Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Acalabrutinib

Proprietary Product Name: Calquence

Sponsor: AstraZeneca Pty Ltd

February 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations 4

I. Introduction to product submission 7

Submission details 7

Product background 8

Regulatory status 9

Product Information 9

II. Registration timeline 9

III. Submission overview and risk/benefit assessment 10

Quality 10

Nonclinical 10

Clinical 12

Risk management plan 20

Risk-benefit analysis 22

Outcome 24

Attachment 1. Product Information 25

Common abbreviations

Abbreviation	Meaning
ACP-5862	Active metabolite of acalabrutinib
AE	Adverse event(s)
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCL-2	B-cell lymphoma 2
BCRP	Breast cancer resistance protein
BID	Twice daily; *bis in die* (Latin)
BTK	Bruton tyrosine kinase
CD5	Cluster of differentiation 5
CLL	Chronic lymphocytic leukaemia
CMI	Consumer Medicines Information
CNS	Central nervous system
COR-B	Comparable Overseas Regulator approach B
CYP3A4/5	Cytochrome P450 3A4/5
DLP	Data lock point
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency (EU)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol 5 dimensions
EU	European Union

Abbreviation	Meaning
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration (US)
GHS	Global health status
GI	Gastrointestinal
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practice(s)
HC	Health Canada
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Council for Harmonisation
IRC	Independent Review Committee
IV	Intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
MAR	Missing at random
MATE1	Multidrug and toxin extrusion protein 1
MCL	Mantle cell lymphoma
MMRM	Mixed model repeated measures
OCE	Oncology Center of Excellence (US FDA)
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PI	Product Information
PO	Oral, *per os* (Latin)
popPK	Population pharmacokinetic
PRO	Patient reported outcome

Abbreviation	Meaning
PSUR	Periodic safety update report
RMP	Risk management plan
SAE	Serious adverse event(s)
SLL	Small lymphocytic lymphoma
TEAE	Treatment emergent adverse event(s)
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum plasma concentration
TTNT	Time to next treatment
URTI	Upper respiratory tract infection
US(A)	United States (of America)
VAS	Visual Analogue Scale

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	22 November 2019
Date of entry onto ARTG:	22 November 2019
ARTG number:	321419
▼ *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved.
Active ingredient:	Acalabrutinib
Product name:	Calquence
Sponsor's name and address:	AstraZeneca Pty Ltd PO Box 131 North Ryde NSW 1670
Dose form:	Hard capsule
Strength:	100 mg
Container:	Blister pack
Pack size:	56 capsules
Approved therapeutic use:	*Calquence is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)*
Route of administration:	Oral
Dosage:	The recommended dose of Calquence for the treatment of CLL is 100 mg (1 capsule) twice daily, either as monotherapy or in combination with obinutuzumab. Administer Calquence prior to obinutuzumab when given on the same day. Refer to the obinutuzumab product information for recommended obinutuzumab dosing information (for details of the combination regimen, see section 5.1 Pharmacodynamic properties in the Product Information). Doses should be separated by approximately 12 hours. Treatment with Calquence should continue until disease progression or unacceptable toxicity. For further information refer to the Product Information.

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd (the sponsor) to register Calquence (acalabrutinib) 100 mg hard capsule for the following indication:

> *Calquence is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).*

Chronic lymphocytic leukaemia (CLL) is one of the chronic lymphoproliferative disorders, that is characterised by accumulation of functionally incompetent lymphocytes. These lymphocytes are usually monoclonal. The disease is considered identical to small lymphocytic lymphoma (SLL), an indolent non-Hodgkin's lymphoma. Hence this is included in the indication statement. The difference being that in CLL the disease arises mainly in the blood, whereas in SLL it is primarily nodal in involvement. The disease primarily affects an elderly population and is the most prevalent form of adult leukaemia. Diagnosis is established using peripheral blood examination and immunophenotyping and requires a minimum of 5 x 10^9/L monoclonal B-cells that co-express surface antigens cluster of differentiation 5 (CD5), CD19, CD20 and CD23.

Treatment is complex and is guided by disease indolence or progression, co-morbidities, previous treatments (if any) and specific mutations such as the 17p deletion and TP53 mutation. Chlorambucil has been a historic mainstay of treatment and subsequently, a group of drugs targeting the CD20 surface antigen were developed (for example, rituximab, obinutuzumab). In addition to these, there are now available novel molecularly targeted agents, such as Bruton tyrosine kinase (BTK) inhibitors (for example, ibrutinib), as well as the phosphoinositide-3 kinase inhibitor idelalisib. There are also the apoptosis regulating drugs, such as the B-cell lymphoma 2 (BCL-2) antagonist venetoclax.

Initial treatment of symptomatic disease can include chemotherapy paired with an anti-CD20 monoclonal antibody for those without the 17p or TP53 mutation (for example, chlorambucil plus (obinutuzumab or rituximab or ofatumumab), or ibrutinib alone), and ibrutinib or idelalisib or venetoclax for those with the mutation(s).

Relapsed disease for those without a 17p or TP53 mutation can be treated with repeat chemotherapy; ibrutinib or venetoclax or idelalisib or ofatumumab (for example, ibrutinib alone, idelalisib plus rituximab, idelalisib plus ofatumumab, ibrutinib plus rituximab plus bendamustine or venetoclex alone). For those with a 17p deletion or TP53 mutation, choices include idelalisib and rituximab, idelalisib and ofatumumab, or venetoclax alone.

Studies of bendamustine and rituximab showed a median progression free survival (PFS) of 11 to 17 months, and idelalisib plus rituximab showed benefit over rituximab alone with median PFS of 19.4 versus 6.5 months. Severe gastrointestinal (GI) symptoms and hepatotoxicity were safety issues. The BTK inhibitor ibrutinib showed improved PFS with those treated in the first line of relapsed/refractory settings, compared to conventional therapies.

