 and 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4
Atrial fibrillation/flutter	**Routine risk minimisation measures**: **Routine risk communication**: SmPC section(s) 4.4 and 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4
Cerebrovascular events	None
Long-term safety	**None**
Use in patients with moderate to severe cardiac impairment	**None**

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is IBD is 31 October 2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of acalabrutinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Calquence (acalabrutinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

3.1.2. Available therapies and unmet medical need

In the frontline setting, the treatment approach is determined by several key factors which include prognostic molecular markers such as cytogenetic abnormalities and mutational status of the B-cell receptor (BCR) immunoglobulin heavy-chain variable (IGHV) genes, age, and co-morbidities.

While fludarabine-based chemoimmunotherapy is standard for treatment-naive younger/fitter patients with CLL, the therapy for older patients or patients with co-morbidities is less well defined. The combination of obinutuzumab+chlorambucil is indicated in patients with comorbidities making them unsuitable for full-dose fludarabine. According to the current ESMO guideline, it is recommended that patients with TP53 deletion/mutation are treated with ibrutinib in front-line. Because of severe infectious complications, the PI3K inhibitor idelalisib combined with rituximab is only recommended for frontline therapy in patients not suitable for Btk inhibitors.

In the relapse and refractory disease, targeted therapies against B cell markers/antigens (venetoclax) or against components of the B cell receptor such as BTK (ibrutinib) or phosphoinositide-3 kinase (PI3K)δ (idelalisib) have demonstrated efficacy with less toxicity. Bendamustine in combination with rituximab is also an alternative in this population.

3.1.3. Main clinical studies

ACE-CL-007 was a Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP- 196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia.

ACE-CL-309 was a Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia. Subjects were required to have received ≥1 prior systemic therapy for CLL to be eligible to enrol. Prior exposure to a B-cell lymphoma (BCL)-2 inhibitor (e.g., venetoclax/ABT-199) or a B-cell receptor (BCR) inhibitor (e.g., BTK inhibitors or PI3K inhibitors) was not allowed.

Both studies excluded subjects with significant cardiovascular disease, history of stroke or intracranial haemorrhage within 6 months before randomization, or known history of a bleeding diathesis, and subjects who required anticoagulation with vitamin K antagonists, treatment with proton-pump inhibitors or a strong CYP3A inhibitor/inducer.

3.2. Favourable effects

In previously untreated CLL (study 007) with a median-follow up of 28 months and an event rate of 52% in the control arm IRC-assessed PFS for Acala+Obin *vs* clb+obi, the primary outcome, showed a HR of 0.10 [95% CI: 0.06, 0.17]; p<0.0001, in favour of the Acala+Obin arm. The sensitivity analyses are supportive of this outcome. The median estimated PFS for the experimental arm was not reached; the median estimated PFS for the control arm was 22.6 months (95%CI: 20.2, 27.6). In terms of HR for PFS, the subgroup analyses consistently favour the experimental arm. IRC-assessed PFS for acalabrutinib monotherapy *vs* clb+obi, the key alpha-controlled secondary outcome, showed a HR of 0.20 [95% CI: 0.13, 0.30]; p<0.0001 in favour of the experimental arm. The sensitivity analyses are supportive of this outcome. The median estimated PFS for acalabrutinib monotherapy was not reached; the median estimated PFS for the control arm was 22.6 months (95%CI: 20.2, 27.6). In terms of HR for PFS, the point estimates for the subgroup analyses consistently numerically favour the acalabrutinib monotherapy arm.

The activity of the acalabrutinib combination is slightly higher in the del17p/TP53 mutation-negative subgroup (95% vs 84% in the positive subgroup), while similar for the subgroups with acalabrutinib monotherapy where the activity corresponds to the activity of the acalabrutinib combination in the del17p/TP53 mutation-positive subgroup. The ORR of the control regimen is roughly similar to what is noted with acalabrutinib monotherapy in the negative subgroup but considerably lower than both experimental arms in positive disease, 56%. HR of 0.47 (0.21, 1.06) is reported for the acalabrutinib combination *vs* control, and a HR of 0.60 (0.28, 1.27) for acalabrutinib monotherapy *vs* control, both in favour of the experimental regimens.

