ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Calquence 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of acalabrutinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Yellow body, blue cap, size 1 (20 mm) hard capsule, marked with “ACA 100 mg” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT).

Calquence as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) not previously treated with a BTK inhibitor.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose of Calquence in monotherapy or in combination with other medicinal products is 100 mg acalabrutinib twice daily (equivalent to a total daily dose of 200 mg).

Calquence dose interval is approximately 12 hours.

For the combination regimens, refer to the prescribing information of each of the medicinal products for their dosing information (for details of the combination regimens, see section 5.1).

Calquence in monotherapy or in combination with obinutuzumab

Treatment with Calquence in monotherapy or in combination with obinutuzumab should be continued until disease progression or unacceptable toxicity.

Calquence in combination with venetoclax with or without obinutuzumab

Treatment with Calquence in combination with venetoclax with or without obinutuzumab, should continue until disease progression, unacceptable toxicity or completion of 14 cycles of treatment (each cycle is 28 days).

Calquence should be administered on Day 1 of Cycle 1 for a total of 14 cycles. Venetoclax should be administered on Day 1 of Cycle 3 for a total of 12 cycles, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg.

If Calquence is given in combination with venetoclax and obinutuzumab, obinutuzumab should be administered at 100 mg on Day 1 of Cycle 2, followed by 900 mg which may be administered on Day 1 or 2. Administer obinutuzumab at 1 000 mg on Day 8 and 15 of Cycle 2, followed by 1 000 mg on Day 1 of Cycles 3 to 7. Obinutuzumab is administered for a total of 6 cycles.

Calquence in combination with bendamustine and rituximab

Calquence should be administered on Day 1 on Cycle 1 (each cycle is 28 days) until disease progression or unacceptable toxicity. Bendamustine should be administered at 90 mg/m^2 on Days 1 and 2 of each cycle for a total of 6 cycles. Rituximab should be administered at 375 mg/m^2 on Day 1 each cycle for a total of 6 cycles. Patients achieving a response (partial response [PR] or complete response [CR]) after the first 6 cycles, may receive maintenance rituximab at 375 mg/m^2 on Day 1 of every other cycle for a maximum of 12 additional doses, starting on Cycle 8 up to Cycle 30.

Dose adjustments

Adverse reactions

Recommended dose modifications of Calquence for Grade ≥ 3 adverse reactions in patients receiving Calquence monotherapy, Calquence in combination with obinutuzumab and Calquence in combination with venetoclax with or without obinutuzumab are provided in Table 1.

Recommended dose modifications for Grade ≥ 3 adverse reactions in patients receiving Calquence in combination with bendamustine and rituximab are provided in Table 2.

Table 1. Recommended dose adjustments for adverse reactions*

Adverse reaction	**Adverse reaction occurrence**	**Dose modification** (Starting dose = 100 mg approximately every 12 hours)
.Grade 3 thrombocytopenia with bleeding .Grade 4 thrombocytopenia .Grade 4 neutropenia lasting longer than 7 days .Grade 3 or greater non-haematological toxicities	First and second	Interrupt Calquence. Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at 100 mg 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 100 mg once daily.
	Fourth	Discontinue Calquence.

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Table 2. Recommended dose adjustments for Grade ≥ 3 adverse reactions* in patients receiving Calquence in combination with bendamustine and rituximab

Adverse reaction	**Bendamustine dose modification†**	**Calquence dose modification**
Neutropenia	If Grade 3 or Grade 4 neutropenia‡: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	If Grade 4 neutropenia lasting longer than 7 days then interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd adverse reaction occurrence).¶ Discontinue Calquence at 4th adverse reaction occurrence.
Thrombocytopenia	If Grade 3 or Grade 4 thrombocytopenia: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	If Grade 3 thrombocytopenia with significant bleeding or Grade 4 then interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd occurrence).¶ Discontinue Calquence at 3rd adverse reaction occurrence for thrombocytopenia with significant bleeding. Discontinue Calquence at 4th adverse reaction occurrence.

Adverse reaction	Bendamustine dose modification†	Calquence dose modification
Other hematologic Grade 4§ or unmanageable Grade 3 toxicity	Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	Interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd adverse reaction occurrence).¶ Discontinue Calquence at 4th adverse reaction occurrence.
Grade 3 or greater non-hematologic toxicities	Interrupt bendamustine. Once toxicity has resolved to Grade 1 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	Interrupt Calquence. Once toxicity has resolved to Grade 2 or baseline, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd adverse reaction occurrence).¶ Discontinue Calquence at 3rd adverse reaction occurrence.

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

†For any toxicities not listed in this table refer to the bendamustine local prescribing information.

‡Consider use of myeloid growth factors before bendamustine dose modifications.

§Grade 4 lymphopenia is an expected outcome for treatment with bendamustine and rituximab. Dose modification due to lymphopenia is expected only if considered clinically important by investigators e.g. associated recurrent infections.

¶Dose may be re-escalated at the discretion of the physician if patient tolerates a reduced dose for ≥ 4 weeks.

Refer to the prescribing information of each of the medicinal products used in combination with Calquence for additional information for management of toxicities.

Interactions

Recommendations regarding use of Calquence with CYP3A inhibitors or inducers and gastric acid reducing agents are provided in Table 3 (see section 4.5).

Table 3. Use with CYP3A inhibitors or inducers and gastric acid reducing agents

	Co-administered medicinal product	Recommended Calquence use
CYP3A inhibitors	Strong CYP3A inhibitor	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	No dose adjustment. Monitor patients closely for adverse reactions if taking moderate CYP3A inhibitors.
	Mild CYP3A inhibitor	No dose adjustment.

	Co-administered medicinal product	Recommended Calquence use
CYP3A inducers	Strong CYP3A inducer	Avoid concomitant use.
Gastric acid reducing agents	Proton pump inhibitors	Avoid concomitant use.
	H2-receptor antagonists	Take Calquence 2 hours before (or 10 hours after) taking a H2-receptor antagonist.
	Antacids	The interval between taking the medicinal products should be at least 2 hours.

Missed dose

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

Special populations

Elderly

No dose adjustment is required for elderly patients (aged ≥ 65 years) (see section 5.2).

Renal impairment

No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in Calquence clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained, and serum creatinine levels monitored periodically. Calquence should be administered to patients with severe renal impairment (< 30mL/min creatinine clearance) only if the benefit outweighs the risk and these patients should be monitored closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Hepatic impairment

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). However, patients with moderate hepatic impairment should be closely monitored for signs of toxicity. It is not recommended to use Calquence in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3-times ULN and any AST) (see section 5.2).

Severe cardiac disease

Patients with severe cardiovascular disease were excluded from Calquence clinical studies.

Paediatric population

The safety and efficacy of Calquence in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration

Calquence is for oral use. The capsules should be swallowed whole with water at approximately the same time each day, with or without food (see section 4.5). The capsules should not be chewed, dissolved or opened as this may affect the absorption of the medicinal product into the body.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haemorrhage

Major haemorrhagic events including central nervous system and gastrointestinal haemorrhage, some with fatal outcome, have occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. These events have occurred in patients both with and without thrombocytopenia. Overall, the bleeding events were less severe events including bruising and petechiae (see section 4.8).

The mechanism for the bleeding events is not well understood.

Patients receiving antithrombotic agents may be at increased risk of haemorrhage. Caution should be used with antithrombotic agents and additional monitoring considered for signs of bleeding when concomitant use is medically necessary. Warfarin or other vitamin K antagonists should not be administered concomitantly with Calquence.

Consider the benefit-risk of withholding Calquence for at least 3 days pre- and post-surgery.

Infections

Serious infections (bacterial, viral or fungal), including fatal events, have occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. These infections predominantly occurred in the absence of neutropenia, with neutropenic infection reported in 10.1% of patients receiving monotherapy and 26.8% in patients receiving combination therapy. Infections due to hepatitis B virus (HBV) and herpes zoster virus (HZV) reactivation, aspergillosis and progressive multifocal leukoencephalopathy (PML) have occurred (see section 4.8).

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.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anaemia and thrombocytopenia, occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. Monitor complete blood counts as medically indicated (see section 4.8).

Second primary malignancies

Second primary malignancies, including skin and non-skin cancers, occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. Skin cancers were commonly reported. Monitor patients for the appearance of skin cancers and advise protection from sun exposure (see section 4.8).