Acalabrutinib is a strong inhibitor of BTK and thus inhibits signalling through the B cell receptor in sensitive cells. Inhibition of activating proteins CD86 and CD69 inhibit malignant B-cell proliferation and survival.

Hence, acalabrutinib is a potent BTK inhibitor and is put forward as another choice in the varied armamentarium of treatments for CLL. This submission for the approval of a CLL indication was supported by two pivotal Phase III studies and 3 supportive ongoing studies.

This is the second evaluation facilitated through Project Orbis, an initiative of the United States (US) Food and Drug Administration (FDA) Oncology Center of Excellence (OCE). Under this project, the FDA, Health Canada (HC) and the TGA collaboratively reviewed the

application. This innovative evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions.

Each regulator agency maintained its regulatory process to make independent decisions about the approval (market authorisation).

Regulatory status

The submission was assessed in concert with the US FDA and Health Canada regulatory agencies as part of the joint initiative Project Orbis.

This submission was assessed simultaneously with concurrent Comparable Overseas Regulator approach B (COR-B) submission PM-2019-03536-1-6 for mantle cell lymphoma (MCL).[1]

Calquence (acalabrutinib) received initial provisional registration on the Australian Register of Therapeutic Goods (ARTG) on 21 November 2019 for the following indication:

> *Calquence is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.*

This indication is approved via the provisional approval pathway, based on overall response rate. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.

The provisional registration period for the above medicine is two years starting on the day specified in the ARTG certificate of registration.

At the time the TGA considered this application, no major jurisdiction worldwide had approved the indication sought in this submission and it was under consideration in the European Union (EU), United States of America (USA) and Canada.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

[1] The COR report-based process is associated with a shortened evaluation and decision timeframe. The aim of this process is to reduce duplication of evaluation of prescription medicines that have already been approved by a COR, while maintaining existing quality, safety and efficacy standards for medicines supplied in Australia. The intention is that the TGA will only need to evaluate data generated specifically for the Australian context. For example, Australian labels, product information and consumer medicine information. However, in some instances, additional data may need to be considered. For example, safety data generated since the COR approval.
Under the COR-B approach, the TGA regulatory decision will still be mostly based on a critical review of the COR assessment reports. The COR-B process has a 175 working day evaluation and decision timeframe, allowing for TGA evaluation of certain data, in addition to the label, PI and RMP.

Table 1: Timeline for Submission PM-2019-04317-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	10 October 2019
Evaluation completed	18 November 2019
Delegate's Overall benefit-risk assessment	21 November 2019
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	22 November 2019
Completion of administrative activities and registration on ARTG	22 November 2019
Number of working days from submission dossier acceptance to registration decision*	35

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

This is a TGA summary of wording used in TGA's Delegate's overview, which discussed numerous aspects of overseas evaluation reports and included some information that was considered commercial-in-confidence and has been redacted.

Quality

There was no requirement for a quality evaluation in a submission of this type. A summary of quality aspects is included in the AusPAR for MCL submission PM-2019-03536-1-6.

Nonclinical

The proposed dosing regimen involves oral administration of one capsule (100 mg) twice daily. A single nonclinical evaluation was performed for this submission and concurrent submission PM-2019-03536-1-6 for MCL.

The following points were summarised in the nonclinical evaluation:

- The submitted nonclinical data were in general accordance with the relevant TGA-adopted International Council for Harmonisation (ICH) guideline;[2] and were of

[2] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH S9 Guidance on nonclinical evaluation for anticancer pharmaceuticals, EMEA/CHMP/ICH/646107/2008.

adequate quality. All pivotal safety-related studies were Good Laboratory Practice (GLP) compliant.

- *In vitro*, acalabrutinib and its main active human metabolite, ACP-5862, were shown to be irreversible inhibitors of BTK. Acalabrutinib and ACP-5862 inhibited B cell signalling in cellular assays and tumour growth inhibition was seen in murine xenograft models of B cell malignancies. The nonclinical data lend some support for the proposed indication, CLL, at the proposed clinical dose. The main human metabolite, ACP-5862, is expected to significantly contribute to the safety and efficacy profile of acalabrutinib.
- In secondary screens against other tyrosine kinases, receptors, ion transporters and ion channels, notable off-target effects include the protein tyrosine kinases, ErbB4 and Tec. Both of these kinases appear to have cardioprotective roles and Tec plays a role in platelet activation. No adverse effects on central nervous system (CNS), respiratory or cardiovascular function were seen in adequately conducted studies.
- Acalabrutinib was readily and rapidly absorbed following oral administration, with a similar time to maximum plasma concentration (T_{max}) in all species. Exposures (area under the concentration-time curve (AUC)) in female mice, rats and humans were generally higher than their male counterparts. There were no consistent sex differences in pharmacokinetic parameters in dogs. Following oral dosing, exposures to ACP-5862 were approximately 4.5, 0.08 and 2.5 to 3.0 times acalabrutinib exposures in rats, dogs and humans. A tissue distribution study in pigmented rats indicated some retention of radioactivity in melanin-containing tissues. There was minimal penetration of blood-brain barrier. *In vitro* studies indicated a major role of cytochrome P450 3A4/5 (CYP3A4/5) in the formation of ACP-5862. Excretion of acalabrutinib and/or its metabolites was predominantly via the faeces in all species. Biliary excretion was evident.
- *In vitro* studies indicated inhibitors/inducers of CYP3A4/5, P-glycoprotein and breast cancer resistance protein (BCRP) may alter acalabrutinib exposures. Acalabrutinib may increase exposure to orally co-administered CYP3A4 or BCRP substrates by inhibition of intestinal CYP3A4 (irreversible) or intestinal BCRP, respectively. ACP-5862 may increase exposure to co-administered multidrug and toxin extrusion protein 1 (MATE1) substrates.
- Acalabrutinib had a moderate to low order of acute intravenous (IV) toxicity in rats.
- Repeat dose toxicity studies were conducted in mice (28 days), rats (up to 26 weeks; two different strains) and dogs (up to 39 weeks) using the proposed clinical route (oral; PO). The studies were adequately conducted. The major target organs for acalabrutinib were the lymphoid tissues (as expected based on the drug's primary pharmacology), liver and kidney, and in rats only, the pancreas and heart. The effects in the pancreas and heart are not expected to be clinically relevant. Degenerative lesions in the liver (hepatocyte degeneration/necrosis) and kidney (and tubular degeneration/necrosis) were accompanied by clinical chemistry indicators of liver damage (elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and renal damage (elevated blood urea nitrogen and creatinine levels). Given the margins, some hepatic or renal effects may be seen in some patients. Based on the primary pharmacology of the drug, an immunosuppressive effect is expected in patients (B cell and immunoglobulin deficiencies).
- Acalabrutinib was not mutagenic in an Ames test and was not clastogenic *in vitro* (in human lymphocytes) or *in vivo* rat micronucleus test. No carcinogenicity studies were conducted, which is considered acceptable.