In relapsed or refractory CLL (study 309) with a median-follow up of 16 months (cutoff January 2019) and an event rate of only 44% in the control arm IRC-assessed PFS showed a HR of 0.31 [95% CI: 0.20, 0.49]; p<0.0001, in favour of the experimental arm. The median estimated PFS for the experimental arm was not reached; the median estimated PFS for the control arm was 16.5 months (95%CI: 14.0, 17.1). The performed sensitivity analyses are supportive of the primary outcome. The subgroup analyses consistently favour the experimental arm. It is noted that the point estimate for PFS HR is 0.21 for the subgroup of subjects with del 17p or TP53 mutation (n=87) while 0.36 in the complementary group. With an event rate of 44% in the control arm, similar as for the primary analysis, the HR for investigator-assesses PFS, a secondary endpoint, was 0.28 (0.18, 0.45), p <0.0001, and thus consistent with the primary analysis. Updated results (cutoff 1 August 2019) based on investigator's assessment: With a median follow-up of 22.1 months (range: 0.53-29.11) in the acalabrutinib arm and 21.9 months (range: 0.03-27.73) in the IR/BR arm, and event rates of 58% in the control arm and 23% in the experimental arm, the PFS HR was 0.27 [95% CI: 0.18, 0.40]; p<0.0001. The outcome is supported by the performed sensitivity analyses. The median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.8 months (95% CI: 14.1, 22.4). With 6 months longer follow-up, and an acceptable PFS maturity of 58% in the control arm, outcomes remain essentially stable.

With a median follow-up of around 16 months event rates for OS were low, 12% in the control arm and 10% in the experimental arm. HR was 0.84 (0.42, 1.66). At the updated analysis, with a median follow-up of 22 months and 21 events in the acalabrutinib arm and 26 events in the control arm, HR was 0.78 (0.44, 1.40).

Per IRC assessment, the median duration of response was 13.6 months in the control arm and not reached in the experimental arm; HR 0.33 (0.19, 0.59); at the updated analysis using investigator-assessed DOR, the corresponding figures were 18 months, not reached, 0.19 (0.11, 0.33). The HR was 0.35 (0.21, 0.58). At the updated analysis, the HR was 0.30 (0.20, 0.46).

3.3. Uncertainties and limitations about favourable effects

In study 007 with an event rate of only 10% in the control arm, and 5% in the Acala+Obin arm and 6% in the monotherapy arm, data on OS is, as expected for a first-line treatment of CLL with a median of 28 months of follow-up, immature. In addition, the massive cross-over from the control arm to acalabrutinib monotherapy makes relative OS data practically non-interpretable.

In study 309 based on event fractions of 34% in the control arm, including cross-over (23%), and 14% in the experimental arm, the median time to next treatment was not reached for any of the study arms. The median time from first dose to subsequent anticancer therapy was 10 months in the experimental arm. Further follow up with special emphasis on time to subsequent therapy will be needed and this is expected to be included in the final clinical study report of the pivotal studies.

3.4. Unfavourable effects

The safety database comprises 1,040 subjects from 9 studies (Mono HemMalig) in patients receiving monotherapy acalabrutinib and 2 studies (ComboCLL, n=223) in patients receiving the combination of acalabrutinib and obinutuzumab, in total 10 studies. Median time of FU is 24.6 months for the Mono HemMalig pooled population. All studies were still ongoing at respective DCO, ranging from Oct 2017 and Feb 2019. With respect to the two randomised pivotal studies (ACE-CL-007 DCO 08 Feb 2019 and ACE-CL-309 DCO 15 Jan 2019), both efficacy and safety data are derived from the first interim analyses.

