Date: 4 May 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Calquence

International non-proprietary name: acalabrutinib
Pharmaceutical form: hard capsule
Dosage strength: 100 mg
Route(s) of administration: oral
Marketing Authorisation Holder: AstraZeneca AG
Marketing Authorisation No.: 67790
Decision and Decision date: approved on 4 March 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

1L	First line
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
AESI	Adverse event of special interest
A-G	Acalabrutinib plus obinutuzumab
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCL	B-cell lymphoma
BCL-2	Antiapoptotic protein B-cell lymphoma 2
BCR	B-cell receptor
BCRP	Breast Cancer Resistance Protein
BTK	Bruton tyrosine kinase
BID	Twice daily
BR	Bendamustine + rituximab
CIRS-G	Cumulative Illness Rating Score-Geriatric
CL	Clearance
CLL	Chronic lymphocytic leukaemia
Cmax	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CR	Complete response
CYP	Cytochrome P450
DCO	data cut-off
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERA	Environmental Risk Assessment
GC	Gas chromatography
GLP	Good Laboratory Practice
H2RA	H2-receptor antagonist
HPLC	High performance liquid chromatography
HR	Hazard ratio
IC50	Half maximal inhibitory concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
ILD	Interstitial lung disease
INN	International Nonproprietary Name
IR	Idelalisib + rituximab (IR)
IRC	Independent Review Committee
ITT	Intention to treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDPE	Low density polyethylene
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MATE	Multidrug and toxin extrusion
Min	Minimum
N/A	Not applicable
NCI	National Cancer Institute

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NO(A)EL	No Observed (Adverse) Effect Level
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PGP	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PI3K	Phosphatidylinositol 3-Kinase
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PopPK	Population PK
PPI	Proton-pump inhibitor
PSP	Pediatric Study Plan (US-FDA)
PSUR	Periodic Safety Update Report
PT	Preferred term
QD	Once daily
RMP	Risk Management Plan
R/R	Relapsed/Refractory
SAE	Serious adverse event
SOC	System Organ Class
SPM	Second primary malignancy
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
USP/NF	United States Pharmacopeia/National Formulary

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance acalabrutinib of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 17 January 2017.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

CALQUENCE monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are 65 years and older or have comorbidities (see "Properties/Effects").

CALQUENCE monotherapy is indicated for the treatment of adult patients with CLL who have received at least one prior therapy (see "Properties/Effects").

2.2.3 Requested Dosage

The recommended dose of CALQUENCE is 100 mg (1 capsule) taken orally approximately every 12 hours either as monotherapy or in combination with obinutuzumab.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	29 November 2019
Formal control completed	23 December 2019
List of Questions (LoQ)	17 April 2020
Answers to LoQ	15 July 2020
Predecision	13 October 2020
Answers to Predecision	9 December 2020
Final Decision	4 March 2021
Decision	approval

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3 Medical Context

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the Western world, with an incidence of about 4:100,000/year. More male than female patients (1.7:1) are affected. The incidence increases to >30:100,000/year at an age of >80 years. The median age at diagnosis is 72 years. About 10% of CLL patients are reported to be younger than 55 years. Depending on the presence or absence of specific risk factors, of which the most important are of a cytogenetic nature such as the presence of del(17p)/TP53 mutation and unmutated IGHV, the 5-year overall survival varies between about 25% (very high risk) and about 95% (low risk). Although there has been significant therapeutic progress, CLL remains an incurable disease. In addition, currently available treatments can be associated with substantial toxicity. Taken together, there is still a need for safer and/or more efficacious therapeutic options for CLL.

Considerations for the selection of therapies for the treatment of previously untreated CLL (first line = 1L treatment setting) typically include the presence of del(17p)/TP53 mutational status and the patient's fitness/age. Recommended treatment options for 1L CLL therapy approved in Switzerland include BTK inhibition, and – in the absence of del(17p)/TP53 mutations – combination chemo-immunotherapy in young, fit patients, or combined chlorambucil plus obinutuzumab in less fit patients.

If the disease does not respond to 1L therapy (refractory CLL, defined as an early relapse within 6 months of treatment) or if relapse occurs within 24-36 months after initial therapy, the therapeutic regimen is typically changed, otherwise the 1L therapy may be repeated. Recommended options for the treatment of relapsed/refractory (R/R)CLL approved in Switzerland include BTK inhibition, PI3K inhibition, BCL2 inhibition and – in the absence of del(17p)/TP53 mutations – combination chemoimmunotherapy.

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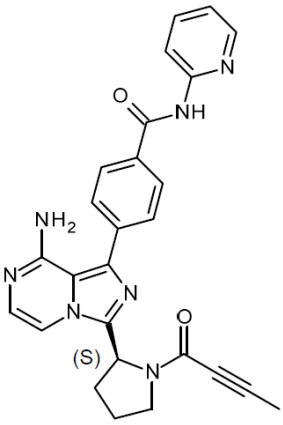
4 Quality Aspects

4.1 Drug Substance

INN: Acalabrutinib
Chemical name: 4-{8-amino-3-[(2*S*)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5- α]pyrazin-1-yl}-*N*-(pyridin-2-yl)benzamide
Molecular formula: $C_{26}H_{23}N_7O_2$
Molecular mass: 465.51 g/mol
Molecular structure:



Physico-chemical properties: Acalabrutinib is a white to yellow crystalline powder. It has one asymmetric centre and is manufactured as the S-enantiomer. The solubility of acalabrutinib is pH-dependent. The drug substance is soluble at acidic pH, and the solubility decreases with increasing pH. Several polymorphic forms have been identified. The manufacturing process consistently produces the same polymorphic form. Acalabrutinib is non-hygroscopic.

Synthesis: The synthesis of the drug substance has been adequately described, and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

Structure elucidation: The structure of acalabrutinib has been fully elucidated using several spectroscopic techniques.

Specifications: The active substance specifications include tests for appearance, identification, water content (Ph. Eur.), sulphated ash (Ph. Eur.), particle size distribution (laser diffraction), residual solvents (GC), assay (HPLC), organic impurities (HPLC), mutagenic impurities (HPLC) and enantiomeric purity (HPLC). The specifications conform to the requirements outlined in ICH guideline Q6A and are considered appropriate in order to ensure a consistent drug substance quality.

Stability: The bulk drug substance is packaged in two LDPE bags. The closed LDPE bags are placed into a secondary rigid container. Appropriate stability data have been generated resulting in a suitable retest period when packaged in the packaging type as described above.

4.2 Drug Product

Description and composition: The drug product is an immediate-release dosage form for oral administration. Calquence capsules are 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.
All excipients used in the drug product are widely used in pharmaceutical preparations for oral solid dosage forms and meet the standards defined in the current Ph. Eur. or USP/NF monographs with the

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exception of the colorants (capsule shell; imprinting ink). The colorants fulfil relevant standards for food additives.

Manufacture: The drug product is manufactured by a standard manufacturing process, which includes blending, dry granulation and capsule-filling processes. Process parameters and in-process controls are defined. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications include the parameters description (visual), identification tests, assay (HPLC), degradation products (HPLC), dissolution, and uniformity of dosage units (Ph. Eur.). All the analytical procedures are adequately described, and non-compendial methods are validated according to the current requirements of ICH Q2(R1). Batch analysis data have been provided. The results are within the specifications and consistent from batch to batch.

Container Closure System: Satisfactory information on the proposed container closure system has been provided. The drug product is packaged in aluminium-aluminium blisters.

Stability: Appropriate stability data have been generated in the packaging material for commercial use and following the relevant international guidelines. Based on these studies, an appropriate shelf-life was established. The storage recommendation is “Store in the original container. Do not store above 30 °C”.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Calquence indicated for CLL, an abridged evaluation was conducted, which was mainly based on the FDA assessment report (1 February 2016) and CHMP evaluation report submitted by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Calquence in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. The safety margins are low, but acceptable for the proposed indication. All safety issues identified in the nonclinical studies are adequately mentioned in the information for the healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Pharmacokinetics

Absorption

After oral administration of the proposed commercial formulation, the absolute bioavailability of acalabrutinib was 25.3%. The acalabrutinib tmax after fasted administration was about 0.5 h.

A high-fat, high-calorie breakfast had no effect on acalabrutinib AUC, but resulted in an about 70% reduction of Cmax and a delay of tmax.

Acalabrutinib was formally classified as a BCS class 2 substance (high permeability and low solubility). However, its solubility is high in acidic conditions up to pH 4 and decreases at higher pH values. Therefore, the effect of co-medications that increase gastric pH on acalabrutinib PK was investigated. The effects of calcium carbonate and omeprazole on acalabrutinib exposure are summarised below:

Co-administered drug/dose	Acalabrutinib Dose	Ratio % (90% CI) Cmax	Ratio % (90% CI) AUC	Enzyme/Transporter/ Mechanism evaluated
Calcium carbonate 1000 mg SD	100 mg SD (initial formulation)	25.41 (17.05, 37.89)	47.35 (32.21, 69.61)	Increase of gastric pH
Omeprazole 40 mg QD for 5 days	100 mg SD (initial formulation)	21.12 (11.27, 39.56)	43.29 (29.61,63.27)	Increase of gastric pH, inhibition of CYP2C19
Omeprazole 40 mg QD for 7 days	100 mg SD (proposed commercial formulation)	27.90 (20.59, 37.83)	64.15 (58.01, 70.94)	Increase of gastric pH, inhibition of CYP2C19

As expected, both calcium carbonate and omeprazole reduced the acalabrutinib exposure (Cmax 72.1% -78.88% ↓, AUC 35.85% - 56.71% ↓).

The highest bioavailability of acalabrutinib was observed after intake with water. Therefore, patients should take acalabrutinib with water only.

The available PK data supported the dosing recommendations with regard to the intake of acalabrutinib with food, PPIs, H2RAs or antacids.

Dose Proportionality

In healthy subjects, there was a slightly more than dose proportional increase in acalabrutinib exposure over a single dose range of 2.5 to 400 mg. Over a dose range of 75 mg QD to 400 mg QD, there was an approximately dose proportional increase in acalabrutinib exposure in healthy subjects. The pop PK analysis showed no evidence of major nonlinearity of acalabrutinib PK. Therefore, a dose proportional increase in the acalabrutinib exposure across the administered dose range (100 mg QD to 400 mg QD, 100 mg BID to 200 mg BID) can also be assumed for cancer patients.

After administration of single doses of 100 mg and 400 mg to healthy subjects, there was a 4.6-fold and 4.8-fold increase in M27 Cmax and AUCinf, respectively. M27 (ACP-5862) is the major pharmacologically active metabolite of acalabrutinib.