- Reproductive toxicity studies examined effects on fertility (rats), embryofetal development (rats and rabbits) and pre/postnatal development (rats). Male and female fertility were unaffected in rats. Acalabrutinib crossed the placenta in rats and could be detected in fetal plasma. No direct effects on embryofetal development were seen in rats or rabbits. Fetal effects in rabbits occurred in the context of maternotoxicity. Acalabrutinib and ACP-5862 were excreted into milk in rats, with levels higher than maternal plasma levels, but pup plasma levels were low. No adverse effects on pup development were seen. Treatment related dystocia was seen in rats at clinically relevant doses.
- While acalabrutinib was phototoxic *in vitro*, this is not expected to be of concern in patients.
- Specified limits for impurities in the drug substance and drug product are considered to be toxicologically acceptable.

Conclusions and recommendations from the nonclinical evaluation:

- No notable nonclinical deficiencies were identified.
- The primary pharmacology studies lend some support for the proposed indications.
- Studies in animals revealed the following findings of potential clinical relevance:
  - some risk of liver toxicity;
  - some risk of kidney toxicity; and
  - dystocia, if taken during pregnancy.
- There are no objections on nonclinical grounds to the proposed registration of Calquence for the proposed indications.
- The draft PI should be amended as directed and the nonclinical safety specification of the risk management plan (RMP) should be modified as directed.

Delegate's summary of the nonclinical evaluation

The nonclinical evaluator found no grounds to object to the approval of the submission. It was noted that studies in animals provided a number of findings of potential clinical relevance, as outlined above.

A number of PI edits were proposed which the sponsor implemented.

Clinical

Pharmacology

The pharmacology of acalabrutinib and its inactive metabolite have been dealt with in the submission for MCL (submission PM-2019-03536-1-6). There are no additional issues for clinical pharmacology arising from this submission.

The population pharmacokinetic (popPK) analysis submitted was considered satisfactory. One should note a hepatic impairment study revealed an approximate 5 fold increase in exposure for those with severe hepatic impairment and thus such patients are recommended to avoid use in the PI, although it is not strictly an absolute contraindication.

Efficacy

The principal data for the CLL indication comes from two studies, designated the ASCEND and ELEVATE-TN clinical trials. The ASCEND trial studied treatment in relapsed or refractory CLL where subjects had to have been treated with at least one prior therapy before enrolment. The ELEVATE-TN trial was a study evaluating first-line treatment for treatment-naïve patients. Both enrolled CD20 positive CLL patients. Diagnosis was via specific laboratory parameters.

The ASCEND and ELEVATE-TN trials were open label, randomised, multicentre studies, comparing acalabrutinib with other current treatment regimens for CLL. These comparator regimens were considered satisfactory comparators by the clinical evaluator. In the ASCEND trial, treatment group randomisation was stratified by 17p deletion (presence or absence); Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1, versus 2);[3] and number of prior therapies (1, 2 or 3 versus 4 or more). In the ELEVATE-TN trial, stratifications included 17p deletion (presence or absence); ECOG performance status (0 or 1 versus 2) and geographic region (North America and Western Europe versus everywhere else).

ELEVATE-TN trial

The ELEVATE-TN trial evaluated treatment with acalabrutinib in treatment-naïve subjects by comparing acalabrutinib monotherapy (Arm C) with acalabrutinib plus obinutuzumab (Arm B) and obinutuzumab in combination with chlorambucil (Arm A).

Study design

Subjects were randomised into these three arms with the stratification factors cited above. The study enrolled 535 subjects and 526 received study treatment.

Each treatment cycle was 28 days. Acalabrutinib was commenced on Day 1 of Cycle 1 and continued daily until unacceptable drug-related toxicity or disease progression. Obinutuzumab was dosed as 100 to 1000 mg IV infusion on Day 1 Cycle 1 for a total of 6 cycles (Day 1 100 mg, Day 2 900 mg; Day 8 and 15 Cycle 1, 1000 mg; Cycles 2 to 6, 1000 mg Day 1 of each cycle). Chlorambucil was given as 0.5 mg/kg orally on Days 1 and 15 of Cycles 1 through 6.

Assessment of response and progression was via the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria for CLL;[4] with the modification that treatment-related lymphocytosis in the absence of other markers of disease progression was not considered progressive disease.

There was investigator discretion to transfer subjects randomised to Arm A to receive acalabrutinib once disease progression had occurred. This treatment then continued until disease progression again occurred, or unacceptable toxicity ensued.

[3] The ECOG Scale of Performance Status is a standardised criteria on a 0 to 5 scale for measuring how the disease impacts a patient's daily living abilities (known to physicians and researchers as a patient's performance status). It describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (such as walking, working, and so on). 0 Fully active, able to carry on all pre-disease performance without restriction
An ECOG status score of 0 signifies 'Fully active, able to carry on all pre-disease performance without restriction'; 1 signifies 'Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; and 2 signifies 'ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours'.
[4] Hallek, M. et al. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood, 2008; 111: 5446-5456.