Atrial fibrillation

Atrial fibrillation/flutter occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated (see sections 4.5 and 4.2). In patients who develop atrial fibrillation on therapy with Calquence, a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk for thromboembolic disease, tightly controlled treatment with anticoagulants and alternative treatment options to Calquence should be considered.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with Calquence therapy. Patients considered at risk for TLS (e.g., presence of bulky disease at baseline) should be assessed for possible risk of TLS and closely monitored as clinically indicated.

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD)/pneumonitis has been reported in patients treated with Calquence in combination with bendamustine and rituximab in MCL. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. cough, dyspnea or hypoxia) and manage ILD/pneumonitis as clinically indicated.

Other medicinal products

Co-administration of strong CYP3A inhibitors with Calquence may lead to increased acalabrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A inducers may lead to decreased acalabrutinib exposure and consequently a risk for lack of efficacy.

Concomitant use with strong CYP3A inhibitors should be avoided. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), treatment with Calquence should be interrupted. Patients should be closely monitored for signs of toxicity if a moderate CYP3A inhibitor is used (see sections 4.2 and 4.5). Concomitant use with strong CYP3A4 inducers should be avoided due to risk for lack of efficacy.

Calquence contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Acalabrutinib and its active metabolite are primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4), and both substances are substrates for P-gp and breast cancer resistance protein (BCRP).

Active substances that may increase acalabrutinib plasma concentrations

CYP3A/P-gp inhibitors

Co-administration with a strong CYP3A/P-gp inhibitor (200 mg itraconazole once daily for 5 days) increased acalabrutinib C_{max} and AUC by 3.9-fold and 5.0-fold in healthy subjects (N=17), respectively.

Concomitant use with strong CYP3A/P-gp inhibitors should be avoided. If the strong CYP3A/*P-gp* inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) will be used short-term, treatment with Calquence should be interrupted (see section 4.2).

Co-administration with moderate CYP3A inhibitors (400 mg fluconazole as single dose or 200 mg isavuconazole as repeated dose for 5 days) in healthy subjects increased acalabrutinib C_{max} and AUC by 1.4-fold to 2-fold while the active metabolite ACP-5862 C_{max} and AUC was decreased by 0.65-fold to 0.88-fold relative to when acalabrutinib was dosed alone. No dose adjustment is required in combination with moderate CYP3A inhibitors. Monitor patients closely for adverse reactions (see Section 4.2).

Active substances that may decrease acalabrutinib plasma concentrations

CYP3A inducers

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

Concomitant use with strong inducers of CYP3A activity (e.g., phenytoin, rifampicin, carbamazepine) should be avoided. Concomitant treatment with St. John's wort, which may unpredictably decrease acalabrutinib plasma concentrations, should be avoided.

Gastric acid reducing medicinal products

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. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased acalabrutinib AUC by 43%.

If treatment with an acid reducing agent is required, consider using an antacid (e.g., calcium carbonate), or an H2-receptor antagonist (e.g., ranitidine or famotidine). For use with antacids, the interval between taking the medicinal products should be at least 2 hours (see section 4.2). For H2-receptor antagonists, Calquence should be taken 2 hours before (or 10 hours after) taking the H2-receptor antagonist.
Due to the long-lasting effect of proton pump inhibitors, separation of doses with proton pump inhibitors may not eliminate the interaction with Calquence and therefore concomitant use should be avoided (see section 4.2).

Active substances whose plasma concentrations may be altered by Calquence

CYP3A substrates

Based on *in vitro* data, it cannot be excluded that acalabrutinib is an inhibitor of CYP3A4 at the intestinal level and may increase the exposure of CYP3A4 substrates sensitive to gut CYP3A metabolism. Caution should be exercised if co-administering acalabrutinib with CYP3A4 substrates with narrow therapeutic range administered orally (e.g., cyclosporine, ergotamine, pimozide).

Effect of acalabrutinib on CYP1A2 substrates

In vitro studies indicate that acalabrutinib induces CYP1A2. Co-administration of acalabrutinib with CYP1A2 substrates (e.g., theophylline, caffeine) may decrease their exposure.

Effects of acalabrutinib and its active metabolite, ACP-5862, on medicinal product transport systems

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP (see section 5.2). To minimise the potential for an interaction in the Gastrointestinal (GI) tract, oral narrow therapeutic range BCRP substrates such as methotrexate should be taken at least 6 hours before or after acalabrutinib.

ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1 (see section 5.2). Patients taking concomitant medicinal products with disposition dependent upon MATE1 (e.g., metformin) should be monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving Calquence.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Calquence.

Pregnancy

There are no or limited amount of data from the use of acalabrutinib in pregnant women. Based on findings from animal studies, there may be a risk to the foetus from exposure to acalabrutinib during pregnancy. Dystocia (difficult or prolonged labour) was observed in the rat and administration to pregnant rabbits was associated with reduced foetal growth (see section 5.3).

Calquence should not be used during pregnancy unless the clinical condition of the woman requires treatment with acalabrutinib.

Breast-feeding

It is not known whether acalabrutinib is excreted in human milk. There are no data on the effect of acalabrutinib on the breast-fed child or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. A risk to the breast-fed child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with Calquence and for 2 days after receiving the last dose.

Fertility

There are no data on the effect of Calquence on human fertility. In a non-clinical study of acalabrutinib in male and female rats, no adverse effects on fertility parameters were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Calquence has no or negligible influence on the ability to drive and use machines. However, during treatment with acalabrutinib, fatigue and dizziness have been reported and patients who experience these symptoms should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Calquence monotherapy

Of the 1 478 patients treated with Calquence monotherapy, the most common (≥ 20%) adverse drug reactions (ADRs) of any grade were infection, diarrhoea, headache, musculoskeletal pain, bruising, cough, arthralgia, fatigue, nausea and rash. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were infection, leukopenia, neutropenia, anaemia, second primary malignancy, and thrombocytopenia.

Calquence in combination with obinutuzumab

Of the 223 patients treated with Calquence in combination with obinutuzumab, the most common (≥ 20%) ADRs of any grade were infection, musculoskeletal pain, diarrhoea, headache, leukopenia, neutropenia, cough, fatigue, arthralgia, nausea, dizziness, and constipation. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were leukopenia, neutropenia, infection, thrombocytopenia and anaemia.

Calquence in combination with venetoclax

Of the 291 patients treated with Calquence in combination with venetoclax, the most common (≥ 20%) ADRs of any grade were infections, neutropenia, headache, bruising, diarrhoea and musculoskeletal pain. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reaction was neutropenia.

Calquence in combination with venetoclax and obinutuzumab

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, the most common (≥ 20%) ADRs of any grade were infections, neutropenia, headache, bruising, diarrhoea, nausea

and musculoskeletal pain. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were neutropenia and thrombocytopenia.

Calquence in combination with bendamustine and rituximab

Of the 297 patients treated with Calquence in combination with bendamustine and rituximab, the most common (≥ 20%) ADRs of any grade were neutropenia, nausea, rash, diarrhoea, musculoskeletal pain, headache, fatigue, vomiting, constipation, anaemia and thrombocytopenia. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were neutropenia, rash, thrombocytopenia, anaemia, pneumonia, second primary malignancies, hypertension and second primary malignancies excluding non-melanoma skin.

Tabulated list of adverse reactions

The below tables present adverse drug reactions (ADRs) identified in clinical studies with patients receiving Calquence monotherapy or combination therapy for haematological malignancies. The median duration of Calquence monotherapy treatment across the pooled dataset was 38.2 months. The median duration of Calquence treatment in patients treated with Calquence in combination with bendamustine and rituximab was 28.6 months. The median duration of Calquence treatment in patients treated with Calquence in combination with venetoclax with or without obinutuzumab was 12.9 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 defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib monotherapy (N=1 478)

MedDRA SOC	MedDRA Term	All Grades (%)	Grade ≥ 3* (%)
Infections and infestations	Upper respiratory tract infection	Very common (25.8)	1.2
	Pneumonia	Very common (15.8)	8.7
	Sinusitis	Very common (11.4)	0.4
	Urinary tract infection	Common (9.9)	1.8
	Bronchitis	Common (9.7)	0.6
	Herpes viral infections†	Common (9.1)	0.9
	Nasopharyngitis	Common (8.3)	0
	Aspergillus infections†	Uncommon (0.7)	0.6
	Hepatitis B reactivation	Uncommon (0.4)	0.3