Pharmacokinetics after multiple Dosing

The acalabrutinib accumulation ratio after BID dosing was 1.4; the linearity index was between 1.15 and 1.34. The estimated time to steady state was about 5 hours.

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The M27 exposure showed a slight increase after multiple dosing with 100 mg BID.

Distribution

At concentrations in the therapeutic range (0.3, 1 and 3 µM), the *in vitro* acalabrutinib plasma protein binding was 99.4%. The binding to human serum albumin decreased from 70.0% to 60.8% with increasing acalabrutinib concentrations. At concentrations between 1 – 10 µM, the acalabrutinib binding to human plasma proteins *in vitro* was 97% - 98% and independent of the acalabrutinib concentrations investigated. The binding to human serum albumin was about 94% and also independent of the acalabrutinib concentrations investigated (1 – 10 µM). The acalabrutinib binding to alpha-1 acid glycoprotein was about 43% at concentrations of 1 µM and 3 µM and 37.1% at 10 µM. The acalabrutinib blood to plasma ratio was about 0.8.

At concentrations in the therapeutic range (0.3, 1 and 3 µM), the *in vitro* M27 plasma protein binding was between 98.8% and 98.9%. The binding to human serum albumin decreased from 92.1% to 90.0% with increasing M27 concentrations. At concentrations between 1 – 10 µM, the M27 binding to human plasma proteins *in vitro* was about 99 % and independent of the M27 concentrations investigated. The M27 blood to plasma ratio was about 0.66.

The plasma protein binding of both acalabrutinib and M27 was approximately 4% to 5% lower in subjects with severe hepatic impairment compared to healthy controls.

After intravenous dosing, the acalabrutinib Vz and Vss was 98 L and 34.2 L, respectively.

Metabolism

In vitro Data

Acalabrutinib was mainly metabolised by CYP3A4. Furthermore, glutathione-S transferase M1 and M2 might be involved in the formation of acalabrutinib glutathione conjugates.

The active metabolite M27 was formed and also eliminated mainly by CYP3A4.

Clinical Data

After administration of ^{14}C-labelled acalabrutinib, the parent compound acalabrutinib accounted for 8.6% of total radioactivity in plasma. The most abundant metabolite was M27, representing 34.7% of total radioactivity. M27 was the only single human metabolite accounting for >10% of radioactivity and was about 4-fold the amount of parent acalabrutinib in the plasma pool. The next most abundant plasma metabolite components after M27 accounted for 10.8% (M7, M8, M9, M10, and M11, collectively), 5.9% (M25), and 2.5% (M3) of radioactivity in the plasma profile. In total, 66.9% of the total radioactivity in plasma could be assigned to acalabrutinib and its metabolites.

Three primary metabolic pathways were identified for acalabrutinib: amide hydrolysis resulting in loss of the 2-aminopyridine (2-AP) group; glutathione (GSH) conjugation of the butynamide moiety; and pyrrolidine hydroxylation, predominantly at the α-methine carbon of the pyrrolidine ring, the latter resulting in the formation of the main metabolite M27.

In agreement with its mechanism of action (irreversible binding to BTK, which is mainly expressed in B-cells), a clear trend in increased ratio of blood to plasma over time was observed for total radioactivity.

M27 has approximately half the pharmacological activity of acalabrutinib.

After single-dose administration of 100 mg acalabrutinib, the metabolite/parent AUCinf ratio was 2.4.

Elimination

After administration of ^{14}C-labelled acalabrutinib, 12% and 83.5% of the radioactive dose were excreted in urine and faeces, respectively.

Unchanged acalabrutinib accounted for 0.5% of excreted dose in urine. The most abundant metabolite component co-eluted and was 2.7% of excreted dose, representing mainly M7, M10, and M11, collectively. The next most abundant urine metabolite components were 1.3 and 0.6% of excreted dose, representing M3 and M16, respectively. Metabolite M27 represented 0.5% of excreted

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dose in urine. In total, 6.3% of the radioactive dose excreted in urine could be assigned to acalabrutinib and its metabolites.

Unchanged acalabrutinib accounted for 1.2% of excreted dose in faeces. The most abundant metabolite component co-eluted and was 12.1% of excreted dose, representing M22, M45, and M23, collectively. The next most abundant faeces metabolite components were 7.5, 5.2, and 3.5% of excreted dose, representing M24, co-eluting M17 and M18, and M27, respectively. In total, 34.2% of the radioactive dose excreted in faeces could be assigned to acalabrutinib and its metabolites.

After intravenous administration, the acalabrutinib CL was 39.4 L/h. The terminal half-life was similar after oral and intravenous administration and about 1.7 h. The main metabolite M27 had a similar tmax as acalabrutinib, but its half-life was longer, at 6.8 h.

Special Populations/Intrinsic Factors

GSTM1, CYP3A5 and ABCG2 genotypes had no apparent effect on acalabrutinib exposure.

The acalabrutinib Cmax and AUC0-tlast derived from total acalabrutinib plasma concentrations were 1.9-fold higher in subjects with mild hepatic impairment (Child Pugh A) compared to subjects with normal hepatic function. The acalabrutinib half-life was similar in these two groups. In subjects with moderate hepatic impairment (Child Pugh B), the acalabrutinib Cmax was similar and AUC0-last 1.5-fold higher compared to subjects with normal hepatic function. The acalabrutinib half-life was prolonged in subjects with moderate hepatic impairment (7.92 h versus 2.24 h). Due to bioanalytical problems, no information on the acalabrutinib fraction unbound could be obtained.

The M27 plasma concentrations were not measured in subjects with mild or moderate hepatic impairment.

The pharmacokinetics of acalabrutinib and M27 in subjects with severe hepatic impairment (Child Pugh C) were investigated in a separate study.

The total acalabrutinib exposure was about 5-fold higher in subjects with severe hepatic impairment compared to healthy controls. The half-life was similar. The unbound acalabrutinib exposure was about 3.6-fold higher in subjects with severe hepatic impairment. There was a correlation between total acalabrutinib exposure and hepatic function parameters.

The total and unbound M27 exposure was similar in subjects with severe hepatic impairment and healthy controls. However, the metabolite/parent ratio (MR) was considerably lower in subjects with severe hepatic impairment. There was no correlation between M27 exposure and hepatic function parameters.

The potential impact of ECOG performance status, race, body weight, disease status (healthy subject or cancer patient), co-administration of PPIs or H2RA, eGFR and hepatic impairment (based on NCI criteria) on acalabrutinib and M27 PK was investigated in a pop PK analysis.

The pop PK dataset included a sufficient number of subjects with mild hepatic impairment, but only 6 subjects and 1 subject, respectively, with moderate and severe hepatic impairment. The dataset included only 2 subjects with severe renal impairment, but a sufficient number of subjects with normal renal function, mild or moderate renal impairment. It included a sufficient number of subjects > 65 years of age. The range of body weights of the included subjects was also sufficiently wide to detect a potential impact on acalabrutinib and M27 PK.

The final pop PK model included the following covariate relationships:

Disease status as covariate of acalabrutinib CL/F
Disease status as covariate of acalabrutinib Vp/F
ECOG 2+ status as covariate of acalabrutinib CL/F
Co-administration of PPIs on the acalabrutinib bioavailability

The final pop PK model described the data for both acalabrutinib and M27 reasonably well.

The impact of these covariates on acalabrutinib and M27 exposure was within the inter-individual variability of Cmax and AUC. PPI reduced acalabrutinib and M27 exposure, healthy subjects had lower acalabrutinib exposure than cancer patients with ECOG status ≤ 1. Cancer patients with ECOG status ≥ 2 had a higher acalabrutinib exposure compared to the reference subject. The M27 exposure was not affected by patient or ECOG status.

Age, eGFR, mild hepatic impairment, race, gender, line of therapy or indication had no impact on acalabrutinib or M27 exposure.
The results of the respective Phase 1 studies and the pop PK analysis supported the dosing recommendations in special populations.

Interactions
The unbound Cmax of acalabrutinib and M27 after 100 mg is 0.036 µM and 0.012 µM, respectively.

In vitro Data – Inhibition of hepatic CYPs
Acalabrutinib directly inhibited CYP2C8 (IC50 37 µM), CYP2C9 (IC50 28 µM) and CYP3A4 (IC50 57 µM and 69 µM). There was also time-dependent inhibition of these three CYPs observed, which may be irreversible for CYP3A4. The remaining CYPs (1A2, 2B6, 2C19 and 2D6) were not inhibited at concentrations up to 100 µM.
M27 directly inhibited CYP2C9 (IC50 6.7 µM) and CYP2C19 (IC50 17 µM). There was time-dependent inhibition of CYP2C8, which may be irreversible. All other CYPs investigated (as for acalabrutinib) were not inhibited at concentrations up to 20 µM.
The static risk assessment of an *in vivo* interaction based on the *in vitro* data indicated a risk of acalabrutinib to inhibit intestinal CYP3A4 in vivo.

In vitro Data – Induction of hepatic CYPs
Acalabrutinib induced all three investigated CYPs (1A2, 2B6 and 3A4). For CYP2B6 and 3A4, a more than 2-fold mRNA increase occurred at the highest investigated concentration of 50 µM only, but an *in vivo* induction of CYP1A2 could not be excluded.
M27 did not induce CYP1A2 or CYP2B6. For CYP3A4, a more than 2-fold mRNA increase was observed at concentrations ≥ 1µM.

Other in vitro Data
Acalabrutinib did not inhibit aldehyde oxidase at concentrations up to 100 µM. At concentrations up to 3 µM, neither acalabrutinib nor M27 inhibited UGT1A1 or 2B7.

In vitro Data – Acalabrutinib or M27 as Substrate of Drug Transporters
Acalabrutinib was a substrate for Pgp and BCRP, but not for OATP1B1, OATP1B3, OAT1, OCT2 or OAT3.
M27 was a substrate for Pgp and BCRP, but not for OATP1B1 or OATP1B3.

In vitro Data – Inhibition of Drug Transporters by Acalabrutinib or M27
Acalabrutinib inhibited both Pgp (IC50 98.3 µM) and BCRP (IC50 40.9 µM). At concentrations up to 20 µM it did not inhibit OAT1B1 or OATP1B3. For OAT1, OAT3 and OCT2, at 20 µM inhibition rates of 10.5%, 35.6% and 59.3%, respectively, were observed. At concentrations of 3 µM, no inhibition of MATE2K and 35.7% inhibition of MATE1 were observed.
Based on the static interaction risk assessment, in vivo inhibition of intestinal BCRP could not be excluded. For the other investigated transporters, in vivo interactions were deemed to be unlikely.
M27 inhibited BCRP (IC50 5.99 µM), OATP1B1 (IC50 10.1 µM), OAT1 (IC50 12.1 µM) and MATE1 (IC50 0.2 µM). At concentrations up to 20 µM it did not inhibit OAT3. For Pgp, OATP1B3, OCT2 and MATE2-k, at 20 µM inhibition rates of 8.6%, 41.3%, 32.0% and 35.6%, respectively, were observed. Based on the static interaction risk assessment, in vivo inhibition of MATE1 could not be excluded. For the other investigated transporters *in vivo* interactions were deemed to be unlikely.