The primary endpoint was to evaluate PFS of obinutuzumab in combination with chlorambucil (Arm A) versus acalabrutinib in combination with obinutuzumab (Arm B) based upon Independent Review Committee (IRC) assessment.

Secondary endpoints included:

- IRC-assessed PFS for obinutuzumab and chlorambucil versus acalabrutinib alone; and
- to evaluate IRC assessed overall response rate (ORR), time to next treatment (TTNT) and overall survival (OS) for the acalabrutinib and obinutuzumab arm (Arm B) versus obinutuzumab and chlorambucil (Arm A), and acalabrutinib monotherapy (Arm C) versus obinutuzumab and chlorambucil (Arm A).

There were multiple exploratory measures, but of interest to the clinical evaluator was the patient derived outcome measures including the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue); the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); and the EuroQol 5 dimensions (EQ-5D), as these give an idea of, progression-free disease notwithstanding, whether patients felt worse, better or about the same while receiving the various treatments.

Discontinuing subjects were followed for disease progression every 3 months. After progression was confirmed, subjects continued to be followed for subsequent anti-cancer therapy, additional malignancy occurrence and survival.

Treatment dose of 100 mg twice daily was based upon observed near complete receptor occupancy at this dose, and clinical pharmacology determined that adjustments were not required for weight, sex, ethnicity, renal or hepatic impairment or ECOG performance status score (except as mentioned previously, treatment was not recommended in severe hepatic impairment.

In terms of subject disposition, 83.7% were 65 or older. 61.3% were male, and 93.3% Caucasian. Median age was 70 (range 41 to 91) and median follow up was 28.3 months (range 0.0 to 40.8).

Results

In terms of the primary endpoint, the acalabrutinib and obinutuzumab arm demonstrated a statistically significant improvement in IRC assessed PFS compared with the obinutuzumab and chlorambucil arm. In essence, acalabrutinib added more efficacy than chlorambucil in this comparison. A 90% reduction in risk of disease progression or death occurred: hazard ratio (HR) = 0.10 (95% confidence interval (CI) 0.06, 0.17) $p < 0.0001$. The median estimated PFS was not reached for acalabrutinib and obinutuzumab (Arm B), but for obinutuzumab and chlorambucil, it was 22.6 months (95% CI 20.2, 27.6). Kaplan Meier estimates supported the better efficacy performance of acalabrutinib and obinutuzumab over chlorambucil and obinutuzumab. This benefit was consistent across all pre-specified subgroups. Indeed those with at least one chromosomal characteristic associated with poor prognosis actually had greater benefit. (HR 0.08, (95% CI 0.04, 0.15)).

The acalabrutinib monotherapy arm also demonstrated improvement in IRC assessed PFS compared with the obinutuzumab and chlorambucil arm, that is, it performed not only better than chlorambucil as per the primary endpoint comparison, but indeed performed better than both these drugs combined in terms of PFS (HR 0.20, (95% CI 0.13, 0.30) $p < 0.0001$). This was again consistent across all subgroups and those with a chromosomal abnormality had a better outcome.

The point was made in the joint consideration of this trial that exposure to the study drug was considerably longer in the acalabrutinib treatment arms and thus may affect outcome to a degree.

Other secondary outcome measures were also favourable. IRC assessed ORR for acalabrutinib + obinutuzumab, acalabrutinib monotherapy, and obinutuzumab + chlorambucil was 93.9%, 85.5% and 78.5%, respectively. The difference between acalabrutinib + obinutuzumab and obinutuzumab + chlorambucil arms was 15.4% in favour of acalabrutinib ($p < 0.0001$). For acalabrutinib monotherapy and obinutuzumab + chlorambucil, the difference was 8.1% in favour of acalabrutinib ($p < 0.0376$).

Median OS was not reached in any treatment arm. The data are too immature to make any conclusive statement about OS.

TTNT was prolonged for acalabrutinib + obinutuzumab (HR = 0.14, (95% CI 0.08, 0.26), $p < 0.0001$) and acalabrutinib monotherapy (HR = 0.24 (95% CI 0.15, 0.40) $p < 0.0001$) compared with the obinutuzumab + chlorambucil arm.

The point was made in the joint evaluation that the secondary endpoint of ORR should have been tested based on the closed-testing procedure, that is, the same alpha level that was allocated for the IRC-assessed PFS interim analysis to control the overall type I error rate. Hence, ORR should be viewed as descriptive only.

Approximately 53 subjects in Arm B (acalabrutinib + obinutuzumab), 56 subjects in Arm C (acalabrutinib monotherapy), and 42 subjects in Arm A (chlorambucil + obinutuzumab) completed the FACIT-Fatigue, the EORTC QLQ-C30, and the EQ-5D Visual Analogue Scale (VAS) patient reported outcomes (PRO) at Baseline, meeting the minimum requirements for scoring (completion rates = 100.0%, 100.0%, and 100.0% for FACIT-Fatigue, EORTC QLQ-C30, and EQ-5D VAS).

Subjects with CLL randomised in this study experienced impacts in fatigue and global health status (GHS) at the start of the study, and subjects in all three treatment arms showed comparable improvements on their health-related quality of life (HRQoL) throughout the study. Among subjects with fatigue at Baseline (SF-population), these improvements were more pronounced. No differences were observed across the treatment arms; however, due to the larger drop-out in Arm A (chlorambucil + obinutuzumab) compared with Arm B (acalabrutinib + obinutuzumab) and Arm C (acalabrutinib monotherapy), the MAR (missing at random) assumptions were not met, and the MMRM (mixed model repeated measures) results should be interpreted with caution. Hence the PRO results give little direction to the patients' overall state of well-being during treatment, or whether or not one treatment regimen led to them feeling 'better' during treatment, regardless of primary outcome measure.