MedDRA SOC	MedDRA Term	All Grades (%)	Grade ≥ 3* (%)
Neoplasms benign, malignant and unspecified	Second Primary Malignancy (SPM)† Non-melanoma skin malignancy† SPM excluding non-melanoma skin†	Very common (17.6) Common (9.9) Common (9.7)	6.7 1.4 5.5
Blood and lymphatic system disorders	Neutropenia†	Very common (19.4)	17.5
	Anaemia†	Very common (17.1)	9.5
	Thrombocytopenia†	Very common (11.5)	6.2
	Lymphocytosis	Uncommon (0.5)	0.3
Metabolism and nutrition disorders	Tumour Lysis Syndrome	Uncommon (0.5)	0.4
Nervous system disorders	Headache	Very common (36.5)	1.2
	Dizziness	Very common (13.9)	0.1
Cardiac disorders	Atrial fibrillation/Flutter†	Common (7.4)	2.3
Vascular disorders	Bruising† Contusion Petechiae Ecchymoses	Very common (30.9) Very common (20.7) Common (8.9) Common (5.7)	0 0 0 0
	Haemorrhage/haematoma† Gastrointestinal haemorrhage Intracranial haemorrhage	Very common (16.3) Uncommon (0.9) Uncommon (0.1)	3.2 0.7 0.1
	Hypertension†	Very common (11.9)	4.9
	Epistaxis	Common (8.0)	0.3
Gastrointestinal disorders	Diarrhoea	Very common (36.7)	2.6
	Nausea	Very common (21.8)	0.8
	Constipation	Very common (15.2)	0.1
	Abdominal pain†	Very common (14.5)	1.2
	Vomiting	Very common (14.0)	0.7
Skin and subcutaneous tissue disorders	Rash†	Very common (20.3)	0.9
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain†	Very common (31.9)	1.8
	Arthralgia	Very common (24.0)	0.9
General disorders and administration site conditions	Fatigue	Very common (23.6)	2.0
	Asthenia	Common (7.0)	0.9

MedDRA SOC	MedDRA Term	All Grades (%)	Grade ≥ 3* (%)
Investigations§ (Findings based on test results)	Haemoglobin decreased±	Very common (47.4)	10.8
	Absolute neutrophil count decreased±	Very common (43.9)	24.0
	Platelets decreased±	Very common (36.9)	9.5

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Includes multiple ADR term.
±Represents the incidence of laboratory findings, not of reported adverse events.
§Presented as CTCAE grade values.

Table 5. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib combination therapy (N=1 095)

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Infections and infestations								
Upper respiratory tract infection	Very common (31.4)	1.8	Very common (18.2)	0.3	Common (8.2)	0.3	Common (6.3)	0
Sinusitis	Very common (15.2)	0.4	Common (6.4)	0	Common (2.7)	0	Common (2.5)	0
Nasopharyngitis	Very common (13.5)	0.4	Common (5.4)	0	Common (1.4)	0	Common (1.1)	0
Urinary tract infection	Very common (13)	0.9	Very common (11.1)	1.7	Common (3.1)	0	Common (6.0)	0.4
Pneumonia	Very common (10.8)	5.4	Very common (16.2)	8.8	Common (3.8)	1.4	Common (5.3)	3.9
Bronchitis	Common (9.9)	0	Common (6.4)	0.3	Common (2.1)	0	Common (2.5)	0
Herpes viral infections†	Common (6.7)	1.3	Very common (12.8)	1.0	Common (4.8)	0	Common (3.5)	0.4
Progressive multifocal leukoencephalopathy	Uncommon (0.4)	0.4	Not known	0	Not known	0	Not known	0

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Hepatitis B reactivation	Uncommon (0.9)	0.1	Common (1.3)	0.3	Not known	0	Not known	0
Aspergillus infections†	Not known	0	Uncommon (0.3)	0.3	Not known	0	Uncommon (0.4)	0.4
Neoplasms benign, malignant and unspecified								
Second primary malignancy†(SPM)	Very common (13)	4.0	Very common (17.8)	7.4	Common (5.2)	1.7	Common (4.2)	1.8
Non-melanoma skin malignancy†	Common (7.6)	0.4	Very common (11.1)	2.0	Common (3.1)	0	Common (1.8)	0.4
SPM excluding non-melanoma skin†	Common (6.3)	3.6	Common (9.8)	5.4	Common (2.7)	1.7	Common (2.5)	1.4
Blood and lymphatic system disorders								
Neutropenia†	Very common (31.8)	30	Very common (54.9)	50.2	Very Common (37.1)	32.3	Very Common (50.4)	46.1
Thrombocytopenia†	Very common (13.9)	9	Very common (22.9)	9.8	Common (5.8)	2.1	Very Common (12.3)	9.2
Anaemia†	Very common (11.7)	5.8	Very common (24.2)	9.4	Common (6.9)	3.8	Common (4.6)	2.1
Lymphocytosis	Uncommon (0.4)	0.4	Uncommon (0.7)	0	Not known	0	Uncommon (0.7)	0.4
Metabolism and nutrition disorders								
Tumour lysis syndrome	Common (1.8)	1.3	Common (1.3)	1.3	Uncommon (0.3)	0.3	Uncommon (0.4)	0.4
Nervous system disorders								
Headache	Very common (43)	0.9	Very common (30.3)	1.3	Very Common (35.1)	1.4	Very Common (28.2)	0.4
Dizziness	Very common (23.8)	0	Very common (14.5)	0.7	Common (5.5)	0	Common (6.7)	0
Cardiac disorders								

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Atrial fibrillation/flutter†	Common (3.1)	0.9	Common (6.7)	4.0	Uncommon (0.7)	0.3	Common (2.1)	0.7
Vascular disorders								
Bruising†	Very common (38.6)	0	Very common (14.1)	0.3	Very common (20.6)	0	Very common (21.8)	0
Contusion	Very common (27.4)	0	Very common (11.1)	0	Very common (14.1)	0	Very common (16.2)	0
Petechiae	Very common (11.2)	0	Common (2.0)	0	Common (4.8)	0	Common (5.3)	0
Ecchymoses	Common (3.1)	0	Common (3.0)	0.3	Common (2.7)	0	Common (3.9)	0
Haemorrhage/haematoma†	Very common (17.5)	1.3	Very common (15.5)	1.0	Common (8.9)	0.7	Common (8.5)	1.1
Gastrointestinal haemorrhage	Common (3.6)	0.9	Uncommon (0.3)	0	Uncommon (0.7)	0.3	Not known	0
Intracranial haemorrhage	Uncommon (0.9)	0	Not known	0	Not known	0	Not known	0
Hypertension†	Very common (13.5)	3.6	Very common (12.5)	5.7	Common (4.1)	2.7	Common (3.9)	2.1
Epistaxis	Common (8.5)	0	Common (2.7)	0	Common (1.7)	0	Common (4.2)	0
Respiratory, thoracic and mediastinal disorders								
Pneumonitis±	-	-	Common (2.4)	0.3	-	-	-	-

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Gastrointestinal disorders								
Diarrhoea	Very common (43.9)	4.5	Very common (37.4)	3.0	Very common (32.6)	1.7	Very common (36.3)	1.4
Nausea	Very common (26.9)	0	Very common (42.8)	1.3	Very common (14.8)	0	Very common (21.8)	0.7
Constipation	Very common (20.2)	0	Very common (24.6)	1.0	Common (6.5)	0.3	Common (8.1)	0
Vomiting	Very common (19.3)	0.9	Very common (25.6)	0.7	Common (5.5)	0	Common (6.7)	0
Abdominal pain†	Very common (14.8)	1.3	Very common (12.1)	2.0	Common (7.9)	1.0	Common (8.1)	0.7
Skin and subcutaneous tissue disorders								
Rash†	Very common (30.9)	1.8	Very common (39.1)	9.8	Very common (12.0)	0.3	Very common (16.2)	1.1
Musculoskeletal and connective tissue disorders								
Musculoskeletal pain†	Very common (44.8)	2.2	Very common (34.3)	3.7	Very common (24.1)	0.7	Very common (21.8)	1.1
Arthralgia	Very common (26.9)	1.3	Very common (17.5)	0.7	Very common (12.7)	1.0	Very common (10.9)	0.4
General disorders and administration site conditions								
Fatigue	Very common (30.5)	1.8	Very common (29.3)	2.7	Very common (14.8)	0.3	Very common (14.4)	0
Asthenia	Common (7.6)	0.4	Very common (10.4)	1.0	Common (4.1)	0	Common (3.2)	0
Investigations¶								
Absolute neutrophil count decreased§	Very common (57.4)	35	Very common (76.8)	56.6	Very common (78.0)	38.1	Very common (81.7)	53.5

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Platelets decreased[§]	Very common (46.2)	10.8	Very common (69.4)	17.8	Very common (42.6)	5.2	Very common (54.9)	13.7
Haemoglobin decreased[§]	Very common (43.9)	9	Very common (79.5)	10.8	Very common (34.7)	6.5	Very common (45.8)	3.5
Alanine aminotransferase increased[‡]	-	-	Common (9.1)	4.4	-	-	-	-
Aspartate aminotransferase increased[‡]	-	-	Common (8.1)	3.0	-	-	-	-

[*]Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[†]Includes multiple ADR terms.
[±]One event with fatal outcome was reported.
[§]Represents the incidence of laboratory findings, not of reported adverse events.
[¶]Presented as CTCAE grade values.
[‡]Adverse reaction only for the Calquence + BR arm in the ECHO study.