TEAEs leading to dose discontinuation of acalabrutinib in ACE-CL-007 were comparable in both acalabrutinib containing arms (Acala+Obin:10.7% and Acala-mono:9.5%) and the discontinuation rates for Obin were comparable in both obinutuzumab containing arms (Acala+Obin: 6.5% and Obin+Clb: 5.9%). TEAEs leading Clb discontinuation was 14.2%. TEAEs Grade ≥3 were reported in 70.2% in the Acala+Obin arm, with the most common AE neutropenia (29.8%) and infections (20.8%). In the Acala-mono arm, the TEAEs Grade ≥3 event rate was 49.7%, with the most common AEs infections (14%) and neutropenia (9.5%). For the Obin+Clb arm TEAEs Grade ≥3 was 69.8% with the most commonly reported AE Grade ≥3 neutropenia (41.1%) and thrombocytopenia (11.8%). SAEs Grade ≥3 were reported in 38.8%, 29.6% and 19.5% in the Acala+Obin arm, Acala-mono arm and Obin+Clb arm, respectively. Infusion related reactions (Obin) occurred in 13.5% in the Acala+Obin arm (Grade ≥3, 2.2%) and in 39.6% in the Obin+Clb arm (Grade ≥3, 5.3%).

SPMs were reported in 5.6% in the Acala+Obin arm, 2.8% in the Acala-mono arm and 1.8% in the Obin+Clb arm.

In the Acala arm in ACE-CL-309, fatal events occurred in the absence of disease progression in 9/154 (5.8%) patients and in the IR/BR arm in 10/4 (n=118/35; 8.4%/11.4%) patients. TEAEs leading to dose discontinuation occurred in 10.4% in the Acala arm and in 52.5% /17.1% in the IR/BR arm. TEAEs Grade ≥3 were reported in the Acala arm in 49.4%, the most common AEs neutropenia (15.6%) and anemia (11.7%). In the IR group TEAE Grade ≥3 occurred in 89.8%, with the most common AEs neutropenia (39.8%) and diarrhea (27%). In the BR group TEAEs Grade ≥3 were reported in 48.6% with the most common AEs neutropenia 31.4% and anemia in 8.6%. SAEs Grade ≥3 were reported in the Acala arm in 26.6% and in IR/BR in 50.8% /25.7%. The major safety issues noted with acalabrutinib treatment based on ECI: Mono HemMalig population. Atrial fibrillation/flutter, any grade, was reported in 4.4% of subjects. Grade ≥3 events were reported in 1.3% of subjects. Anemia, neutropenia, and thrombocytopenia were reported in 13.8%, 15.7%, and 8.9% of subjects, respectively. Overall frequency of haemorrhage events; 46.3%. Major haemorrhage event was reported in 3.6%, with the most frequently reported sites; the GI tract, the CNS and epistaxis. SPMs were reported in 12.2% whereof the most frequent were skin malignancies (BCC 3.8% and SCCS 2.9%). SPMs, excluding nonmelanoma skin neoplasms, were reported in 6.5% of the subjects.

The frequencies in the Mono HemMalig population were consistent with what was observed in the Acala mono arms of the 2 pivotal studies. The most commonly reported TEAEs any grade in the Mono HemMalig population, were headache (37.8%), diarrhea (36%7), upper respiratory tract infection (22.0%), nausea (21.7%), fatigue and asthenia (26.6%), most of which were of severity Grade 1 or 2. Frequently occurring event were also; cough, rash, musculoskeletal pain. SOC Bleeding events occurred in (46.3%; e.g. haematuria, epistaxis, bruising, etc), Fatal TEAE occurred in 4.5%.