Clinical Data – Impact of other Drugs on Acalabrutinib

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Co-administered drug/dose	Acalabrutinib Dose	Ratio % (90% CI) Cmax	Ratio % (90% CI) AUC	Enzyme/Transporter/ Mechanism evaluated
Itraconazole 200 mg BID for 6 days	50 mg SD	Acalabrutinib: 390 (320, 476)	Acalabrutinib: 497 (438, 564)	Inhibition of CYP3A4 and Pgp
Rifampicin 600 mg SD	100 mg SD	122.65 (102.92, 146.16)	128.50 (117.88, 140.07)	Inhibition of OATP1B1/3
Rifampicin 600 mg QD for 9 Days	100 mg SD	31.54 (23.63, 42.11)	20.62 (17.51, 24.29)	Induction of CYPs and Transporters

The results of the clinical studies were in agreement with the *in vitro* data identifying CYP3A4 as the main enzyme involved in the metabolism of acalabrutinib and M27. The M27 plasma concentrations were not measured in the studies summarised above.

Obinutuzumab had no major impact on acalabrutinib or M27 exposure.

The results of the clinical interaction studies supported the dosing recommendations for the co-administration of CYP3A4 inhibitors or inducers.

Clinical Data – Impact of Acalabrutinib on other Drugs

No clinical studies have investigated the potential impact of acalabrutinib on other drugs, although the *in vitro* data indicated some interaction potential (inhibition of intestinal CYP3A4 and BCRP, induction of CYP1A2).

PBPK simulations predicted no effect of acalabrutinib after 100 mg BID dosing on either midazolam (CYP3A4 substrate) or rosiglitazone (CYP2C8 and 2C9 substrates) PK.

Pharmacodynamics

After single-dose administration of 100 mg and 400 mg acalabrutinib, neither a QTcF prolongation or shortening, nor a relationship between acalabrutinib plasma concentrations and QTcF was observed in healthy subjects. Moxifloxacin showed the expected effect, i.e. assay sensitivity was demonstrated in the tQT study.

For both acalabrutinib treatments, there were no QTcF intervals > 450 ms and no changes > 30 ms. After 100 mg and 400 mg acalabrutinib, there were 11% and 16% of PR intervals ≥ 200 ms, respectively, but no intervals ≥ 220 ms. There were no heart rates < 50 bpm or > 90 bpm, but changes ≥ 30 % increased from 9% after 100 mg to 21% after 400 mg.

Compared to the acalabrutinib and M27 steady-state exposure after 100 mg BID in cancer patients, supratherapeutic exposure was achieved for both analytes in the tQT study (acalabrutinib Cmax 3.6-fold, M27 Cmax 4.6–fold).

Acalabrutinib at multiple daily doses up to 400 mg had no effect on ECG parameters in cancer patients (heart rate, PR interval, QTcF, QTcB). There was no clinically relevant relationship between acalabrutinib plasma concentrations and QTcF.

6.2 Dose Finding and Dose Recommendation

Dose selection for the proposed new indication was based on the results of study ACE-CL-001, a Phase 1/2, multicentre, open-label, non-randomised, sequential group, dose-escalation study including patients with treatment-naïve and R/R CLL / SLL. Acalabrutinib was administered in once daily (qd) dosages ranging from 100 to 400 mg qd and in twice daily (bid) dosages of 100 and 200 mg bid. Based on the review of efficacy, safety/tolerability and PK-PD data, the applicant identified acalabrutinib 100 mg bid as the recommended dosage, as it was found to be well tolerated and provided near complete, sustained BTK occupancy with minimum interpatient variability over the daily dose interval. Overall, based on the data provided, dose finding and selection for the proposed new indication can be accepted. Because the available exposure-response relationship data seem to

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suggest a rather weak correlation between exposure and efficacy and safety, the lack of data for lower bid dosages, such as 75 mg bid, is considered to be acceptable.

6.3 Efficacy

Two pivotal, controlled Phase 3 studies were submitted in support of the proposed new indication: Study ACE-CL-007 [ELEVATE-TN] in previously untreated CLL patients (Study 007) and Study ACE-CL-309 [ASCEND] in patients with R/R (Relapse / Refractory) CLL (Study 309).

Study 007 – First line (1L) indication
Study 007 was an international, randomised, multicentre, open-label, Phase 3 study that randomised a total of 535 patients (intention-to-treat (ITT) population) in a 1:1:1 ratio to one of the three following treatment arms (each treatment cycle lasted 28 days):

- Acalabrutinib in combination with obinutuzumab (A-G), Arm B, N=179.
- Acalabrutinib monotherapy, Arm C, N=179
- Chlorambucil in combination with obinutuzumab (CLB-G), Arm A, N= 177

For details see the attached information for healthcare professionals, Properties / Effects section. While acalabrutinib was dosed until disease progression or unacceptable drug-related toxicity, obinutuzumab and chlorambucil were administered in a fixed-duration schedule over a maximum of 6 cycles.

Eligible were patients with previously untreated active CD20+ CLL requiring treatment as per IWCLL 2008 criteria, aged ≥ 65 years of age, OR >18 and < 65 years of age in the presence of creatinine clearance 30 to 69 mL/min and/or a Cumulative Illness Rating Score-Geriatric (CIRS-G) > 6 (so-called “unfit” patients), and with ECOG performance status ≤ 2. Among others, the following were not eligible: patients with a known central nervous system (CNS) lymphoma or leukaemia, prolymphocytic leukaemia, or a history of, or currently suspected, Richter’s syndrome.

Patients were stratified by the presence of 17p deletion (yes vs. no), ECOG performance status (0 or 1 vs. 2), and geographic region (North America and Western Europe vs. other). For relevant baseline characteristics, see the attached information for healthcare professionals, Properties / Effects section.

In total, 45 patients randomised to the comparator treatment CLB-G (Arm A), who had disease progression as confirmed by an Independent Review Committee (IRC), crossed over to acalabrutinib monotherapy 100 mg bid at the investigator’s discretion and as allowed per protocol.

After a median duration of exposure to study medication of about 28 months in the investigational treatment Arms B and C, compared with about 5.5 months in comparator Arm A, and following an overall median time on study (follow-up time) of approximately 28 months at the data cut-off (DCO) date of 08 February 2019, efficacy results for Study 007 were as follows:

- PFS in investigational Arm B (A-G) as assessed by the IRC (primary endpoint)
  - The primary endpoint of the study was met
  - 7.8% (14 patients) of patients experiencing PFS events (vs. 52.5% (93) in comparator Arm A (CLB-G))
  - Median PFS not reached (vs. 22.6 months)
  - Hazard ratio (HR)=0.10 [95%CI 0.06, 0.18]
  - Landmark PFS rates: 12 months: 95.9% (vs. 84.6%); 18 months: 94.8% (vs. 65.6%); 24 months: 92.7% (vs. 46.7%); 36 months: 89.6% (vs. 31.3%).

The results of the sensitivity analyses supported the results of the primary analysis. The results of the subgroup analyses were also in line with the results of the primary analysis, including subgroups with traits associated with poor prognosis, such as the presence of del(17p) and/or *TP53* mutations, unmutated *IGHV*, and elevated serum β2 microglobulin.

- PFS in investigational Arm C (acalabrutinib monotherapy) as assessed by the IRC (key secondary endpoint)
  - The key secondary endpoint of the study was met

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- 14.5% (26 patients) of patients experiencing PFS events (vs. 52.5% (93) in comparator Arm A (CLB-G))
- Median PFS not reached (vs. 22.6 months)
- HR=0.20 [95%CI 0.13, 0.31]
- Landmark PFS rates: 12 months: 92.9% (vs. 84.6%); 18 months: 90.5% (vs. 65.6%); 24 months: 87.3% (vs. 46.7%); 36 months: 63.9% (vs. 31.3%).

The results of the sensitivity and subgroup analyses were in line with the results of the primary analysis of the secondary endpoint IRC-assessed PFS Arm C vs. Arm A.

Further secondary efficacy endpoints

- Overall response rate (ORR) in investigational Arm B (A-G) as assessed by the IRC
  - ORR: 93.9% (vs. 78.5% in comparator Arm A (CLB-G))
  - Complete response (CR): 12.8% (vs. 4.5%)
- ORR in investigational Arm C (Acalabrutinib monotherapy) as assessed by the IRC
  - ORR: 85.5% (vs. 78.5% in comparator Arm A (CLB-G))
  - CR: 0.6% (vs. 4.5%)
- Overall survival (OS) in investigational Arm B (A-G)
  - 5.0% (9 patients) of patients experiencing OS events (vs. 9.6% (17 patients) in comparator Arm A (CLB-G)).
  - Median OS not reached
  - HR=0.47 [95%CI 0.21, 1.06]
- OS in investigational Arm C (Acalabrutinib monotherapy)
  - 6.1% (11 patients) of patients experiencing OS events (vs. 9.6% (17) in comparator Arm A (CLB-G)).
  - Median OS not reached
  - HR=0.60 [95%CI 0.28, 1.27]

Summary of efficacy Study 007

The primary and the key secondary endpoints, a statistically significant improvement in IRC-assessed PFS in the two acalabrutinib-containing treatment regimens versus the comparator treatment CLB-G, were met. ORR was only improved by the combination treatment A-G versus the comparator treatment CLB-G, but not by acalabrutinib monotherapy. OS data were immature at data cut-off.

Although Study 007 was not designed to compare both acalabrutinib treatments, the results of additional non-prespecified comparative analyses provided by the applicant in response to the list of questions of Swissmedic were all in favour of the combination.

Uncertainties with regard to efficacy concern the immaturity of the primary and relevant secondary time-to-event endpoints and long-term efficacy, especially with respect to OS. The applicant has to submit the final clinical study report as a post-approval requirement.