Description of selected adverse reactions

Serious infections when treating patients with Calquence in combination with venetoclax with or without obinutuzumab

Of the 291 patients treated with Calquence in combination with venetoclax, severe (Grade ≥ 3) infections were reported in 12.4% of the patients (most frequently reported COVID-19 or COVID-19 pneumonia). Fatal infections occurred in 3.1% of patients (most frequently reported COVID-19 or COVID-19 pneumonia).

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, severe (Grade ≥ 3) infections were reported in 23.6% of the patients (most frequently reported COVID-19 or COVID-19 pneumonia). Fatal infections occurred in 5.6% of patients (most frequently reported COVID-19 or COVID-19 pneumonia).

Discontinuation and dose reduction due to adverse reactions

Of the 1 478 patients treated with Calquence monotherapy, discontinuation due to adverse reactions were reported in 14.6% of the patients. These main adverse reactions included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 5.9% of patients. These main adverse reactions included hepatitis B reactivation, sepsis, and diarrhoea.

Of the 223 patients treated with Calquence in combination with obinutuzumab, discontinuation of Calquence due to adverse reactions were reported in 10.8% of the patients. These main adverse reactions

included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 6.7% of patients. These main adverse reactions included neutropenia, diarrhoea and vomiting.

Of the 291 patients treated with Calquence in combination with venetoclax, discontinuation of Calquence due to adverse reactions were reported in 7.6% of the patients and dose reduction of Calquence due to adverse reactions were reported in 5.8% of patients. These main adverse reactions leading to discontinuation included COVID-19 pneumonia and COVID-19 and the adverse reaction leading to dose reduction was neutropenia.

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, discontinuation of Calquence due to adverse reactions were reported in 13.7% of the patients and dose reductions of Calquence due to adverse reactions were reported in 6.3% of patients. These main adverse reactions leading to discontinuation included COVID-19 pneumonia and COVID-19 and the adverse reaction leading to dose reduction was neutropenia.

Of the 297 patients treated with Calquence in combination with bendamustine and rituximab, discontinuation of Calquence due to adverse reactions were reported in 42.8% of the patients. These main adverse reactions included COVID-19, COVID-19 pneumonia, neutropenia and pneumonia. Dose reductions due to adverse reactions were reported in 10.1% of patients. These main adverse reactions included neutropenia and nausea.

Elderly

Of the 1 478 patients in clinical studies of Calquence monotherapy, 42% were greater than 65 years and less than 75 years of age and 20.6% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Of the 223 patients in clinical studies of Calquence in combination of obinutuzumab therapy, 47% were greater than 65 years and less than 75 years of age and 26% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Of the 291 patients treated with Calquence in combination with venetoclax, 28.9% were greater than 65 years and less than 75 years of age and 4.5% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, 24% were greater than 65 years and less than 75 years of age and 6.3% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EL02.

Mechanism of action

Acalabrutinib is a selective 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 with minimal off-target interactions.

Pharmacodynamic effects

In patients with B-cell malignancies dosed with acalabrutinib 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

The effect of acalabrutinib on the QTc interval was evaluated in 46 healthy male and female subjects in a randomised, double-blind thorough QT study with placebo and positive controls. At a supratherapeutic dose, 4-times the maximum recommended dose, Calquence did not prolong the QT/QTc interval to any clinically relevant extent (e.g., not greater than or equal to 10 ms) (see sections 4.4, 4.8 and 5.3).

Clinical efficacy and safety

Patients with previously untreated CLL

Calquence monotherapy or in combination with obinutuzumab

The safety and efficacy of Calquence monotherapy or in combination with obinutuzumab in previously untreated CLL were evaluated in a randomised, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. 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, were included in ELEVATE-TN, 27.9% patients had a CrCl of < 60 mL/min. Of the patients who were < 65 years of age, 16.1% had a median CIRS-G score of 8. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.

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

- 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 1 000 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 1 000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.

- Calquence monotherapy: Calquence 100 mg was administered twice daily until disease progression or unacceptable toxicity.
- Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1,000 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 1 000 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. Table 6 summarises the baseline demographics and disease characteristics of the study population.

Table 6. Baseline patient characteristics in (ELEVATE-TN) patients with previously untreated CLL

Characteristic	**Calquence plus obinutuzumab N=179**	**Calquence monotherapy N=179**	**Obinutuzumab plus chlorambucil N=177**
Age, years; median (range)	70 (41-88)	70 (44-87)	71 (46-91)
Male; %	62	62	59.9
Caucasian; %	91.6	95	93.2
ECOG performance status 0-1; %	94.4	92.2	94.4
Median time from diagnosis (months)	30.5	24.4	30.7
Bulky disease with nodes ≥ 5 cm; %	25.7	38	31.1
Cytogenetics/FISH Category; %			
17p deletion	9.5	8.9	9
11q deletion	17.3	17.3	18.6
TP53 mutation	11.7	10.6	11.9
Unmutated IGHV	57.5	66.5	65.5
Complex karyotype (≥ 3 abnormalities)	16.2	17.3	18.1
Rai stage; %			
0	1.7	0	0.6
I	30.2	26.8	28.2
II	20.1	24.6	27.1
III	26.8	27.9	22.6
IV	21.2	20.7	21.5

The primary endpoint was progression-free survival (PFS) of Calquence+G arm versus GClb arm 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. Efficacy results are presented in Table 7.

Table 7. Efficacy results per IRC Assessments in (ELEVATE-TN) patients with CLL

	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)
PD, n (%)	9 (5)	20 (11.2)	82 (46.3)
Death events (%)	5 (2.8)	6 (3.4)	11 (6.2)
Median (95% CI), months	NR	NR (34.2, NR)	22.6 (20.2, 27.6)
HR† (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
P-value	< 0.0001	< 0.0001	-
24 months estimate, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
Overall Survival[a]			
Death events (%)	9 (5)	11 (6.1)	17 (9.6)
Hazard Ratio (95% CI) †	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	-
Best overall response rate* (CR + CRi + nPR + PR)			
ORR, n (%) (95% CI)	168 (93.9) (89.3, 96.5)	153 (85.5) (79.6, 89.9)	139 (78.5) (71.9, 83.9)
P-value	< 0.0001	0.0763	-
CR, n (%)	23 (12.8)	1 (0.6)	8 (4.5)
CRi, n (%)	1 (0.6)	0	0
nPR, n (%)	1 (0.6)	2 (1.1)	3 (1.7)
PR, n (%)	143 (79.9)	150 (83.8)	128 (72.3)

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.
[a] Median OS not reached for both arms.

PFS results for Calquence with or without obinutuzumab were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation or unmutated IGHV), the PFS HRs of Calquence with or without obinutuzumab versus obinutuzumab plus chlorambucil was 0.08 [95% CI (0.04, 0.15)] and 0.13 [95% CI (0.08, 0.21)], respectively.