Overall this study (n = 535) demonstrated statistically significant improvement in PFS as assessed by IRC in the acalabrutinib containing arms versus obinutuzumab+chlorambucil. In addition, overall response rate for the acalabrutinib plus obinutuzumab arm was 94% versus 79% for the obinutuzumab plus chlorambucil arm ($p < 0.0001$). There is considerable evidence for superior efficacy over the comparator treatments.

ASCEND trial

The ASCEND trial was a randomised open label Phase III study of acalabrutinib versus investigator's choice of either idelalisib plus rituximab, or bendamustine plus rituximab in subjects with relapsed or refractory CLL.

Study design

As at data cut off, 310 subjects had been randomised to treatment.

Subjects were randomised in a 1:1 ratio to either Arm A of acalabrutinib monotherapy, or Arm B of the investigator's choice of either of the aforementioned comparator treatments. Ultimately, 155 subjects were assigned to acalabrutinib, 119 to idelalisib/rituximab, and 36 to bendamustine/rituximab. Randomisation was based upon the stratification factors

of 17p deletion (present or not), ECOG score (0 to 1 or 2), and number of prior therapies (1 to 3 versus 4 or more).

The primary endpoint was PFS as assessed by independent review committee with IWCLL criteria.[4] Secondary endpoints included investigator-assessed PFS, IRC and investigator assessed ORR and duration of response (DOR), as well as OS, TTNT and various PROs.

Part of the study design allowed for those randomised to Arm B to crossover to acalabrutinib monotherapy if eligibility criteria were met during the study duration.

Each treatment cycle was 28 days. Subjects in Arm A received acalabrutinib 100 mg twice daily (BID) in continuous 28 day cycles until disease progression or unacceptable toxicity. Subjects receiving idelalisib/rituximab received idelalisib orally from Day 1 continuously until disease progression or unacceptable toxicity. Rituximab was given on Day 1, then every 2 weeks for 4 doses and then every 4 weeks for 3 doses for a total of eight infusions. For those on the bendamustine/rituximab regimen, bendamustine was given as an IV infusion on Days 1 and 2 of each 28 day cycle for a maximum of 6 cycles, with rituximab given on Day 1 of Cycles 1 to 6.

Demographically, 62.9% of subjects were 65 years old or greater and 21.0% were 75 years or more. 67.1% were male and 92.3% were Caucasian. Median age was 67 (range 32 to 90 years). Median follow up was 15.5 months (range 0.5 to 20.8).

Results

In terms of primary endpoint, acalabrutinib monotherapy demonstrated a statistically significant improvement in PFS as assessed by IRC when compared with the two other treatment regimens, with a 69% risk reduction in disease progression or death (HR = 0.31 (95% CI: 0.20, 0.49, $p < 0.0001$)). The median estimated PFS was not reached for acalabrutinib. The median estimate for the other treatment arm was 16.5 months (95% CI: 14.0, 17.1). This again suggests that the ultimate median PFS for acalabrutinib will be longer than that typically conferred by comparator, currently available regimens based on historical trial data.

It was noted that secondary endpoints were not adjusted for multiplicity and thus should be regarded as exploratory. Kaplan Meier estimates were considered misleading as they present estimates at a single time point and do not represent the overall effect of treatment. With these statements in mind, the secondary endpoints presented included the following.

The Kaplan Meier estimate of the proportion of subjects without a PFS event at 12 months was 87.8% and 68.0% for the acalabrutinib and other treatment arm, respectively. For 18 months the estimate was 79.0% and 38.6%, respectively. This PFS benefit was consistent across all pre-specified subgroups. Indeed, those with at least 1 chromosomal characteristic typically indicating poor prognosis had an even greater benefit with acalabrutinib (HR = 0.27 (95% CI: 0.17, 0.44)).

The sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis, with HR ranging from 0.29 to 0.31, with $p < 0.0001$ for all analyses.

Investigator assessed PFS as a key secondary endpoint was consistent with the primary endpoint (HR = 0.28 (95% CI: 0.18, 0.45) $p < 0.0001$). IRC assessed ORR was 81.3% and 75.5% for the acalabrutinib and idelalisib/bendamustine/rituximab treatment arms, respectively. Investigator assessed ORR was 79.4% and 83.2%, respectively (note investigators placed the comparator arm ahead of acalabrutinib in ORR). ORR demonstrated no statistically significant difference between treatment groups, and the superior PFS is considered attributable at least in part to the considerably longer duration of exposure possible with acalabrutinib.

Median OS was not reached in either arm. HR was 0.84 (95% CI: 0.42, 1.66: p = 0.6089) in favour of acalabrutinib but not of statistical significance. OS data, as for the ELEVATE-TN trial, are immature.

Duration of response was in favour of acalabrutinib; HR = 0.33 (95% CI: 0.19, 0.59) (IRC assessment). During the study, disease progression occurred, based on IRC assessment, in 9.5% and 35.9% of subjects in the acalabrutinib and idelalisib/bendamustine/rituximab treatment groups, respectively. The Kaplan Meier estimate of the proportion of responders without a PFS event at 12 months was 85.5% for the acalabrutinib treatment group and 59.5% for the other treatment arm.

Time to next treatment was also significantly prolonged in favour of the acalabrutinib treatment group. (HR = 0.35 (95% CI: 0.21, 0.58; p < 0.0001)). The Kaplan Meier estimate of the percentage of those not yet having started another anti-cancer treatment at 12 months was 88.9% and 79.7% for the acalabrutinib and other treatments, respectively.

This study demonstrated statistically significant favourable differences in PFS as the primary outcome measure for those taking acalabrutinib in relapsed or refractory CLL in comparison to other treatments. A variety of secondary measures, as shown above, were also in favour of acalabrutinib. Median OS was not reached although this is not surprising given the natural course of the disease. While median PFS was not reached for acalabrutinib, one can conclude it is comparable or longer than those historically found with comparable treatments.