Study 309 – Relapsed / refractory (R/R) indication

Study 309 was an international, randomised, multicentre, open-label, Phase 3 study that randomised a total of 310 patients (ITT population) in a 1:1 ratio to one of the following treatment arms (each treatment cycle lasted 28 days):

- Acalabrutinib (monotherapy), Arm A, N=155: Acalabrutinib, 100 mg bid orally.
- Arm B, N=155
  - Idelalisib + rituximab (IR) [N=119 (77%)]
  - Bendamustine + rituximab (BR) [N=36 (23%)]

For details see the attached information for healthcare professionals, Properties / Effects section. While acalabrutinib and idelalisib were dosed until disease progression or unacceptable drug-related toxicity, rituximab and bendamustine were administered in a fixed-duration schedule over a maximum of 6 cycles.

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Eligible were adult patients with ECOG performance status ≤ 2 and relapsed / refractory active CD20+ CLL requiring treatment as per IWCLL 2008 criteria. Among others, the following were not eligible: patients with a known CNS lymphoma or leukaemia, prolymphocytic leukaemia or a history of, or currently suspected, Richter's syndrome, or those who had received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before the first dose of study drug. Patients were also excluded in case of 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), and prior radio- or toxin-conjugated antibody therapy was also not allowed.

Patients were stratified by the presence of 17p deletion (yes vs. no), ECOG performance status (0 or 1 vs. 2), and number of prior therapies (1-3 vs. ≥4). For relevant baseline characteristics, see the attached information for healthcare professionals, Properties / Effects section.

In total, 35 patients in Arm B (29 patients previously on IR and 6 patients previously on BR), who had IRC-confirmed disease progression, crossed over to acalabrutinib monotherapy 100 mg bid at the investigator's discretion and as allowed per protocol.

After a median duration of exposure of about 16 months to acalabrutinib, 11.5 months to idelalisib and 5.5 months to bendamustine and rituximab, and following an overall median time on study of approximately 16 months at the data cut-off (DCO) date of 15 January 2019, efficacy results in Study 309 for patients with R/R CLL and a median of two prior therapies (range: 1-10) were as follows:

- PFS in investigational Arm A (Acalabrutinib) as assessed by the IRC (primary endpoint)
  - The primary endpoint of the study was met
  - 17.4% (27 patients) of patients experiencing PFS events (vs. 43.9% (68) in comparator Arm B (IR/BR))
  - Median PFS not reached (vs. 16.5 months)
  - HR=0.31 [95%CI 0.20, 0.49]
  - Landmark PFS rates: 6 months: 96.1% (vs. 93.9%); 12 months: 87.8% (vs. 68.0%); 18 months: 79.0% (vs. 38.6%).

The results of the sensitivity analyses supported the results of the primary analysis. The results of the subgroup analyses were also in line with the results of the primary analysis, including subgroups with traits associated with poor prognosis such as the presence of del(17p) and/or *TP53* mutations, unmutated *IGHV*, and elevated serum β2 microglobulin.

In its response to Swissmedic's List of Questions, the applicant had provided an Efficacy Addendum for Study 309 including updated results based on a clinical DCO date of 01 August 2019 (additional 6 months compared with the previous DCO date in January 2019). However, this analysis was not prespecified and PFS results were investigator-assessed (secondary endpoint; see below) and not IRC-assessed (primary endpoint). Overall, the updated efficacy data provided for Study 309 confirm the results reported at the previous DCO.

Further secondary efficacy endpoints

- PFS in investigational Arm A (Acalabrutinib) as assessed by the investigator
  - 15.5% (24 patients) of patients experiencing PFS events (vs. 43.9% (68) in comparator Arm B (IR/BR))
  - Median PFS not reached (vs. 16.2 months)
  - HR=0.28 [95%CI 0.18, 0.45]
- ORR in investigational Arm A (Acalabrutinib) as assessed by the IRC / investigator
  - ORR: 81.3% (vs. 75.5% in comparator Arm B (IR/BR)) / 79.4% (vs. 83.2%)
  - CR: 0 (vs. 1.3%) / 1.3% (vs. 3.2%)
- OS in investigational Arm A (Acalabrutinib)
  - 9.7% (15 patients) of patients experiencing OS events (vs. 11.6% (18) in comparator Arm B (IR/BR)).
  - Median OS not reached
  - HR=0.84 [95%CI 0.42, 1.66]

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Updated OS data from an unplanned analysis based on a clinical DCO date of 01 August 2019 (see above) showed still immature OS data: 13.5% and 16.8% events in Arms A and B, respectively (HR 0.78 (95%CI 0.44, 1.40)), confirming the results reported at the previous DCO.

- Duration of response (DoR) in investigational Arm A (Acalabrutinib) as assessed by the IRC / investigator
  - Median DoR not reached (vs. 13.6 months) / not reached (vs. 13.9 months)
  - HR=0.33 [95%CI 0.19, 0.59] / 0.20 [95%CI 0.10, 0.42]

Summary of efficacy Study 309
The primary endpoint, a statistically significant improvement in IRC-assessed PFS for the acalabrutinib treatment (Arm A) versus the comparator treatment Arm B (IR / BR), was met. However, ORRs, including the CR rates, were comparable between both treatments. Similarly, OS results including landmark OS rates up to 21 months did not differ meaningfully between Arms A and B.

It should be noted that eligibility in Study 309 was restricted to patients with R/R CLL without prior exposure to a B-cell lymphoma (BCL)-2 inhibitor or BCR inhibitor, such as BTK inhibitors or PI3K inhibitors, and prior radio- or toxin-conjugated antibody therapy was also not allowed. In addition, baseline disease characteristics and prior CLL therapy showed shorter median times from diagnosis to randomisation and from last prior CLL therapy to first dose of study treatment, as well as a lower median number of prior therapies and a higher proportion of patients with only one prior therapy in Arm A compared with Arm B. Thus, patients in the comparator Arm B seemed to have had shorter remission times and were more intensely pretreated, suggesting more active disease and a worse prognosis in the comparator arm. Uncertainties with regard to efficacy concern the immaturity of the primary and relevant secondary time-to-event endpoints and long-term efficacy, especially with respect to OS. The applicant has to submit the final clinical study report as a post-approval requirement.

6.4 Safety

The safety analysis of the two pivotal Studies 007 and 309 included a comparison with pooled safety data from a total of 10 clinical studies. Median durations of exposure to acalabrutinib ranged from 19.3 months to 29.5 months in the safety pool, and were 28 months and 16 months for Study 007 and Study 309, respectively. The size of the safety database and the extent of exposure were regarded as adequate.

The results of the pooled analyses for **all-grade TEAEs** are in agreement with the results of Studies 007 and 309: almost all patients had at least one TEAE while on study medication (about 95%), with about 50% of the patients on acalabrutinib monotherapy and about 70% on combined A-G treatment experiencing TEAEs of grade ≥ 3. The patterns and frequencies of the most common TEAEs (> 20%) are consistent in the pooled safety data and pivotal Studies 007 and 309, and include **headache** (~30-40%), **diarrhoea** (~30-40%), **upper respiratory tract infection** (~20-30%), **contusion** (~20-30%), **nausea** (~20-25%), **fatigue** (~20-30%), and **cough** (~20-30 %). Incidence rates of TEAEs by both SOC and PT were generally higher on combined A-G treatment than acalabrutinib monotherapy with differences > 10% at the PT level observed for **fatigue**, **dizziness**, **neutropenia**, **maculopapular rash**, and **infusion-related reactions**.

Comparable rates for TEAEs leading to acalabrutinib study drug discontinuation of about 10% were observed in the pivotal studies and pooled safety data, with **infections**, **neoplasms** and **haematological disorders (thrombocytopenia)** as leading causes. Higher rates of TEAEs leading to reduction or delay were observed for the combined treatment compared with acalabrutinib monotherapy in Study 007 and the pooled safety data.

SAE rates are in line between pooled analyses and the two pivotal studies, with SAEs reported in about one third of patients on acalabrutinib monotherapy, and at a slightly higher rate of almost 40% on combined A-G treatment; in both cases the vast majority of SAEs were of grade ≥ 3. The most common SAEs in pivotal studies and safety pool included **serious infections** (mainly **respiratory**

tract including pneumonia, but also **sepsis**, urinary tract infections, and cellulitis) and anaemia (~2%). The single most common PT among SAEs was **pneumonia** (~5-6%).

The numbers and patterns of **overall deaths** observed in the two pivotal studies are in line with the pooled safety analysis, with incidences of deaths of up to about 8-9% in the CLL population. As in the pivotal studies, **fatal AEs** accounted for most of the deaths in the CLL population. The rates and the patterns of fatal AEs observed in the two pivotal studies are consistent with the pooled safety data, showing incidences for fatal AEs of about 3-5%. The leading causes of fatal AEs in pivotal studies and safety pool were **infections**, in particular **pneumonia** and **sepsis**, and including **opportunistic infections** (such as Candida and Aspergillus infections), **neoplasms** or fatal complications related to neoplasms and **cardiovascular events** (cardiac ischaemic events, cerebrovascular accidents, pulmonary embolism).

Importantly, overall mortality and rates of fatal AEs in Studies 007 and 309 were lower in the acalabrutinib treatment arms than in those on comparator therapies, with the lowest rates observed in the combined A-G treatment Arm B of Study 007. The latter is confirmed by the pooled safety data, which showed the lowest rates for patients on combination therapy.

Cardiac events were observed in about 10-15% of patients treated with acalabrutinib in the pivotal studies and pooled safety data, with slightly higher rates for combined A-G treatment. The leading cause was **atrial fibrillation,** reported in about 3-5% of patients. AE incidences of **anaemia** and **thrombocytopenia** were approximately 15% and 10-15%, respectively, while **neutropenia** was reported more frequently, with rates of about 15-30% and with notably higher rates of neutropenia for the combined A-G treatment than for acalabrutinib monotherapy. Corresponding laboratory abnormalities were even higher. Atrial fibrillation has been labelled in the information for healthcare professionals.

Hepatotoxicity occurred in about 3-7% of patients in the pivotal studies and pooled safety data, and was mostly related to liver function test increases, particularly in transaminase levels. The rates were higher for combined A-G treatment than for acalabrutinib monotherapy.

Hypertension was reported in about 9-13.5% of CLL patients in the safety pool, which is slightly higher than the rates observed in the two pivotal studies of about 5-7%. The rates were higher for combined A-G treatment than for acalabrutinib monotherapy. Hypertension has been labelled in the information for healthcare professionals.

Infections, including opportunistic infections are among the most common AEs related to acalabrutinib treatment. They were reported in about two-thirds to three-quarters of all patients, with higher rates for combined A-G treatment than for acalabrutinib monotherapy. The leading causes were **respiratory tract infections** (upper and lower respiratory tract, sinusitis, nasopharyngitis, bronchitis) **and pneumonia**, but included other frequent infections such as **urinary tract infections,** and **cellulitis**. Infections were more common for combined A-G treatment than for acalabrutinib monotherapy. Infections have been labelled in the information for healthcare professionals.