Table 8. Subgroup analysis of PFS (Study ELEVATE-TN)

	Calquence monotherapy			Calquence+G		
	N	**Hazard Ratio**	**95% CI**	**N**	**Hazard Ratio**	**95% CI**
All subjects	179	0.20	(0.13, 0.30)	179	0.10	(0.06, 0.17)
Del 17P						
Yes	19	0.20	(0.06, 0.64)	21	0.13	(0.04, 0.46)
No	160	0.20	(0.12, 0.31)	158	0.09	(0.05, 0.17)

	Calquence monotherapy			Calquence+G		
	N	**Hazard Ratio**	**95% CI**	**N**	**Hazard Ratio**	**95% CI**
TP53 mutation Yes No	 19 160	 0.15 0.20	 (0.05, 0.46) (0.12, 0.32)	 21 158	 0.04 0.11	 (0.01, 0.22) (0.06, 0.20)
Del 17P or/and TP53 mutation Yes No	 23 156	 0.23 0.19	 (0.09, 0.61) (0.11, 0.31)	 25 154	 0.10 0.10	 (0.03, 0.34) (0.05, 0.18)
IGHV mutation Mutated Unmutated	 58 119	 0.69 0.11	 (0.31, 1.56) (0.07, 0.19)	 74 103	 0.15 0.08	 (0.04, 0.52) (0.04, 0.16)
Del 11q Yes No	 31 148	 0.07 0.26	 (0.02, 0.22) (0.16, 0.41)	 31 148	 0.09 0.10	 (0.03, 0.26) (0.05, 0.20)
Complex Karyotype Yes No	 31 117	 0.10 0.27	 (0.03, 0.33) (0.16, 0.46)	 29 126	 0.09 0.11	 (0.03, 0.29) (0.05, 0.21)

With long term data, the median follow-up was 58.2 months for Calquence+G arm, 58.1 months for Calquence arm and 58.2 months for the GClb arm. The median investigator assessed PFS for Calquence+G and Calquence monotherapy was not reached; and was 27.8 months in GClb arm. At the time of most recent data cut off, a total of 72 patients (40.7%) originally randomised to the GClb arm crossed over to Calquence monotherapy. The median overall survival had not been reached in any arm with a total of 76 deaths: 18 (10.1%) in the Calquence+G arm, 30 (16.8%) in the Calquence monotherapy arm, and 28 (15.8%) in the GClb arm.

Table 9. Efficacy Results per INV assessment in (ELEVATE-TN) Patients with CLL

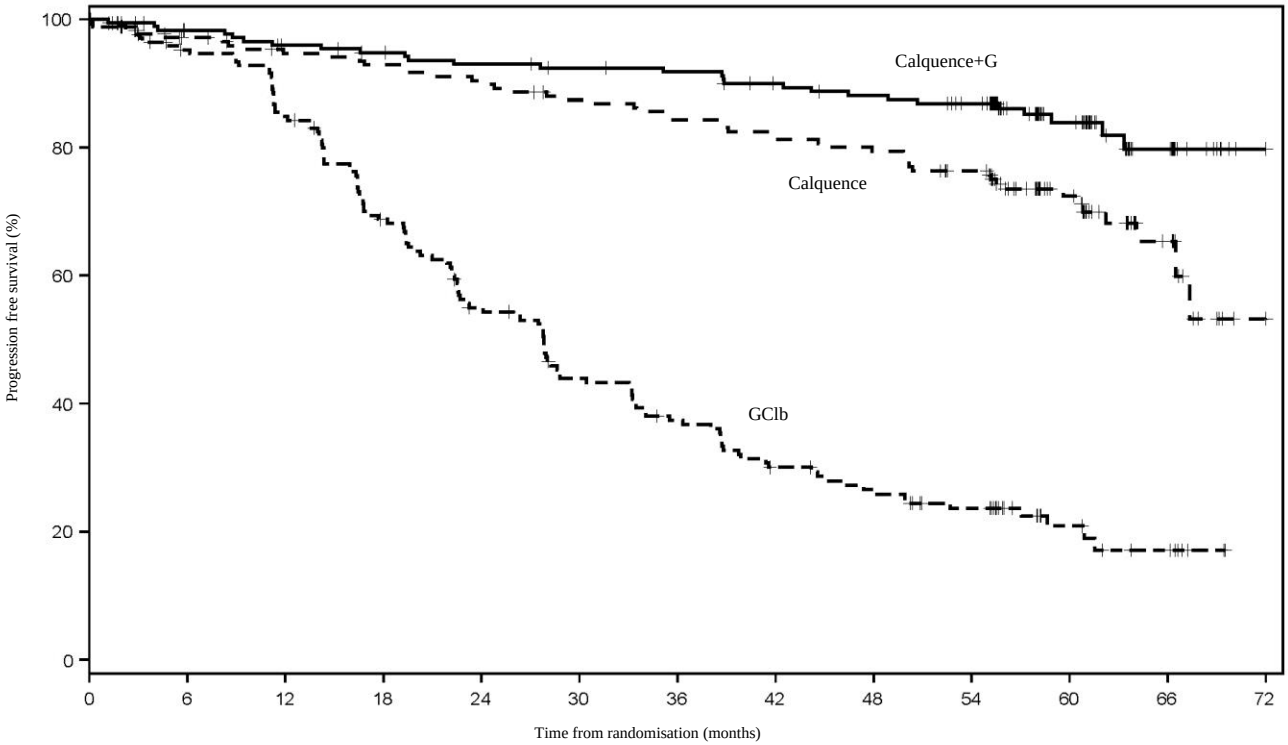
	Calquence plus obinutuzumab N=179	Calquence monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
Progression-free survival			
Number of events (%)	27 (15.1)	50 (27.9)	124 (70.1)
PD, n (%)	14 (7.8)	30 (16.8)	112 (63.3)
Death events (%)	13 (7.3)	20 (11.2)	12 (6.8)
Median (95% CI), months*	NR	NR (66.5, NR)	27.8 (22.6, 33.2)
HR† (95% CI)	0.11 (0.07, 0.16)	0.21 (0.15, 0.30)	-
Overall survival			
Death events (%)	18 (10.1)	30 (16.8)	28 (15.8)
Hazard Ratio (95% CI) †	0.55 (0.30, 0.99)	0.98 (0.58, 1.64)	-

CI=confidence interval; HR=hazard ratio; NR=not reached

*95% confidence interval based on Kaplan-Meier estimation.

†Estimate based on stratified Cox-Proportional-Hazards model for Hazard Ratio (95% CI) stratified by 17p deletion status (yes vs no).

Figure 1. Kaplan-Meier Curve of INV-Assessed PFS in (ELEVATE-TN) Patients with CLL (ITT Population)



Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	70
Calquence	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	120	93	63	39	22	6	1
Calquence+G	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	133	99	65	39	27	7	1
GClb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	40	38	31	30	20	13	8	7	2	0

Patients with previously untreated CLL – Fixed duration therapy

Calquence in combination with venetoclax with or without obinutuzumab

The safety and efficacy of Calquence in combination with venetoclax with or without obinutuzumab in previously untreated CLL was evaluated in a randomised, multi-centre, open-label Phase 3 study (AMPLIFY) of 867 patients. Patients received Calquence plus venetoclax, Calquence plus venetoclax and obinutuzumab, or Investigator's choice of chemoimmunotherapy, either FCR (fludarabine plus cyclophosphamide plus rituximab) or BR (bendamustine plus rituximab). AMPLIFY included patients previously untreated for CLL without del(17p) or TP53 mutation that were 18 years of age and older. The trial allowed patients to receive antithrombotic agents except warfarin and other vitamin K antagonists.

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

- Calquence plus venetoclax (AV): Calquence 100 mg was administered twice daily starting on Cycle 1 Day 1 for a total of 14 cycles or until disease progression or unacceptable toxicity. On Cycle 3 Day 1 patients started the venetoclax 5-week dose-titration schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles. Each cycle was 28 days.

- Calquence plus venetoclax plus obinutuzumab (AVO): Calquence 100 mg was administered twice daily starting on Cycle 1 Day 1 for a total of 14 cycles or until disease progression or unacceptable toxicity. On Cycle 3 Day 1 patients started the venetoclax 5-week dose-titration schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles. Obinutuzumab 1 000 mg was administered on Day 1 or Day 1 and 2 (100 mg on Day 1 and 900 mg on Day 1 or 2), 8 and 15 of Cycle 2 followed by 1 000 mg on Day 1 of Cycles 3-7. Each cycle was 28 days.

- Investigator's choice of chemoimmunotherapy (FCR/BR):
    - Fludarabine plus cyclophosphamyde plus rituximab (FCR): Fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) were administered on Days 1-3 up to a maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on Day 1 Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.
    - Bendamustine plus rituximab (BR): Bendamustine 90 mg/m^2 was administered on Days 1 and 2 up to maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on Day 1 Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.

Patients were stratified by age (> 65 years or ≤ 65 years), IGHV mutational status (mutated versus unmutated), Rai stage (high risk [≥ 3] versus non-high risk) and geographic region (North America and Western Europe versus other). Table 10 summarises the baseline demographics and disease characteristics of the study population.