With respect to differences between the Mono HemMalig population and the ComboCLL population, the following aspect are worth noticing: neutropenia: ComboCLL 31.8% (Gr≥3: 30.0%); Mono HemMalig 15.7% (Gr≥3:14.2%); thrombocytopenia: ComboCLL 13.9% (Gr≥3: 6.7%); Mono HemMalig 8.9% (Gr≥3: 3.6%); infections: ComboCLL 74.0% (Gr≥3: 21.5%); Mono HemMalig 66.7% (Gr≥3:~8%);

hepatotoxicity: ComboCLL 7.2%; Mono HemMalig 3.7%; hypertension: ComboCLL 13.5%; Mono HemMalig 7.6%; infusion related reactions: ComboCLL 19.3%; Mono HemMalig 0.8%; Any Grade ≥3 AE: ComboCLL (70.4%); Mono HemMalig (54.1%). The rate of Atrial fibrillation, Haemorrhage and Major haemorrhage and anemia occurred at a similar rate in both populations.

3.5. Uncertainties and limitations about unfavourable effects

The size of the database suggests confidence with respect to most safety issues, but final study reports from the pivotal studies and safety updates from Study D8220C00008, a Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with CLL are awaited (see RMP).

Cardiac events, beyond atrial fibrillation, occurred at a higher rate in acalabrutinib-containing arms in both pivotal studies, compared to the comparator arms and must be further characterised. Use in patients with moderate to severe cardiac impairment is included in the safety specifications as missing information. Therefore, data from the final reports for the ongoing studies will be informative to further characterise the safety profile of acalabrutinib. Report from a cohort to Study D8220C00008 with the primary objective the safety of Calquence in patients with moderate to severe cardiac impairment will be provided in Q3 2020 (see RMP).

The inherent risk, for CLL patients, to develop SPMs makes the true acalabrutinib-related increase of SPM still not fully characterised and SPMs are presently included as Important identified risk in the safety specification. SPMs will also be further characterised in the upcoming PAM (Study D8220C00008), see RMP.

3.6. Effects Table

Effects Table for ACE-CL-007; CLL Previously untreated. (DCO 08 Jan 2019).

Effect	Short Description	Unit	Acala+Obin n=178	Acala N=179	Clbl+obin n=169	Uncertainties / Strength of evidence	References
Favourable Effects							
PFS	IRC	HR	0.10 [95% CI: 0.06, 0.17]; p<0.0001	0.20 [95% CI: 0.13, 0.30]; p< 0.0001		Median follow-up 28 months. Event rate 52% in ctrl. Median PFS control 22.6 months	
ORR	IRC	%	93.9% (95% CI: 89.3 – 96.5)	85.5% (95% CI: 79.6 – 89.9)	78.5% (95% CI: 71.9 – 83.9)		
Time to next treatment		HR	0.14 [95% CI: 0.08 – 0.26]	0.24 [95% CI: 0.15 – 0.40]		No median reached in any arm.	
Unfavourable Effects Of note, different duration of treatment; Obin was administered in 6 doses (1/28d) and Clb was administered for 6 cycles, each of 28 d. Acala was dosed daily until unacceptable toxicity or PD.							
TEAE Gr ≥3		%	70.2	49.7	69.8		

Effect	Short Description	Unit	Acala+Obin n=178	Acala N=179	Clbl+obin n=169	Uncertainties / Strength of evidence	References
TEAE Drug-related	At least possibly related	%	80.9	65.7	91.1		
TEAE discontinuation:							
Discont. of Acala /Obi		%	10.7 / 6.2	9.5 -	-		
Discont. of Clb /Obi		%	-	-	14.2 / 5.9		
TEAE Death		%	2.2	3.4	5.9		
SAE Any Gr		%	38.8	31.8	21.9		
SAE Gr ≥3		%	32.6	29.6	19.5		

Abbreviations:
Notes:

Effects Table for ACE-CL-309; Acalabrutinib; R/R CLL (DCO 15 Jan 2019).