ILD/pneumonitis and **tumour lysis syndrome** (TLS) were reported at rates of about 1% (ILD/pneumonitis) and below 1% (TLS), which were comparable to the two pivotal studies.

Haemorrhages: Haemorrhagic events occurred in 33-48% of patients across the pooled safety data, whereas corresponding rates in the two pivotal studies appeared to be slightly lower, between about 25-40%. However, the rates of **major haemorrhages** were comparable, at about 2-3%. As in Studies 007 and 309, the leading causes of major haemorrhages were **gastrointestinal haemorrhages** in the safety pool. Other major bleeding events included **epistaxis**, **retinal** and **intracranial haemorrhages**. Haemorrhages have been labelled in the information for healthcare professionals.

Second primary malignancies (SPMs): A substantial proportion of 10-15% of patients experienced SPMs following acalabrutinib treatment in the two pivotal studies. While, in Study 007, the imbalance between acalabrutinib treatment arms and the comparator treatments was small and apparently limited to skin tumours, there was a notable imbalance in the proportions of patients reported with SPMs in Study 309, with approximately three times higher rates after acalabrutinib treatment than in

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the comparator treatment arm. Many other tumours were reported, too, albeit with only small numbers on an individual tumour level. The numbers observed in the two pivotal studies are confirmed by pooled safety data, the latter suggesting no increase in SPMs by combined therapy. Historical data from CLL patients show that the incidence of SPMs, haematological and solid tumours, is higher than that for the age- and sex-matched population, and is higher in CLL patients who had received prior chemotherapy compared to untreated patients or those with an unknown treatment status. For solid tumours, the excess risk appears to be mainly due to skin and respiratory cancers, but increased frequencies were also noted for brain, stomach and bladder SPMs (Kumar et al. 2019; Robak et al. 2004; Robak and Robak 2007; Royle et al. 2011). In addition, based on historical data, SPM rates appear to be similar between acalabrutinib and another BTK inhibitor (Bond et al. 2020; Byrd et al. 2019; Coutre et al. 2019).It should also be noted that the SPM rate was higher in Study 309 compared with Study 007, although the follow-up/exposure times were substantially shorter (16 vs. 28 months), suggesting that factors unrelated to acalabrutinib were also involved. To some extent, it is reassuring that most SPMs were non-melanoma skin cancers, which can be monitored and generally have favourable treatment outcomes. Furthermore, when evaluating the benefit-risk ratio, it should be borne in mind that overall mortality and the rates of fatal AEs in Studies 007 and 309 were lower in the acalabrutinib treatment arms than for those on comparator therapies. In addition, the incidence of SPMs does not appear to differ meaningfully from that for another BTK inhibitor, which may suggest the presence of a class effect.

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Potential CNS effects: A high proportion of patients with **contusions,** about 20-30%, was reported in the pooled safety data. In addition, **dizziness** (about 11.5-24%) and **falls** (about 8-15%) were observed in a notable proportion of CLL patients on monotherapy and combination therapy, respectively, with higher rates for combined acalabrutinib + obinutuzumab treatment than for acalabrutinib monotherapy. A similar picture was seen in Study 007, where syncope occurred in 2-3% of those patients receiving acalabrutinib treatments, and with potentially related injuries such as skin abrasions/lacerations, haematoma/increased tendency to bruise, limb injuries and bone fractures. The substantial proportion of patients experiencing headache, which is the most common AE for acalabrutinib treatment, may be explained by relevant CNS effects of acalabrutinib. In particular, it cannot be excluded that such CNS effects lead to contusions, falls and related injuries through dizziness/vertigo, which is of concern for the target population of elderly people. Contusions, dizziness and falls are described in the information for healthcare professionals, while falls and syncope will be characterised further by defining them as AESIs for PSUR reporting.

Summary of differences between acalabrutinib monotherapy and combined A-G treatment:
More **AEs of grade ≥ 3** were reported for the combination (approximately 70% vs. 50%), mainly due to higher incidences of **neutropenia** and, to a lesser degree, thrombocytopenia. Similarly, more **SAEs** were observed for the combination (approximately one third vs. 40%), mainly due to higher incidences of **serious infections** such as pneumonia. Generally, frequencies of TEAEs were higher for the combined A-G treatment than for acalabrutinib monotherapy, with differences > 10% at the PT level observed for **fatigue**, **dizziness**, **neutropenia**, **maculopapular rash**, and **infusion-related reactions**. Of further note, higher rates were also reported for infections, musculoskeletal events,

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increased transaminases, contusion, and falls. However, AEs leading to treatment discontinuation were comparable, and lower death rates (reduction by about 2%), including a trend to lower fatal AEs, were reported for the combination compared with the monotherapy. Of further note, SPM rates were comparable between both treatment regimens.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Both pivotal trials met their primary endpoint and demonstrated prolongation of PFS as the main treatment benefit. Based on historical data, the effects of acalabrutinib treatment in both pivotal studies on PFS, ORR and OS are in line with published results for another BTK inhibitor approved in Switzerland for the treatment of CLL in both the 1L and R/R setting. Results of additional post-hoc analyses suggest better efficacy for combined acalabrutinib + obinutuzumab compared with acalabrutinib monotherapy in the 1L treatment of CLL, although pivotal Study 007 was not designed to investigate this comparison. Furthermore, efficacy data are immature, and updated results from the final analyses will be evaluated to confirm this conclusion. To this end, the applicant has committed to submit the final clinical study reports for studies 007 and 309 along with tabulated summaries of updated safety data concerning SPMs, Richter Transformation, PML (progressive multifocal leukoencephalopathy), pneumonitis/ILD and CNS effects.

Although important risks have been identified, the safety of acalabrutinib is in line with what one could expect from a BTK inhibitor. The increased toxicity of combined acalabrutinib + obinutuzumab treatment compared with acalabrutinib monotherapy has been sufficiently addressed in the information for healthcare professionals, and is counterbalanced by potential efficacy advantages of the combined therapy. Clinicians experienced in oncology are able to manage the safety profile of acalabrutinib observed to date.

In summary, a positive benefit-risk ratio has been determined for the approved indication (see information for healthcare professionals in the Appendix). The approved indication adequately reflects the patient population investigated in both pivotal studies. Particularly concerning the therapy of patients with previously untreated CLL (1L indication), based on pivotal Study 007 the indication has been approved for patients aged 65 years and above, or adult patients with coexisting conditions, and obinutuzumab has been specified as the combination partner of acalabrutinib in the indication wording.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Calquence was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

CALQUENCE, hard capsules

Composition

Active substances

Acalabrutinib

Excipients

Capsule content:
Microcrystalline cellulose
Colloidal silicon dioxide
Partially pregelatinized starch (maize)
Magnesium stearate (E572)
Sodium starch glycolate (Type A)

Capsule Shell:
Gelatine
Titanium dioxide (E171)
Yellow iron oxide (E172)
FD&C Blue 2 (Indigotine/Indigo carmine) (E132)

Printing Ink*:*
Shellac – 45% (20% esterified) in ethanol
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonium hydroxide 28%
1 hard capsules contains 0.25 mg sodium.

Pharmaceutical form and active substance quantity per unit

Hard Capsule with 100 mg acalabrutinib.

Size 1 hard gelatine capsule with a yellow body and blue cap, marked in black ink with «ACA 100 mg».

Indications/Uses

CALQUENCE monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are 65 years and older or have comorbidities (see “Properties/Effects”).

CALQUENCE monotherapy is indicated for the treatment of adult patients with CLL who have received at least one prior therapy (see “Properties/Effects”).

Dosage/Administration

Treatment with CALQUENCE should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Usual dosage

The recommended dose of CALQUENCE for the treatment of CLL is 100 mg (1 hard capsule) twice daily, either as monotherapy or in combination with obinutuzumab. Refer to the obinutuzumab prescribing information for recommended obinutuzumab dosing information. (For details of the combination regimen, see section “Properties/Effects”).

Doses should be separated by approximately 12 hours.

Treatment with CALQUENCE should continue until disease progression or unacceptable toxicity.

Mode of administration

CALQUENCE should be swallowed whole with water at approximately the same time each day. CALQUENCE can be taken with or without food. The capsule should not be chewed, dissolved, or opened.

Missed dose

If a patient misses a dose of CALQUENCE by more than 3 hours, instruct the patient to take the next dose at its regularly scheduled time. Extra capsules of CALQUENCE should not be taken to make up for a missed dose.

Dose adjustment following undesirable effects/interactions

Recommended dose modifications of Calquence for Grade ≥ 3 adverse reactions are provided in Table 1.

Table 1. Recommended Dose Adjustments for Adverse Reactions*

Adverse reaction	**Adverse reaction occurrence**	**Dose modification** (Starting dose = 100mg approximately every 12 hours)
Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia Or Grade 4 neutropenia lasting longer than 7 days Any other unmanageable Grade 3 or any other Grade 4 toxicities	First and second	Interrupt Calquence Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at 100mg approximately every 12 hours
	Third	Interrupt Calquence Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at a reduced frequency of 100mg once daily
	Fourth	Discontinue Calquence

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Table 2. Use with CYP3A Inhibitors or Inducers and Gastric Acid Reducing Agents

	Co-administered Medicinal Product	**Recommended CALQUENCE Use**
CYP3A Inhibitors	Strong CYP3A Inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitor	100 mg once daily.
CYP3A Inducers	Strong CYP3A Inducers	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg twice daily.
	Proton Pump Inhibitors	Avoid concomitant use.

Gastric Acid Reducing Agents	H2-Receptor Antagonists	Take CALQUENCE 2 hours before taking a H2-receptor antagonist.
	Antacids	Separate dosing by at least 2 hours.

Special dosage instructions

Patients with impaired renal function

No dose adjustment is recommended in patients with mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73m^2 as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics and safety of CALQUENCE in patients with severe renal impairment (eGFR less than 29 mL/min/1.73m^2) or end-stage renal disease have not been studied (see section “Pharmacokinetics”).

Patients with impaired hepatic function

No dose adjustment is recommended in patients with mild or moderate hepatic impairment (Child-Pugh A, Child-Pugh B, or total bilirubin between 1.5-3 times the upper limit of normal [ULN] and any AST). It is not recommended to administer CALQUENCE in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3 times ULN and any AST) (see section “Pharmacokinetics”).

Elderly patients (≥ 65 years)

No dose adjustment is necessary based on age (see section «Pharmacokinetics»).

Children and adolescents

The safety and efficacy of CALQUENCE in children and adolescents aged less than 18 years have not been established.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Second Primary Malignancies

Second primary malignancies, including skin and non-skin cancers, occurred in 13.4% of patients treated with CALQUENCE monotherapy (median time of follow-up 26.4 months) and in 13% treated with combination therapy of CALQUENCE and obinutuzumab (median time of follow-up 30.2 months).