Table 10. Baseline Patient Characteristics in (AMPLIFY) Patients with Previously Untreated CLL

Characteristic	AV N=291	AVO N=286	FCR/BR N=290
Age, years; median (range)	61 (31-84)	61 (29-81)	61 (26-86)
Male; %	61.2	69.2	63.1
Caucasian; %	91.1	86.7	86.9
ECOG performance status 0-1; %	90.0	95.1	90.3
Median time from diagnosis to randomization (months)	28.5	26.1	29.6
Bulky disease with nodes ≥ 5 cm; %	38.8	35.0	42.8
Cytogenetics/FISH Category; %			
11q deletion	17.5	19.6	15.9
Complex karyotype (≥ 3 abnormalities)	15.5	16.1	14.5
Unmutated IGHV; %	57.4	59.1	59.3
Rai stage; %			
0	1.0	0.3	1.4
I	16.2	21.3	21.4
II	35.7	37.8	33.4
III	23.7	17.8	20.3
IV	23.4	22.7	23.4

The primary endpoint was IRC-assessed PFS for AV versus Investigator's choice of chemoimmunotherapy (FCR/BR) arm as assessed by IWCLL 2018 criteria. Additional efficacy endpoints were IRC-assessed PFS of AVO versus Investigator's choice (FCR/BR) arm and OS in both AV arm vs. Investigator's choice (FCR/BR) arm and AVO vs. Investigator's choice (FCR/BR) arm.

Efficacy results are presented in Table 11. The Kaplan-Meier curve for IRC-PFS is shown in Figure 2.

Table 11. Efficacy results in (AMPLIFY) patients with previously untreated CLL

	AV N=291	AVO N=286	FCR/BR[a] N=290
Progression-free survival[*]			
Number of events (%)	89 (30.6)	56 (19.6)	95 (32.8)
PD, n (%)	77 (26.5)	23 (8.0)	66 (22.8)
Death events (%)	12 (4.1)	33 (11.5)	29 (10.0)
Median (95% CI), months	NC (51.1, NC)	NC (NC, NC)	47.6 (43.3, NC)
HR[†] (95% CI)	0.65 (0.49, 0.87)	0.42 (0.30, 0.59)	-
P-value	0.0038	<0.0001	-
Overall Survival[b]			
Death events (%)	23 (7.9)	37 (12.9)	44 (15.2)
HR[†] (95% CI)	0.42 (0.25, 0.70)[c]	0.75 (0.48, 1.16)	-

NC= Not calculable; CI= Confidence interval; PD= Progressive disease.

[*]Per IRC assessment.

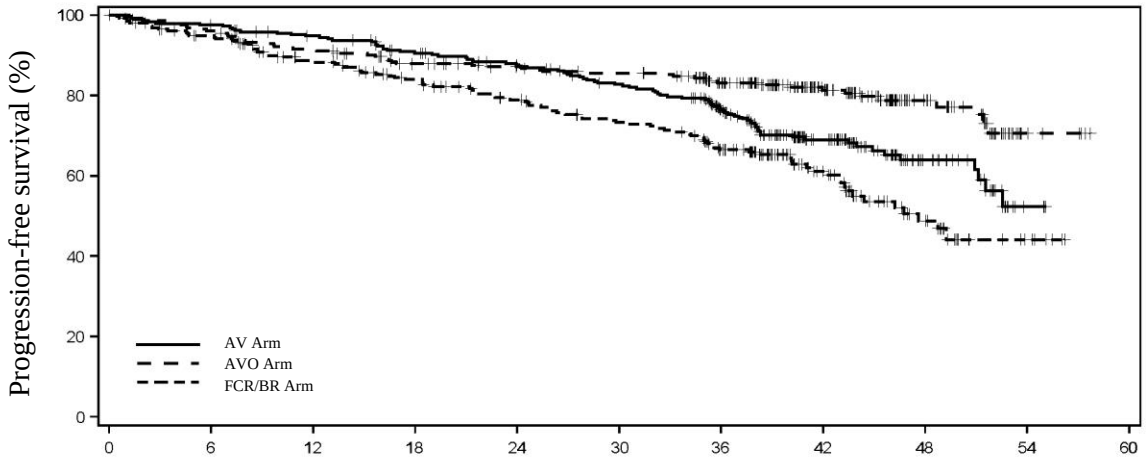
[†]Based on stratified Cox-Proportional-Hazards model.

[a]Per Investigator's choice 143 patients were planned to receive FCR and 147 patients were planned to receive BR.

[b]OS data at additional 6 months follow-up from PFS interim analysis.

[c]The p-value is not significant after adjusting for multiplicity.

Figure 2. Kaplan-Meier Curve of IRC-Assessed PFS in (AMPLIFY) patients with CLL (ITT Population)



Patients at risk											
AV Arm	291	282	269	251	237	219	177	102	35	3	0
AVO Arm	286	272	258	237	225	219	191	116	51	7	0
FCR/BR Arm	290	236	208	189	170	154	127	66	28	6	0

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 not including BCL-2 inhibitors or B-cell receptor inhibitors. Patients received Calquence monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.

Patients were randomised 1:1 to receive either:

- Calquence 100 mg twice daily until disease progression or unacceptable toxicity, or
- Investigator's choice:
  - Idelalisib 150 mg twice daily in combination with rituximab 375 mg/m2 IV on Day 1 of the first cycle, followed by 500 mg/m2 IV every 2 weeks for 4 doses, then every 4 weeks for 3 doses for a total of 8 infusions
  - 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. Table 12 summarizes the baseline demographics and disease characteristics of the study population.

Table 12. Baseline patient characteristics in (ASCEND) patients with CLL

Characteristic	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Age, years; median (range)	68 (32-89)	67 (34-90)
Male; %	69.7	64.5
Caucasian; %	93.5	91.0
ECOG performance status; %		
0	37.4	35.5
1	50.3	51.0
2	12.3	13.5
Median time from diagnosis (months)	85.3	79.0
Bulky disease with nodes ≥ 5 cm; %	49.0	48.4
Median number of prior CLL therapies (range)	1 (1-8)	2 (1-10)
Number of Prior CLL Therapies; %		
1	52.9	43.2
2	25.8	29.7
3	11.0	15.5
≥ 4	10.3	11.6
Cytogenetics/FISH Category; %		
17p deletion	18.1	13.5
11q deletion	25.2	28.4
TP53 mutation	25.2	21.9
Unmutated IGHV	76.1	80.6
Complex karyotype (≥3 abnormalities)	32.3	29.7
Rai Stage; %		
0	1.3	2.6
I	25.2	20.6
II	31.6	34.8
III	13.5	11.6
IV	28.4	29.7

The primary endpoint was PFS as assessed by IRC IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 16.1 months, PFS indicated a 69% statistically significant reduction in the risk of death or progression for patients in the Calquence arm. Efficacy results are presented in Table 13. The Kaplan-Meier curve for PFS is shown in Figure 3.

Table 13. Efficacy results per IRC Assessments in (ASCEND) patients with CLL

	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Progression-free survival*		
Number of events (%)	27 (17.4)	68 (43.9)
PD, n (%)	19 (12.3)	59 (38.1)

Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR† (95% CI)	0.31 (0.20, 0.49)	
P-value	< 0.0001	
15 months estimate, % (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
Overall survival[a]		
Death events (%)	15 (9.7)	18(11.6)
Hazard Ratio (95% CI) †	0.84 (0.42, 1.66)	-
Best overall response rate* (CR + CRi + nPR + PR)**		
ORR, n (%) (95% CI)	126 (81.3) (74.4, 86.6)	117 (75.5) (68.1, 81.6)
P-value	0.2248	-
CR, n (%)	0	2 (1.3)
PR, n (%)	126 (81.3)	115 (74.2)
Duration of Response (DoR)		
Median (95% CI), months	NR	13.6 (11.9,NR)