Effect	Short Description	Unit	Acala n=154	IR/BR n=118/ 35	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	IRC	HR	0.31 [95% CI: 0.20, 0.49]; p<0.0001		Median follow-up 16 months. Event rate 44% in control arm. Median in control arm was 16.5 months.	
ORR	IRC	%	81.3 (95% CI: 74.4, 86.6)	75.5 (95% CI: 68.1, 81.6)		
Median duration of response	IRC	mo	Not reached	13.6		
Unfavourable Effects Of note, different duration of treatment; Acala and idelalisib was dosed daily until unacceptable toxicity or PD. In IR, Rituximab was administered for 6 cycles. BR was administered for 6 cycles, each of 28 d.						
TEAE Gr ≥3		%	49.4	89.8 / 48.6		
TEAE Drug-related		%	65.6	94.1 / 68.6		

Effect	Short Description	Unit	Acala n=154	IR/BR n=118/ 35	Uncertainties/ Strength of evidence	References
Any TEAE discontinuation		%	10.4	52.5 / 17.1		
Discont. of Acala		%	10.4	-		
Discont. of Ritux (R) only		%	-	4.2 / 8.6		
Discont. of Idela/ Idela+(R)		%	-	41.5 / 8.5		
Discont. of Benda/ Benda+(R)		%	-	2.9 / 8.6		
TEAE Death		%	5.2	7.6 / 11.4		
SAE Any Gr		%	28.6	55.9 / 25.7		
SAE Gr ≥3		%	26.6	50.8 / 25.7		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The PFS benefit noted with both experimental regimens, Acala+Obin and acalabrutinib monotherapy, is deemed robust and of clear clinical relevance. The safety profile is in line with the known safety of a BTK inhibitor. With respect to safety, the AE burden is higher in the combination arm, but both arms display a reasonable side effect profile given the intended use and both regimens can be approvable; the selection of that considered most suitable for the individual patient should be based on the data generated in study 007.

The pivotal study 007 only enrolled subjects ≥65 years of age or younger with comorbidities. However, extrapolation of efficacy also to younger and more fit patients is considered acceptable. Regarding subjects with del 17p/TP53-mutated disease data from the 007 study show similar point estimates for HR PFS in the group with these genomic aberrations as in the group without for both the Acala+Obin and the acalabrutinib monotherapy arm, and ORR for both the combination and the acalabrutinib monotherapy was as high as 83-84% in del 17p/TP53-mutated disease, similar as for acalabrutinib monotherapy in del 17p/TP53-negative disease, while only 56% in the control arm. Thus, data on ORR support retained activity in del 17p/TP53-mutated disease for both Acala+Obin and acalabrutinib monotherapy, but as data relative to a suboptimal control are of limited use, absolute data on PFS and ORR with DOR per treatment arm and genetic risk status (del 17p or TP53-mutation *vs* the complementary group) suggest that also the acalabrutinib-containing study arms performed

numerically inferior in subjects with del 17p or TP53 mutation-positive disease. The acalabrutinib monotherapy indication in previously untreated disease also lends support from the data obtained in the relapsed/refractory setting.

In relapsed or refractory CLL the PFS benefit noted with the experimental regimen, acalabrutinib monotherapy, is deemed robust with retained activity in del 17p/TP53-mutated disease, and of clear clinical relevance. No major unfavourable effects unexpected for a BTK inhibitor have been observed. At an updated analysis per investigator assessment with 6 months longer follow-up, and PFS maturity of 58% in the control arm, outcomes remain essentially stable.

The proposed indication for Calquence in the relapsed/refractory setting includes patients previously treated with ibrutinib or venetoclax; external data reasonably support the use of BTK inhibitors in subjects previously treated with venetoclax, and the use of acalabrutinib in subjects intolerant, but not resistant, to ibrutinib. This is deemed in line with what could mechanistically be expected.

3.7.2. Balance of benefits and risks

The benefits of Calquence either in monotherapy or in combination with obinutuzumab outweigh the risks. As per the above discussion, extrapolation to the full treatment-naïve population is deemed reasonable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Calquence:

> as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL);
>
> as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy;

is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Calquence is not similar to Gazyvaro and Imbruvica within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of Calquence is favourable in the following indication:

"Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regards to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regards to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that acalabrutinib is a new active

substance as it is not a constituent of a medicinal product previously authorised within the European Union.