The most frequent second primary malignancy was non-melanoma skin cancer, which occurred in 7.7% (any grade) of patients treated with monotherapy and in 7.6% of patients treated with combination therapy of CALQUENCE and obinutuzumab.
Monitor patients for the appearance of skin cancers.

Infections

Infections have occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy (66.7%) and in combination with obinutuzumab (74.0%), most often due to upper respiratory tract infection (22.0% and 31.4%, respectively) and sinusitis (10.7% and 15.2%, respectively). Serious infections (bacterial, viral or fungal), including fatal events have occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy (17.6%) and in combination with obinutuzumab (21.5%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia. Infections due to hepatitis B virus (HBV) and herpes zoster virus (HSV) reactivation, aspergillosis and progressive multifocal leukoencephalopathy (PML) have occurred (see section “Underiable effects”).

Viral reactivation cases of hepatitis B reactivation have been reported in patients receiving CALQUENCE. Hepatitis B virus (HBV) status should be established before initiating treatment with CALQUENCE. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of CALQUENCE within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected, then appropriate diagnostic evaluations should be undertaken and treatment with CALQUENCE should be suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Haemorrhage

Serious haemorrhagic events, including fatal events, have occurred in patients with haematologic malignancies (n=1040) treated with CALQUENCE monotherapy. Major haemorrhage (Grade 3 or higher bleeding events, serious, or any central nervous system events) occurred in 3.6% of patients, with fatalities occurring in 0.1% of patients. The most common major haemorrhage were haematoma (0.5%), epistaxis, gastrointestinal haemorrhage, haematuria (each 0.3%), retinal haemorrhage, gastric haemorrhage and intracranial haemorrhage (each 0.2%), Overall, bleeding events including bruising and petechiae of any grade occurred in 46% of patients with haematological malignancies. The mechanism for the bleeding events is not well understood.

Warfarin or other vitamin K antagonists should not be co-administered with CALQUENCE.

Patients receiving antithrombotic agents may be at increased risk of haemorrhage. Use caution with antithrombotic agents. Additional monitoring of patients for signs and symptoms of bleeding is necessary when concomitant use is medically necessary.

Based on a benefit-risk assessment, CALQUENCE should not be administered for at least 3 days pre- and post-surgery.

Cytopenias

Cytopenias have occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy and in combination with obinutuzumab. Overall frequencies for neutropenia were 12.3% and 25.1%, respectively, for anaemia 13.3% and 10.8%, respectively and for thrombocytopenia 6.1% and 10.3%, respectively. Treatment-emergent Grade 3 or 4 cytopenias occurred in patients with haematologic malignancies treated with CALQUENCE monotherapy and in combination with obinutuzumab, including neutropenia (11.2% and 23.8%, respectively), anaemia (7.8% and 5.4%, respectively) and thrombocytopenia (3.6% and 6.7%, respectively) based on laboratory measurements.

Monitor complete blood counts as medically appropriate.

Artial Fibrillation

In patients with haematologic malignancies (n=1040) treated with CALQUENCE monotherapy, Grade 3 atrial fibrillation/flutter occurred in 1.2% of patients, and any grade in 4.0% of patients. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as appropriate.

Tumor Lysis Syndrome (TLS)

Tumour lysis syndrome has been reported with acalabrutinib therapy. Patients with high tumour burden prior to treatment are at risk of tumour lysis syndrome. Monitor patients closely and take appropriate precautions.

Potential at-risk populations that have not been investigated

Patients with central nervous system (CNS) lymphoma or leukemia; known prolymphocytic leukemia or history of or currently suspected Richter's syndrome; Significant cardiovascular disease; uncontrolled active systemic fungal, bacterial, viral, or other infection, including active hepatitis B or C infection, and known history of infection with human immunodeficiency virus (HIV); drug-induced pneumonitis; history of stroke or intracranial hemorrhage within 6 months before first dose of study drug; history of bleeding diathesis; anticoagulation with warfarin or equivalent vitamin K antagonists; treatment with proton-pump inhibitors or requiring steroids at daily doses >20 mg prednisone equivalent systemic exposure daily have been excluded from the clinical trials.

This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, i.e. is essentially «sodium-free».

Interactions

Active Substances that may increase acalabrutinib plasma concentrations

CYP3A Inhibitors

Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased acalabrutinib C_{max} and AUC by 3.9-fold and 5.1-fold in healthy subjects (N=17), respectively.

Active substances that may decrease acalabrutinib plasma concentrations

CYP3A Inducers

Co-administration of a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} and AUC by 68% and 77% in healthy subjects (N=24), respectively.

Gastric Acid Reducing Medications

Acalabrutinib solubility decreases with increasing pH. Co-administration of acalabrutinib with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects.
Acalabrutinib 100mg was co-administered with the mechanism based CYP3A inhibitor grapefruit juice alone or in combination with omeprazole 40mg. Grapefruit juice (240 mL) was given once 12 hours before dose intake, and a second time together with the 100 mg acalabrutinib dose.
When co-administered with alone grapefruit juice (N=12) the geometric mean ratio (GMR) % (90% CI) C_{max} was 65.04 (45.30 - 93.38) and $AUC_{0\text{-last}}$ 83.49 (71.93 - 96.91).
When co-administered with grapefruit juice in combination with omeprazole 40mg (N=12) the GMR % (90%CI) C_{max} was 56.32 (39.23 - 80.86) and $AUC_{0\text{-last}}$ 84.47 (72.78 - 98.05).

Effect of Aclabrutinib and its active metabolite, ACP-5862 on the metabolism of other substances

In vitro, acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, UGT1A1, and UGT2B7. ACP-5862 is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6, CYP3A4/5, UGT1A1, and UGT2B7 *in vitro*. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4 mRNA; ACP-5862 weakly induces CYP3A4.

CYP3A SubstratesBased on in vitro and clinical data, and PBPK modelling, no interaction with CYP3A4 substrates is expected at the clinically relevant concentrations (see section “Properties/Effects”).

Effects of Acalabrutinib and its active metabolite, ACP-5862, on Drug Transport Systems

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP (see section “Pharmacokinetics”).
ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1.

Interactions with transport proteins

In vitro, acalabrutinib and its active metabolite, ACP-5862, are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1 and OATP1B3, *in vitro*. ACP-5862 is not a substrate of OATP1B1 or OATP1B3.

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

Effect of food on acalabrutinib

In healthy subjects, administration of a single 75 mg dose of acalabrutinib with a high fat, high calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 73% and T_{max} was delayed 1-2 hours.

Pregnancy, lactation

Pregnancy

There are insufficient clinical data on CALQUENCE use in pregnant women. Based on findings from animal studies, there may be a risk to the foetus and an dysfunctional labor (dystocia) from exposure to acalabrutinib during pregnancy (see section “Preclinical data”).

CALQUENCE must not be administered during pregnancy unless clearly indicated.
Women of childbearing potential or patients with a partner of childbearing potential should use a very reliable method of contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE. If a hormonal method of contraception is used, an additional barrier method should also be used.
If the patient becomes pregnant while taking CALQUENCE, the patient must be informed about the potential hazard to the foetus.

Lactation

It is not known whether acalabrutinib or its metabolites are excreted in human milk. There are no data on the effect of acalabrutinib on the breast-fed infant or on milk production. Acalabrutinib and its active metabolite were excreted in rat milk (see «Preclinical data»).A risk to the suckling child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with CALQUENCE and for 2 weeks after receiving the last dose.

Fertility

There are no data on the effect of CALQUENCE on human fertility. In a nonclinical study of acalabrutinib in male and female rats, no adverse effects on fertility parameters were observed (see section “Preclinical Data”).

Effects on ability to drive and use machines

The influence of Acalabrutinib on the ability to drive and use machines has not been studied. As during treatment with acalabrutinib the events of headache, fatigue, dizziness, falls and syncopes have been reported, patients who experience these symptoms should be advised not to drive or use machines until symptoms abate. Patients should be made aware of the possible occurrence of these effects.

Undesirable effects

CALQUENCE monotherapy

The overall safety profile of acalabrutinib is based on pooled data from 1040 patients with haematologic malignancies receiving acalabrutinib monotherapy and pooled data from 223 patients treated with a combination of acalabrutinib and obinutuzumab.

Of the 1040 patients treated with Calquence monotherapy, the most common (≥ 10%) adverse drug reactions (ADRs) of any grade reported were musculoskeletal pain (44.1%), headache (37.8 %), diarrhoea (36.7 %), bruising (34.1%), upper respiratory tract infection (22%), nausea (21.7 %), fatigue (21.3 %), cough (21.0%), rash (20.3%), arthralgia (19.1%), neutropenia (15.7 %), constipation (14.5 %), pyrexia (14.3%), anemia (13.8 %), dizziness (13.4 %), vomiting (13.3 %), haemorrhage / haematoma (12.6%), second primary malignancy (12.2 %), abdominal pain (12.5 %), sinusitis (10.7%), and dyspnea (10.7%)..
The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were infection (17.6%), neutropenia (14.2%), and anaemia (7.8%).

The most frequent serious adverse drug reactions (≥1%) which included fatal events were infections to include pneumonia (4.9%) and sepsis (2.2%) and second primary malignancies (4.5%). The infections predominantly occurred in the absence of Grade 3 or 4 neutropenia (see section “Warnings and Precautions”).

Dose reductions due to adverse events were reported in 4.2% of patients. Discontinuation due to adverse events were reported in 9.3% of the patients with the most common events leading to disccontiunation being pneumonia (0.5%), thrombocytopenia (0.5%), and myelodysplastic syndrome (0.3%)..

Calquence combination therapy

Of the 223 patients treated with CALQUENCE combination therapy, the most common (≥ 10%) ADRs of any grade reported in patients were musculoskeletal pain (69.4%), diarrhoea (43.9%), headache (43%), bruising (38.6%), neutropenia (31.8%), upper respiratory tract infection (31.4%), rash (30.9%), fatigue (30.5%), nausea (26.9%), arthralgia (26.9%), dizziness (23.8%), constipation (20.2%), vomiting (19.3%), haemorrhage / haematoma (17.5%), sinusitis (15.2%), abdominal pain (14.8%), thrombocytopenia (13.9%), nasopharyngitis (13.5%), second primary malignancy (13%), urinary tract infection (13%), anaemia (11.7%), and pneumonia (10.8%). The most commonly reported (≥ 5%) Grade ≥3 adverse drug reactions were neutropenia (30%), thrombocytopenia (9%), anaemia (5.8%), and pneumonia (5.4%).