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; PD=progressive disease

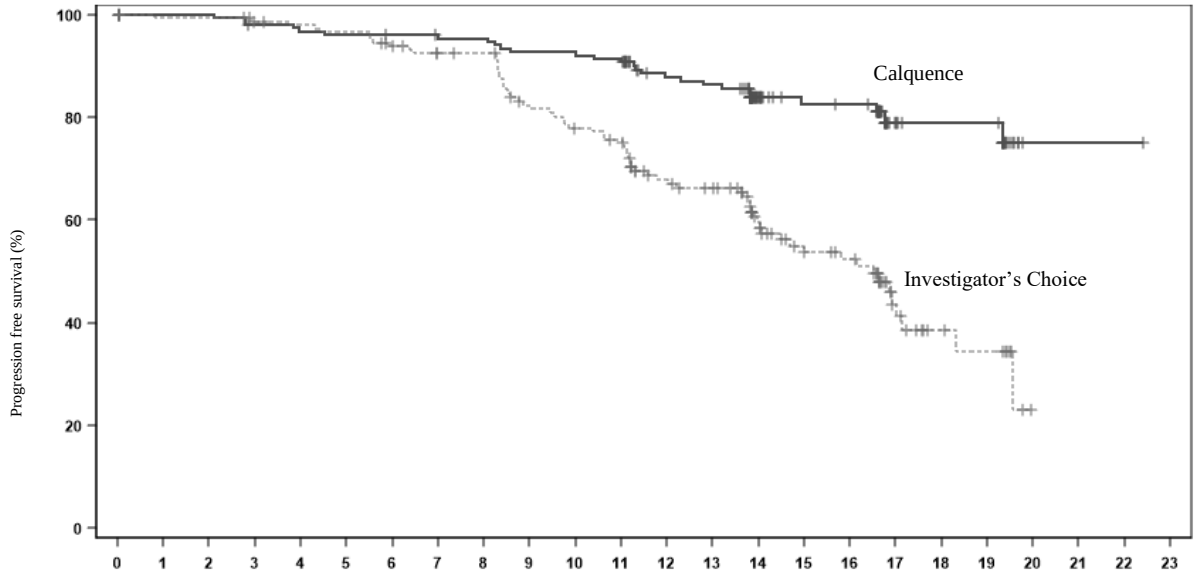
*Per IRC assessment

[a] Median OS not reached for both arms. P<0.6089 for OS.

**CRi and nPR have values of 0.

†Based on stratified Cox-Proportional-Hazards model

Figure 3. Kaplan-Meier curve of IRC-assessed PFS in (ASCEND) patients with CLL (ITT Population)



Time from randomisation (months)

Number of patients at risk																								
Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Calquence	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
Investigator's Choice	155	150	150	146	144	142	136	130	129	112	105	101	82	77	56	44	39	18	10	8	0			

PFS results for Calquence were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation and unmutated IGHV), the PFS HR was 0.27 [95% CI (0.17, 0.44)].

Table 14. Subgroup analysis of IRC-assessed PFS (Study ASCEND)

	Calquence monotherapy		
	N	**Hazard Ratio**	**95% CI**
All subjects	155	0.30	(0.19, 0.48)
Del 17P Yes No	 28 127	 0.21 0.33	(0.07, 0.68)(0.21, 0.54)
TP53 mutation Yes No	 39 113	 0.24 0.33	(0.11, 0.56) (0.20, 0.57)
Del 17P or TP53 mutation Yes No	 45 108	 0.21 0.36	(0.09, 0.48) (0.21, 0.61)
IGHV mutation Mutated Unmutated	 33 118	 0.32 0.32	(0.11, 0.94) (0.19, 0.52)
Del 11q Yes No	 39 116	 0.28 0.31	(0.11, 0.70) (0.19, 0.53)
Complex Karyotype Yes No	 50 97	 0.32 0.23	(0.16, 0.63) (0.12, 0.44)

At final analysis, with a median follow-up of 46.5 months for Calquence and 45.3 months for the IR/BR, a 72% reduction in risk of investigator-assessed disease progression or death was observed for patients in the Calquence arm. The median investigator assessed PFS was not reached in Calquence and was 16.8 months in IR/BR. Efficacy results per Investigator Assessments (INV) are presented in Table 15. The Kaplan-Meier curve for INV assessed PFS is shown in Figure 4.

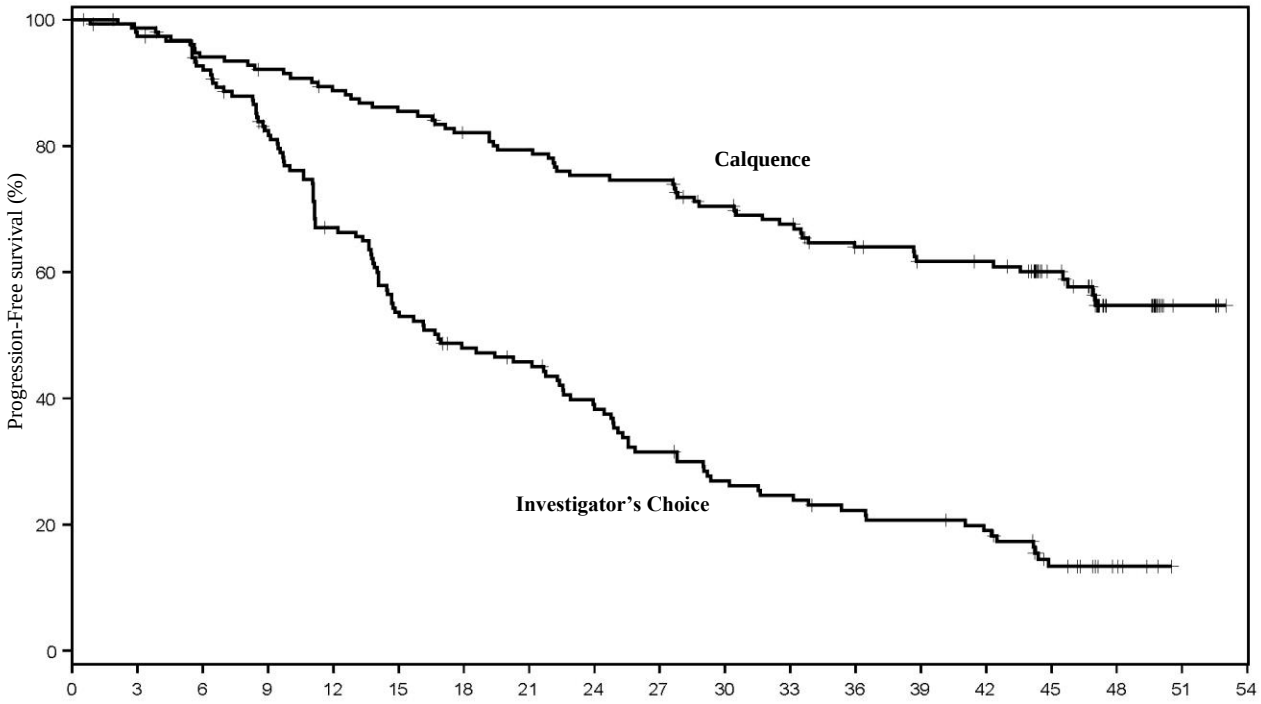
Table 15. Efficacy results at final analysis per INV assessments in (ASCEND) patients with CLL

	Calquence monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-free survival*		
Number of events (%)	62 (40.0)	119 (76.8)
PD, n (%)	43 (27.7)	102 (65.8)
Death events (%)	19 (12.3)	17 (11.0)
Median (95% CI), months	NR	16.8 (14.1, 22.5)
HR† (95% CI)	0.28 (0.20, 0.38)	
Overall survival[a]		
Death events (%)	41 (26.5)	54 (34.8)
Hazard Ratio (95% CI) †	0.69 (0.46, 1.04)	-

	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155

CI=confidence interval; HR=hazard ratio; NR=not reached; PD=progressive disease
*Per INV assessment.
[a] Median OS not reached for both arms P=0.0783 for OS.
†Based on stratified Cox-Proportional-Hazards model.

Figure 4. Kaplan-Meier curve of INV-assessed PFS at final analysis in (ASCEND) patients with CLL



Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Calquence	155	151	143	139	133	128	121	117	111	110	100	94	85	80	79	52	21	4	0
Investigator's Choice	155	147	138	118	95	76	66	62	52	42	35	32	28	26	23	12	5	0	

Investigator assessed PFS results at final analysis for Calquence were consistent across subgroups, including high risk features and were consistent with the primary analysis.

Patients with previously untreated MCL

The safety and efficacy of Calquence in patients with previously untreated MCL was evaluated in ECHO, a randomised, double-blind, placebo-controlled, multi-centre, phase 3 study. ECHO included 598 patients 65 years of age and older with confirmed MCL that was previously untreated.
Patients were randomised in 1:1 ratio in 2 arms to receive:

- Calquence plus bendamustine and rituximab (Calquence + BR) arm: Calquence 100 mg was administered twice daily from Day 1 of Cycle 1, continuously. Bendamustine, 90 mg/m^2, was intravenously administered over 30 minutes on Days 1 and 2 of each of six 28-day cycles; and

rituximab, 375 mg/m^2, was intravenously administered on Day 1 of each cycle of six 28-day cycles. Calquence + BR was administered for a maximum of 6 treatment cycles (induction treatment).