Safety

While safety data derived from multiple sources, the two principal studies (the ASCEND and ELEVATE-TN trials) were key new data for this submission. The submission for the MCL indication (submission PM-2019-03536-1-6) provided the initial safety profile for acalabrutinib. Eight other studies in CLL and other haematologic malignancies provided supportive data (in the summary of clinical safety for CLL).

Total exposure is summarised in Table 2.

Table 2: Total subjects from clinical studies that contributed safety data to this submission

	Total N[a]	Pivotal Studies		CLL Supportive Studies			Hematologic Malignancies Supportive Studies				
		ACE-CL-007	ACE-CL-309	ACE-CL-001	15-H-0016	ACE-CL-003	ACE-LY-002	ACE-LY-003[b]	ACE-LY-004	ACE-MY-001[b]	ACE-WM-001
Phase		3	3	1/2	2	1/2	1b	2	2	1b	2
Status		Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Data cutoff date		08Feb2019	15Jan2019	04Jan2019	07Dec2018	01Nov2018	30Oct2017	01Jan2019	12Feb2018	30Apr2018	01Nov2018
Indication		CLL	CLL	CLL/SLL /RS/PLL	CLL/SLL	CLL/SLL	ABC/DLBCL	FL	MCL	MM	WM
Acalabrutinib Monotherapy Pivotal Population	333	179	154	NA	NA	NA	NA	NA	NA	NA	NA
Acalabrutinib Monotherapy CLL Population	762[c]	224	190	301	48	NA	NA	NA	NA	NA	NA
Combination CLL Population	223	178	NA	NA	NA	45	NA	NA	NA	NA	NA
Total Acalabrutinib CLL Population	985[c]	402	190	301	48	45	NA	NA	NA	NA	NA
Acalabrutinib Monotherapy Hematologic Malignancies Population	1040[c]	224	190	301	48	NA	21	14	124	13	106
Treatment Arm											
Acalabrutinib Monotherapy		179	154	301	48	NA	21	14	124	13	106
Acalabrutinib + Obinutuzumab		178	NA	NA	NA	45	NA	NA	NA	NA	NA
Crossover from Control Arm to Acalabrutinib		45	36								

a The total number is based on the actual number of subjects treated with acalabrutinib.

b Other combination groups are not included in the analysis.

c Subjects who crossed over from control arm to acalabrutinib monotherapy are included in this pooled population.

ABC DLBCL=activated B-cell diffuse large B-cell lymphoma; CLL=chronic lymphocytic leukemia; FL=follicular lymphoma; MCL=mantle cell lymphoma; MM=multiple myeloma; NA=not applicable: PLL=prolymphocytic leukemia; RS=Richter's syndrome; SLL=small lymphocytic leukemia; WM=Waldenström macroglobulinemia.

Subject numbers involved are sufficient to circumscribe a safety profile.

ELEVATE-TN trial

The ELEVATE-TN trial included 178 subjects in the acalabrutinib + obinutuzumab arm, 224 in acalabrutinib monotherapy (incorporating crossover patients), and 169 in the obinutuzumab + chlorambucil arm. The monotherapy group includes 45 subjects that crossed over to receive acalabrutinib from the obinutuzumab + chlorambucil arm upon IRC confirmed disease progression.

Median exposure for ELEVATE-TN trial subjects to acalabrutinib was 27.7 months (range 0.7 to 40.3) in the acalabrutinib + obinutuzumab arm, and 27.7 (range 0.3 to 40.2) in the acalabrutinib monotherapy arm, with 88.8% and 86.0% respectively receiving at least a year of treatment. Of note is the median duration of obinutuzumab at 5.5 months (range 0.9 to 7.1) in the acalabrutinib + obinutuzumab arm and 5.6 months (range 0.9 to 7.4) in the obinutuzumab + chlorambucil arm. The median exposure to chlorambucil in the sole arm it was used was 5.5 months (range 0.5 to 7.2). For those 45 crossover patients, median exposure was 11 months (range 2.0 to 23.5).

Common treatment emergent adverse events (TEAE) occurring in the acalabrutinib + obinutuzumab arm were headache, diarrhoea and neutropaenia occurring in 39.9%, 38.8% and 31.5% of subjects, respectively. Other events occurring in 20% or more of subjects included cough, contusion, arthralgia, fatigue, nausea and upper respiratory tract infection (URTI). In acalabrutinib monotherapy, the most common TEAE were headache (36.9%), diarrhoea (34.6%), and nausea (22.3%).

Most common Grade 3 or higher TEAE for acalabrutinib + obinutuzumab, acalabrutinib monotherapy, and obinutuzumab + chlorambucil, respectively, were neutropaenia (29.8%, 9.5% and 41.4%), thrombocytopaenia (8.4%, 2.8% and 11.8%) and anaemia (5.6%, 6.7% and 7.1%). Note the considerably lower incidence of neutropaenia in the acalabrutinib monotherapy arm. In fact, the overall rate of TEAEs was reported less frequently in the

acalabrutinib monotherapy arm versus acalabrutinib + obinutuzumab or obinutuzumab + chlorambucil (65.7% versus 80.9% and 91.1%, respectively).

Treatment emergent serious adverse events (SAE) occurred in 38.8%, 31.8% and 21.9% in the acalabrutinib + obinutuzumab, acalabrutinib monotherapy, and obinutuzumab + chlorambucil treatment arms. Most of these were Grade 3 or above (32.6%, 29.6% and 19.5%, respectively).

TEAE leading to a withholding of acalabrutinib were fairly common, occurring in 43.8% and 34.1% of the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms, respectively; however, events causing discontinuation were much fewer (6.2% and 5.9%, respectively). Events resulting in dose reduction occurred in 6.7% and 3.9%, respectively.