In pooled analysis of patients treated with combination of Acalabrutinib with Obinutuzumab (n=223) versus patients treated with Acalabrutinib monotherapy (n=1040) higher overall frequency of the following adverse reactions was observed: infections (74 vs 66.7%) including Grade ≥3 infections (21.5 vs 17.6%), upper respiratory tract (31.4 vs 22%) and other very common infections, musculoskeletal and connective tissue disorders (58.3 vs 51.6%) primarily driven by arthralgia (26.9 vs 19.1%) and pain in extremity (13.9 vs 8.9%), fatigue (30.5 vs 21.3%), contusion (27.4 vs 21.7%), dizziness (23.8 vs 13.4%) and falls (14.8 vs 7.9%). The overall frequency of ≥Grade 3 AE (70.4 vs 54.1%) was also increased in combination pool vs monotherapy pool and was primarily driven by higher incidence of Grade ≥3 neutropenia (23.8 vs 11.2%). In addition, higher rates with ≥10% PT differences of neutropenia (25.1 vs 12.3%), infusion related reactions (19.3 vs 0.8%) and maculo-papular rash (17 vs 4.9%) were observed.

The ADRs identified in clinical studies with patients receiving Acalabrutinib monotherapy versus combination therapy of Acalabrutinib with Obinutuzumab are described in Table 3.

The median duration of acalabrutinib monotherapy treatment across the pooled dataset was 24.6 months.

Adverse drug reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are sorted by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is based on the CIOMS III convention and is defined as: very common (≥1/10); common (>1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 3. Adverse drug reactions* of Patients with Haematological Malignancies treated with acalabrutinib monotherapy (n=1040) and with acalabrutinib in combination with obinutuzumab (n=223)

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequencyall CTCAE-Grades [Frequency of CTCAE Grade ≥3]†	
		Monotherapy	**Combination therapy**
Infections and Infestations	Upper respiratory tract infection	Very common (22%) [0.8%]	Very common (31.4%) [1.8%]
	Sinusitis	Very common (10.7%) [0.3%]	Very common (15.2%) [0.4%]
	Pneumonia	Common (8.7%) [5.1%]	Very common (10.8%) [5.4%]
	Urinary tract infection	Common (8.5%) [1.5%]	Very common (13%) [0.9%]
	Nasopharyngitis	Common (7.4%) [0%]	Very common (13.5%) [0.4%]
	Bronchitis	Common (7.6%) [0.3%]	Common (9.9%) [0%]
	Herpes viral infections[1]	Common (5.9%) [0.7%]	Common (6.7%) [1.3%]
	Sepsis[1]	Common (2.6%) [2.5%]	Common (4%) [4%]
	Aspergillus infections[1]	Uncommon (0.5%) [0.4%]	Very rare (0%) [0%]
	Hepatitis B reactivation	Uncommon (0.1%) [0.1%]	Uncommon (0.9%) [0.1%]
Neoplasms benign, malignant and unspecified[7]	Second Primary Malignancy[2]	Very common (13.4%) [4.9%]	Very common (13%) [4.0%]
	SPM excluding non-melanoma skin[3]	Common (7.7%) [4.5%]	Common (6.3%) [3.6%]
	Non-Melanoma Skin Malignancy	Common (6.6 %) [0.5%]	Common (7.6%) [0.4%]
Blood and lymphatic system disorders			
	Neutropenia[1]	Very common (15.7 %) [14%]	Very common (31.8%) [30%]
	Anemia	Very common (13.8 %) [8%]	Very common (11.7%) [5.8%]
	Thrombocytopenia	Common (8.9 %) [4.8%]	Very common (13.9%) [9%]
	Lymphocytosis	Uncommon (0.3%) [0.2%]	Uncommon (0.4%) [0.4%]

	Absolute neutrophil count decreased[8]	Very common (41,8 %) [20,7%]	Very common (57.4%) [35%]
	Haemoglobin decreased[8]	Very common (42,6 %) [10,1%]	Very common (43.9%) [9%]
	Platelets decreased[8]	Very common (31,1 %) [6,9%]	Very common (46.2%) [10.8%]
Metabolism and nutrition disorders	Tumour Lysis Syndrome[4]	Uncommon (0.5 %) [0.4%]	Uncommong (1.8%) [1.3%]
Nervous system disorders	Headache	Very common (37.8 %) [1.1%]	Very common (43%) [0.9%]
	Dizziness / Vertigo[1]	Very common (16%) [0.4%]	Very common (26%) [0%]
Cardiac disorders	Atrial Fibrillation/Flutter[5]	Common (4.4 %) [1.3%]	Common (3.1%) [0.9%]
Vascular disorders	Bruising[1]	Very common (34.1%) [0%]	Very common (38.6%) [0%]
	Contusion	Very Common (21.7%) [0%]	Very common (27.4%) [0%]
	Petechiae	Very Common (10.7%) [0%]	Very common (11.2%) [0%]
	Ecchymoses	Common (6.3%) [0%]	Common (3.1%) [0%]
	Haemorrhage / haematoma[1]	Very common (12.6%) [1.8%]	Very common (17.5%) [1.3%]
	Gastrointestinal haemorrhage	Common (2.3%) [0.6%]	Common (3.6%) [0.9%]
	Intracranial haemorrhage	Common (1%) [0.5%]	Common (3.1%) [0%]
	Epistaxis	Common (7 %) [0.3%]	Common (8.5%) [0%]
	Hypertension	Common (7.6%) [3.5%]	Very common (13.5%) [3.6%]

Respiratory, thoracic and mediastinal disorders	Cough	Very common (21.0%) [0.1%]	Very common (30.5%) [0.4%]
Gastrointestinal disorders	Diarrhoea	Very common (36.7 %) [2.6%]	Very common (43.9%) [4.5%]
	Nausea	Very common (21.7 %) [1.2%]	Very common (26.9%) [0%]
	Constipation	Very common (14.5 %) [0.1%]	Very common (20.2%) [0%]
	Abdominal pain[1]	Very common (12.5 %) [1%]	Very common (14.8%) [1.3%]
	Vomiting	Very common (13.3 %) [0.9%]	Very common (19.3%) [0.9%]
Skin and subcutaneous tissue disorders	Rash[1]	Very common (20.3%) [0.6%]	Very common (30.9%) [1.8%]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[6]	Very common (44.1%) [1.8%]	Very common (69.4%) [2.5%]
	Arthralgia	Very common (19.1%) [0.7%]	Very common (26.9%) [1.3%]
General disorders and administration site conditions	Fatigue	Very common (21.3 %) [2%]	Very common (30.5%) [1.8%]
	Asthenia	Common (5.3 %) [0.8%]	Common (7.6%) [0.4%]

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[1] Includes multiple ADR terms.

[2] Second primary malignancies were defined by SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non-haemoatological malignant tumours SMQ), SMQ Malignant lymphomas [narrow], and SMQ Myelodysplastic syndrome [narrow]).

[3] Second primary malignancies (excl non-melanoma skin) were defined by the criteria for second primary malignancies excluding PTs mapping to High Level Term Skin neoplasms malignant and unspecified (excl melanoma).

[4] One case of drug-induced Tumour Lysis Syndrome was observed in acalabrutinib arm in the ASCEND Study

[5] Includes any PT containing atrial fibrillation or atrial flutter.

[6] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal discomfort, myofascial pain syndrome, neck pain, pain in extremity, myalgia, spinal pain

[7] Includes events beyond the end of studies reporting period

[8] Treatment-emergent haematological laboratory abnormalities

Elderly patients

Of the 1040 patients in clinical trials of CALQUENCE monotherapy, 41% were ≥ 65 years of age and less than 75 years of age and 22% were 75 years of age or older. Patients who were 75 years of age or older had higher frequency of Grade ≥3 AE (65.4%) as compared to patients in ≥ 65 years of age and less than 75 years of age group (54.2%) or those less than 65 years of age (47.4%). Higher rates of all grade anaemia (18.9%, 11.1% and 12.4%, respectively), all grade pneumonia (12.7%, 8.5% and 6.4%, respectively) including grade ≥3 pneumonia (7.9%, 4.2% and 4.4%, respectively), as well as all grade urinary tract infections (12.3%, 9.4% and 5.2%, respectively) were observed in patients of 75 years of age and older as compared to the other two age groups.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for acalabrutinib overdose and symptoms of overdose have not been established. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

Properties/Effects

ATC code

L01EL02

Mechanism of action

Acalabrutinib is a selective small-molecule inhibitor of Bruton tyrosine kinase (BTK). BTK is a signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis.
Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK (IC_{50} ≤ 5 nM) with minimal off-target interactions. In a screen of 380 mammalian wild-type kinases, the only additional kinase interactions at clinically relevant concentrations of acalabrutinib and ACP-5862 were with BMX and ERBB4, with 3- to 4-fold less potency than BTK.

In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69, inhibited malignant B-cell proliferation and survival, and had minimal activity on other immune cells (T cells and NK cells).

Pharmacodynamics

In patients with B-cell malignancies dosed with 100 mg twice daily, median steady state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology

In a dedicated QT study, at a dose 4 times the maximum recommended dose, CALQUENCE does not prolong the QT/QTc interval to any clinically relevant extent (e.g., not greater than or equal to 10 ms).

Clinical efficacy

Patients with Previously Untreated CLL

The safety and efficacy of CALQUENCE in previously untreated CLL were evaluated in a randomised, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. The CLL had to be CD20+, diagnosed according to IWCLL 2008 criteria and active/needing treatment. Furthermore, absolute neutrophil count and platelets had to be independent of growth factor or transfusion support and had

to be above 750 and 50,000 cells/µL, respectively (in case of bone marrow involvement above 500 and 30,000 cells/µL, respectively). Patients with CNS involvement, prolymphocytic leukemia or Richter syndrome were excluded from participation. Patients received CALQUENCE plus obinutuzumab, CALQUENCE monotherapy, or obinutuzumab plus chlorambucil. Patients 65 years of age or older or between 18 and 65 years of age with coexisting medical conditions (creatinine clearance 30-69 mL/min and/or CIRS-G score > 6) were included in ELEVATE-TN. The trial also allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

Patients were randomised in a 1:1:1 ratio into 3 arms to receive

1. CALQUENCE plus obinutuzumab (CALQUENCE+G): CALQUENCE 100 mg was administered twice daily starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.
2. CALQUENCE monotherapy: CALQUENCE 100 mg was administered twice daily until disease progression or unacceptable toxicity.
3. Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6. Each cycle was 28 days.

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and geographic region (North America and Western Europe versus Other). After confirmed disease progression, 45 patients randomised on the GClb arm crossed over to CALQUENCE monotherapy.

The baseline characteristics were generally balanced in the three arms (Calquence plus obinutuzumab [n=179], Calquence monotherapy [n=179] and obinutuzumab plus chlorambucil [n=177]): median age 70, 70 and 71 years, respectively; 62%, 62% and 59.9% were male, respectively; 94.4%, 92.2% and 94.4% had an ECOG performance status of 0-1, respectively; the median time from diagnosis was 30.5, 24.4 and 30.7 months, respectively; cytogenetic factors (del17p, del11q, TP53 mutation, unmutated IGHV, complex karyotype) as well as Rai stage were all generally balanced.

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 28.3 months, PFS by IRC indicated a 90% statistically significant reduction in the risk of disease progression or death for previously untreated CLL patients in the CALQUENCE+G arm compared to the GClb arm. At the time of analysis, median overall survival had not been reached in any arm with a total of 37 deaths: 9 (5%) in the CALQUENCE+G arm, 11 (6.1%) in the CALQUENCE monotherapy arm, and 17 (9.6%) in the GClb arm. Efficacy results are presented in Table 3..

Table 3. Efficacy Results in (ELEVATE-TN) Patients with CLL

Characteristic	**CALQUENCE plus Obinutuzumab N=179**	**CALQUENCE-Monotherapy n=179**	**Obinutuzumab plus Chlorambucil n=177**
Progression-Free Survival *			
Number of events (%)	14 (7.8)	26 (14.5)	93 (52.5)
Median (95%-KI), months	n.e.	n.e. (34.2; n.e.)	22.6 (20.2; 27.6)
HR† (95%-KI)	0.10 (0.06; 0.17)	0.20 (0.13; 0.30)	-
Overall Response Rate *			
ORR, n (%) (95%-KI)	168 (93.9) (89.3; 96.5)	153 (85.5) (79.6; 89.9)	139 (78.5) (71.9; 83.9)
CR, n (%)	23 (12.8)	1 (0.6)	8 (4.5)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; CRi=complete response with incomplete blood count recovery; nPR=nodular partial response; PR=partial response

* Per IRC assessment

† Based on stratified Cox-Proportional-Hazards model

PFS results for CALQUENCE with or without obinutuzumab were consistent across subgroups, including high risk features (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV)..

Richter's transformation was reported for 6 patients (3.4%) in the acalabrutinib monotherapy arm (no patients in the combination therapy arm) during the randomized period and for 1 patient (2.2%) in the chlorambucil / obinutuzumab arm during the crossover period.

Patients with CLL who received at least one prior therapy

The safety and efficacy of CALQUENCE in relapsed or refractory CLL were evaluated in a randomised, multi-centre, open-label phase 3 study (ASCEND) of 310 patients who received at least one prior therapy. Prior treatment with a B-cell lymphoma (BCL)-2 inhibitor (e.g. Venetoclax), a B-cell receptor (BCR) inhibitor (e.g. BTK or PI3K inhibitors) or radio- or toxin-conjugated antibody therapy was not permitted. The CLL had to be CD20+, diagnosed according to IWCLL 2008 criteria and active/needing treatment. Furthermore, absolute neutrophil count and platelets had to be independent of growth factor or transfusion support and had to be above 750 and 50,000 cells/µL, respectively (in case of bone marrow involvement above 500 and 30,000 cells/µL, respectively). Patients with CNS involvement, prolymphocytic leukemia or Richter syndrome were excluded from participation. Patients received CALQUENCE monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. The trial allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

Patients were randomised 1:1 to receive either:

1. CALQUENCE 100 mg twice daily until disease progression or unacceptable toxicity, or
2. Investigator's choice:
    1. Idelalisib 150 mg twice daily until disease progression or unacceptable toxicity in combination with ≤ 8 infusions of rituximab (375 mg/m2/500 mg/m^2) on Day 1 of each 28-day cycle for up to 6 cycles
    2. Bendamustine 70 mg/m^2 (Day 1 and 2 of each 28-day cycle) in combination with rituximab (375 mg/m^2/500 mg/m^2) on Day 1 of each 28-day cycle for up to 6 cycles

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2) and number of prior therapies (1 to 3 versus ≥ 4). After confirmed disease progression, 35 patients randomised on investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab crossed over to CALQUENCE.

The baseline characteristics were generally balanced in the two arms (Calquence montherapy [n=155]): median age 68 and 67 years, respectively; 69.7% and 64.5% were male, respectively; 87.7% and 86.5% had an ECOG performance status of 0-1, respectively; the median time from diagnosis was 85.3 and 79 months, respectively; the median time since last prior CLL therapy to first dose was 26.4 and 22.7 months, respectively; cytogenetic factors (del17p, del11q, TP53 mutation, unmutated IGHV, complex karyotype) as well as Rai stage were all generally balanced.

The primary endpoint was PFS as assessed by IRC IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). At the time of the first pre-specified

analysis with a median follow-up of 16.1 months, CALQUENCE demonstrated a clinically meaningful and statistically significant improvement in IRC-assessed PFS compared with IR/BR (hazard ratio 0.31 [95% CI, 0.20 to 0.49] P < 0.0001)]. At the time of analysis, median overall survival had not been reached in any arm with a total of 33 deaths: 15 (9.7%) in the CALQUENCE monotherapy arm and 18 (11.6%) in the investiator's choice of either idelalisib plus rituximab or bendamustine plus rituximab arm. In a further not pre-specified analysis after a median follow-up period of 22 months, the median PFS, which in contrast to the primary endpoint as assessed by the investigator, was not achieved in the Calquence arm and was 16.8 months in the IR/BR arm (hazard ratio 0.27 [95% KI 0.18 to 0.40]). The data on overall survival remained immature with 21 (13.5%) and 26 (16.8%) events in the Calquence and comparator arm, respectively. Efficacy results of the pre-specified analysis are presented in Table 4.

Table 4. Efficacy Results in (ASCEND) Patients with CLL

	CALQUENCE Monotherapy n=155	**Investigator's choice of idelalisib + rituximab (n=119) or bendamustine + rituximab (n=36) n=155**
Progression-Free Survival *		
Number of events (%)	27 (17.4)	68 (43.9)
Median (95%-KI), months	n.e.	16.5 (14.0; 17.1)
HR† (95%-KI)	0.31 (0.20; 0.49)	
Overall Response Rate *		
ORR, n (%) (95%-KI)	126 (81,3) (74.4; 86.6)	117 (75.5) (68.1; 81.6)
CR, n (%)	0	2 (1.3)
Dauer des Ansprechens (DoR)		
Median (95%-KI), months	n.e.	13.6 (11.9; n.e.)

CI=confidence interval; HR=hazard ratio; NR=not reached; CR=complete response; PR=partial response

* Per IRC assessment

† Based on stratified Cox-Proportional-Hazards model

PFS results for CALQUENCE were consistent across subgroups, including high risk features (17p deletion, 11q deletion, TP53 mutation, and unmutated IGHV)..

Richter's transformation was reported for 4 patients (2.6%) in the acalabrutinib monotherapy arm and for 3 patients (2.0%) in the idelalisib plus rituximab / bendamustine plus rituximab arm during the

randomized period, and for 2 patients (5.7%) in the idelalisib plus rituximab / bendamustine plus rituximab arm during the crossover period.

Pharmacokinetics

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862, were studied in healthy subjects and 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 400 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 drug concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) of 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.

Absorption

The median time to peak plasma concentrations (T_{max}) was 0.75 hours, and 1.0 hour for ACP-5862. The absolute bioavailability of CALQUENCE was 25%.

Distribution

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.

Metabolism

In vitro, acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major metabolite in plasma 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.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The median $t_{1/2}$ of the active metabolite, ACP-5862, was 6.9 hours (range: 2.7 to 9.1) hours.

The mean apparent oral clearance (CL/F) was 134 L/hr for acalabrutinib and 22 L/hr for ACP-5862. 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 in urine and faeces.

Kinetics in specific patient groups

Based on population PK analysis, 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.

Renal impairment

Acalabrutinib undergoes minimal renal elimination. A pharmacokinetic study in patients with renal impairment has not been conducted.
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 pharmacokinetics 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 trials (see section “Dosage/Administration”).

Hepatic impairment

Acalabrutinib is metabolized in the liver. In dedicated hepatic impairment 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. 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).

Preclinical data

Repeat dose toxicity

Daily oral administration of acalabrutinib for up to 6 months duration in rats and 9 months in dogs was tolerated at exposure levels that exceed human therapeutic exposures at the recommended dose (1.1-fold in rats, 8.2-fold in dogs, based on AUC).

In rats, renal effects including tubular degeneration were observed at exposures 7 times or greater than that of the recommended human dose. Renal effects were reversible with complete recovery in rats exposed at levels 4.2 times the recommended human dose and partial recovery in rats at the higher exposures (6.8-fold or greater).

In rats, dose-responsive reversible liver findings including individual hepatocyte necrosis were observed after exposures 4.2 times or greater than that of the recommended human dose.

Cardiac toxicities (myocardial haemorrhage, inflammation, necrosis) were observed in rats that died during the study and at exposures equivalent to 6.8 times or greater than that of the human recommended dose. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the maximum tolerated dose (MTD). At exposures representing 4.2 times the human recommended dose, no cardiac toxicities were observed.

Genotoxicity/Mutagenicity

Acalabrutinib was not mutagenic in a bacterial reverse mutation assay, in an *in vitro* chromosome aberration assay, or in an *in vivo* mouse bone marrow micronucleus assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Reproductive toxicity

No effects on fertility were observed in male or female rats at exposures 10 or 9 times the human AUC exposure at the recommended dose, respectively.

In a combined fertility and embryofoetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryofoetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9-times the AUC in patients at the recommended dose of 100 mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma.

In an embryofoetal study in pregnant rabbits, acalabrutinib was administered orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Decreased foetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity (doses ≥ 100 mg/kg/day), which were 2.4-times greater than the human exposure levels at the recommended dose.

In a rat reproductive study, dystocia (prolonged /difficult labour) was observed at exposures > 2.3-times the clinical exposure at 100 mg twice daily.
Acalabrutinib and its active metabolite were present in the milk of lactating rats.
In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition and lactation, at doses of 50, 100, and 150 mg/kg/day. Dystocia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2-times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papilla was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5-times the AUC in patients at 100 mg approximately every 12 hours.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Store in the original packaging.
Do not store above 30°C.
Keep out of the reach of children.

Authorisation number

67790 (Swissmedic)

Packs

CALQUENCE 100 mg hard capsules:
Aluminium/Aluminium blisters. Cartons of 10 x 6 hard capsules [A].

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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