The most common cause of death within 30 days of the last dose of study treatment was infection, largely sepsis and pneumonia. Indeed, with the application of a 'grouping' of common event terms, analysis revealed an incidence of pneumonia in the acalabrutinib monotherapy arm of 4%, myocardial infarction or ischaemia of 2% and cardiac failure of 2%. In the acalabrutinib + obinutuzumab arm, sepsis occurred in 3% and myocardial infarction or ischaemia in 2%.

Events of special interest included cardiac arrhythmias, haemorrhage, cytopaenia, infection and second primary malignancies. These were based upon the known and potential risks of acalabrutinib. While haemorrhage, arrhythmias, cytopaenia and infections all featured in trial data, they were not of a pattern to result in unfavourable risk-benefit overall. Rates of secondary primary malignancy were similar across arms in the ELEVATE-TN trial, most being basal and squamous cell carcinomas of the skin. Seven patients given acalabrutinib on various treatment arms developed Richter's syndrome (that is, transformation to a more aggressive lymphoma).

No new concerns have been identified from post market experience which was estimated at 735 patient years.

While use of acalabrutinib poses risks, these are known and overall risk-benefit appears to be positive. Adverse events can be mitigated to an extent via supportive care and vigilant monitoring. The draft PI document contains information relating to key safety issues including infections, haemorrhage, cytopaenias, secondary primary malignancies and cardiac arrhythmias.

ASCEND trial

Median duration of exposure to acalabrutinib in this trial was 15.7 months (range 1.1 to 22.4) and 85.7% of subjects were dosed with drug for a year or more. Median duration of idelalisib was 11.5 months (range 0.1 to 21.1) and rituximab 5.5 months (range 0.9 to 8.5).

Common TEAE in 10% or more of acalabrutinib treated subjects included headache (22.1%), neutropaenia (19.5%), diarrhoea (18.2%) anaemia and cough (both 14.9%), upper respiratory tract infection (URTI; 14.3%), pyrexia (12.3%), thrombocytopaenia (11.0%) and pneumonia and respiratory tract infection (both 10.4%). Acalabrutinib has a significant array of side effects.

Those commonly reported Grade 3 or above TEAE with acalabrutinib were neutropaenia (15.6%), anaemia (11.7%) and pneumonia (5.2%). These Grade 3 or higher TEAE figures compared favourably with the other treatment arm in terms of rates of neutropaenia (15.6% versus 39.8%) diarrhoea (1.3% versus 23.7%) and raised liver enzymes. Generally speaking, the adverse event profile matched the known safety profile of the drug. Six fatal TEAE occurred in acalabrutinib recipients, compared to idelalisib/rituximab (5) and bendamustine/rituximab (2).

Treatment emergent SAE occurred in 28.6%, 55.9% and 25.7% of those receiving acalabrutinib, idelalisib/rituximab and bendamustine/rituximab, respectively. Those of

Grade 3 severity or higher occurred in 26.6%, 50.8% and 25.7%, respectively. Thus, one can see that most of the SAE in total were of this severity. Of those reported for acalabrutinib, atrial fibrillation was the only one occurring more than once.

TEAE resulting in discontinuation were in 10.4%, 52.5% and 17.1% of acalabrutinib, idelalisib/rituximab and bendamustine/rituximab treatment receivers, respectively. Secondary primary malignancy and infection were the leading causes of this in the acalabrutinib arm. Those causing a dose reduction were 3.9%, 12.7% and 14.3% for these treatment groups, respectively. TEAE leading to drug withholding occurred in 33.8%, 64.4% and 20.0% in those same groups, respectively. Respiratory tract infection and neutropaenia were the main causes of dose interruption for acalabrutinib. Hence, one can see that the study drug was well tolerated in comparison to other regimens and resulted in both fewer dose reductions and temporary withdrawals of drug as well as treatment discontinuation as a result of adverse effects. The exception to this generalisation being the bendamustine/rituximab cohort where treatment withdrawals were most minimal.

Haematology, other clinical laboratory values, and other vital signs were predictable for the most part. Lymphocytosis occurred for more subjects treated with acalabrutinib (70.8%) when compared with idelalisib/rituximab (50.9%) or bendamustine/rituximab (2.9%). Significant increases in liver enzymes were not a feature of the drug, although it is recommended that those with severe hepatic impairment from other causes should avoid use of the drug.

Incidence of second primary malignancy, as one of the adverse events of interest, was noted to be substantially higher in the ASCEND trial than in the ELEVATE-TN trial. Most of these were skin cancers, and the draft PI contains appropriate statements on this. One should temper this with the understanding that incidences were not exposure adjusted. Haemorrhage and opportunistic infection are known side effects of acalabrutinib and while significant, their rates do not represent something that would make risk-benefit unfavourable.

In general, the safety profile was acceptable given the nature of the disease under treatment and the safety profile of treatment regimens with comparable efficacy outcomes. However, an increase in second primary malignancies was noted, which has been incorporated into the PI document.

Risk management plan

The following was noted in the RMP evaluation:

- In this submission, Calquence is proposed to be used for the treatment of CLL in adults. The proposed dosing regimen involves oral administration of one capsule (100 mg) twice daily until disease progression or unacceptable toxicity.
- The sponsor has submitted core risk management plan version 1.0 (date 26 February 2018; data lock point (DLP) 29 May 2017 (Study ACE-LY-004), 3 April 2017 (Study ACE-CL-001), 1 June 2017 (Studies ACE-WM-00, 15-H-0016, ACE-LY-002, ACE-LY-003 andACE-MY-001)) and Australian specific Annex (ASA) version 1.0 (date 25 July 2019) in support of submission PM-2019-03536-1-6. After the first round evaluation the sponsor provided updated core RMP version 2 (date 19 August 2019; DLP 8 February 2019) and ASA version 1.0 Succession 2 (date 20 September 2019) which are acceptable for evaluation for both submissions PM-2019-03536-1-6 and PM-2019-04317-1-6. After the second round evaluation the sponsor provided updated ASA version 1.0 Succession 3 (date 8 November 2019).
- Evaluation of submissions PM-2019-03536-1-6 and PM-2019-04317-1-6 is contained in a single RMP evaluation report.

- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies for both submissions are summarised in Table 3.[5]

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Haemorrhage	✓	–	✓	–
	Infections	✓	–	✓	
	Anaemia	✓	–	✓	–
	Leukopenia	✓	–	✓	–
	Thrombocytopenia	✓	–	✓	–
	Second primary malignancy	✓	–	✓	–
	Atrial fibrillation/flutter	✓	–	✓	–
Important potential risks	Nil	–	–	–	–
Missing information	Long term safety	✓	✓*	–	–
	Use in patients with moderate to severe cardiac impairment	✓	✓*	–	–

* Global Phase IIIb, multicentre, open-label, single-arm clinical study; Study D8220C00008 (Assure).

- The summary of safety concerns is the same for both submissions. At the second round of evaluation the sponsor reclassified the important potential risks of infections, anaemia, leukopenia, thrombocytopenia, second primary malignancy and atrial fibrillation/flutter as important identified risks. The sponsor also removed use in pregnancy and lactation, and use in patients with severe hepatic impairment as missing information. The summary of safety concerns is considered acceptable subject to final review of clinical and nonclinical data by the Delegate.
- The sponsor has proposed routine pharmacovigilance activities for all safety concerns and has proposed modifications to a global, Phase III, multicentre clinical study involving patients with CLL addressing missing information regarding use in patients with moderate to severe cardiac impairment, and long term safety. This approach is acceptable for both submissions.

[5] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- The sponsor has proposed routine risk minimisation activities and no additional risk minimisation activities, which is acceptable for both submissions.

Delegate's comments on the RMP

The RMP has been negotiated and is considered satisfactory by the TGA. The product's safety concerns and associated risk monitoring and mitigation strategies were reviewed by the RMP unit and after some editing determined to be satisfactory.

Proposed conditions of registration as outlined in the RMP evaluation report are:

> *The Calquence Core Risk Management Plan version 2; date; DLP 8 February 2019 (RMP) (version 2, dated 19 August 2019, data lock point 8 February 2019), with Australian Specific Annex (version 1.0, succession 2, dated 20 September 2019) included with submission PM-2019-04317-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*
>
> *Calquence (acalabrutinib) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Calquence must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

There are no outstanding RMP issues for this submission.

Risk-benefit analysis

Delegate's considerations

The dossier presents two main clinical studies for the treatment of CLL with acalabrutinib, in patients who are both naïve to treatment as well as those for which CLL has proven refractory or has relapsed under current treatment. Supportive data from other studies are present as well as safety data encompassing the known experience with acalabrutinib.

A statistically and clinically significant increase in PFS has been shown for acalabrutinib in relation to a variety of acceptable alternative treatment regimens. In addition to displaying statistical significance in favour of acalabrutinib, various secondary endpoints were also

supportive for its use. Importantly, they were not negative in assessing risk/benefit balance for the drug. It should be noted there are several possible other treatments for this condition, and comparison with other therapies such as venetoclax, duvelisib and ibrutinib did not form part of the dossier. Both venetoclax and ibrutinib are on the ARTG with an indication for CLL. In Australia, idelalisib is approved for relapsed/refractory CLL, and the combination of obinutuzumab and chlorambucil, as well as bendamustine are approved for first-line treatment of CLL. Rituximab is approved for CD20 positive CLL at any stage of treatment. Hence while not encompassing all treatment options, the comparators in the clinical trials of ELEVATE-TN and ASCEND are reasonable.

While OS data are not yet available and thus it is difficult to assess what longer periods of progression free survival ultimately mean to final patient outcomes, PFS is an accepted outcome measure in oncology trials and this has been demonstrated to provide superior duration in the case of acalabrutinib when compared with the conventional treatments chosen for trial comparison.

The drug's safety profile contains some significant adverse events which are acceptable essentially because of the gravity of the disease that the product is treating. The array of adverse events for each oncology drug are somewhat unique to each product, with some overlap, and acalabrutinib is no exception. There are significant blood dyscrasias and infectious adverse events, which primarily need to be combatted through stringent monitoring, preventative management, and early treatment.

Overall, efficacy as determined by PFS was demonstrated for first line and refractory/relapsing CLL in adult patients, and other than a signal with respect to secondary primary malignancies, safety profile was essentially that circumscribed by the initial studies in MCL. The safety profile was not such to render the overall risk benefit unfavourable, given the improvements in PFS demonstrated in the efficacy data.

The drug provides a significant new treatment for CLL for suitable Australian patients.

Conditions of registration

Conditions of registration should include the standard conditions for all prescription medicine products, as well as those required by the RMP evaluator. In addition, the drug will be subject to the requirement for ongoing data to be provided given the initial approval in MCL is a provisional registration.

Outstanding issues

There are no outstanding issues for this particular submission.

Proposed action

The application may be approved.

Advisory Committee Considerations[6]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Calquence (acalabrutinib) 100 mg hard capsule, for the new indication:

> *Calquence is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).*

As such, the full indications at this time were:

> *Calquence is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.*
>
> *Calquence is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).*

Specific conditions of registration applying to these goods

- Calquence (acalabrutinib) is to be included in the Black Triangle Scheme. The PI and CMI for Calquence must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.
- The Calquence Core Risk Management Plan version 2; date; DLP 8 February 2019 (RMP) (version 2, dated 19 August 2019, data lock point 8 February 2019), with Australian Specific Annex (version 1.0, succession 3, dated 7 November 2019) included with submission PM-2019-04317-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 9 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter or for the entire period of provisional registration, whichever is longer. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

[6] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Calquence approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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