- Placebo plus bendamustine and rituximab (Placebo + BR) arm: Placebo was administered twice daily from Day 1 of Cycle 1, continuously. Bendamustine, 90 mg/m^2, was intravenously administered over 30 minutes on Days 1 and 2 of each of six 28-day cycles; and rituximab, 375 mg/m^2, was intravenously administered on Day 1 of each cycle of six 28-day cycles. Placebo + BR was administered for a maximum of 6 treatment cycles (induction treatment).

Calquence or placebo was administered continuously until disease progression or unacceptable toxicity. After the induction treatment, patients who were achieving a response (PR or CR) received rituximab maintenance at 375 mg/m^2 on Day 1 of every other cycle for maximum of 12 additional doses up to Cycle 30. Patients randomised to placebo + BR arm who had confirmed PD were eligible to cross over to Calquence monotherapy at 100 mg twice daily dose until their second disease progression or unacceptable toxicity.

Patient randomisation was stratified by geographic region (North America versus Western Europe versus Other) and simplified MIPI (Mantle Cell Lymphoma International Prognostic Index) score (0-3 versus 4-5 versus 6-11).

The median age was 71 years (65-86), 70.7% were males, 78.3% were Caucasians, 93.1% had an ECOG performance status of 0-1. The simplified MIPI score was low (0-3) in 33.1%, intermediate (4-5) in 42.8% and high (6-11) in 24.1% of patients. A total of 37.7% of patients had tumour bulk ≥ 5 cm and 86% had Ann Arbor stage IV disease. Aggressive variants of MCL such as blastoid and pleomorphic forms were seen in 7.7% and 5.5% of patients respectively. A total of 47.8% patients had Ki-67 score of ≥ 30%. The baseline characteristics were similar for both arms.

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per 2014 Lugano Classification for non-Hodgkin's lymphoma (NHL) in subjects with previously untreated MCL. Additionally, overall response rate (ORR) was also assessed by an IRC.

IRC-assessed PFS was assessed at a median follow-up of 49.8 months.

With an additional 6 months of follow-up from the primary PFS analysis, and a median follow-up of 63.0 months, the median overall survival had not been reached in either arm. There were a total of 218 deaths: 105 (35.1%) in the Calquence + BR arm and 113 (37.8%) in the placebo + BR arm. Efficacy results are presented in Table 16. The Kaplan-Meier curves for PFS are shown in Figure 5.

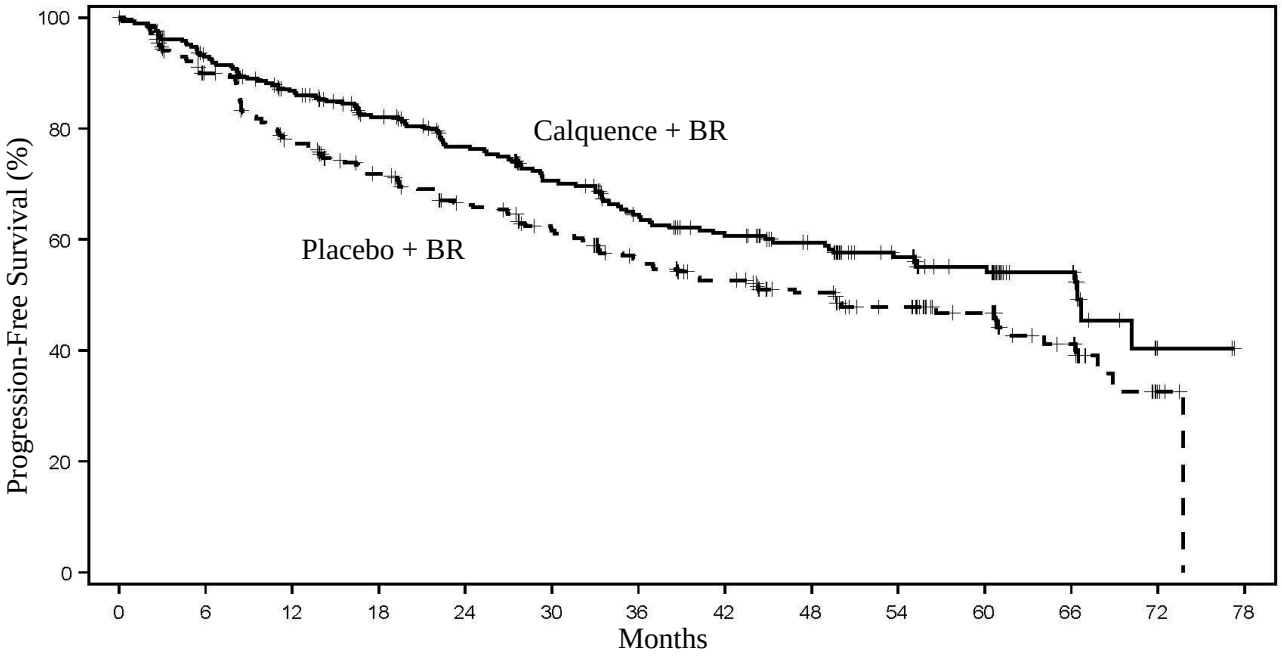
Table 16. Efficacy Results in Patients with previously untreated MCL in ECHO

	Calquence + BR N=299	**Placebo + BR N=299**
IRC-assessed PFS		
Median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
HR (95% CI) (stratified)*	0.73 (0.57, 0.94)	
p-value‡	0.0160	
IRC-assessed ORR		
CR + PR n (%)	272 (91.0)	263 (88.0)
95% CI	87.3,93.8	83.9, 91.3
CR n (%)	199 (66.6)	160 (53.5)
PR n (%)	73 (24.4)	103 (34.4)

	Calquence + BR N=299	Placebo + BR N=299
p-value	0.2196	-

HR = hazard ratio, CR = complete response, PR = partial response, NE = not evaluable
*Stratified by randomisation stratification factors: Geographic Regions (North American, Western Europe, Other) and simplified MIPI Score (Low risk [0 to 3], Intermediate risk [4 to 5], High Risk [6 to 11]) as collected via IXRS. Estimated based on stratified Cox Proportional Hazards model for hazard ratio (95% CI).
‡ Estimated based on stratified log-rank test for p-value.

Figure 5. Kaplan-Meier Curve of IRC-Assessed PFS in patients with previously untreated MCL (ECHO)



Number of patients at risk

Calquence + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

Patients with MCL who received at least one prior therapy

The safety and efficacy of CALQUENCE in MCL were evaluated in an open-label, multi-centre, single-arm Phase 2 study (ACE-LY-004) of 124 previously treated patients. All patients received CALQUENCE 100 mg orally twice daily until disease progression or unacceptable toxicity. The trial did not include patients who received prior treatment with either BTK or BCL-2 inhibitors. The primary endpoint was investigator-assessed overall response rate (ORR) per the Lugano classification for non-Hodgkin's lymphoma (NHL). Duration of Response (DoR) was an additional outcome measure. Efficacy results at final (54 months) analysis are presented in Table 17.

At final analysis, the median age was 68 (range 42 to 90) years, 79.8% were male and 74.2% were Caucasian. At baseline, 92.8% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46.3 months and the median number of prior treatments was 2 (range 1 to 5), including 17.7% with prior stem cell transplant. The most common prior regimens were CHOP-based (51.6%) and ARA-C (33.9%). At baseline, 37.1% of patients had at least one tumour with a longest diameter ≥ 5 cm, 72.6% had extra nodal involvement including 50.8% with bone marrow involvement.

The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 43.5% and high in 16.9% of patients.

Table 17. ORR and DOR in (ACE-LY-004) Patients with MCL at 54 months final analysis

	Investigator Assessment at 54 months **N=124** **n (%) (95% CI[*])**
Overall Response Rate (ORR)	
Overall Response Rate	101 (81.5%) (73.5, 87.9)
Complete Response	59 (47.6%) (38.5, 56.7)
Partial Response	42 (33.9%) (25.6, 42.9)
Non-Evaluable[†]	3 (2.4%) (0.5, 6.9)
Duration of Response (DoR)	
Median (months)	28.6 (17.5, 39.1)

CI=Confidence Interval
[*]95% exact binomial confidence interval.
[†]Includes subjects without any adequate post-baseline disease assessment.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Calquence in all subsets of the paediatric population for the treatment of mature B-cell neoplasms (for information on paediatric use, see section 4.2).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862, were studied in healthy subjects and in patients with B-cell malignancies. Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and ACP-5862 exhibit almost linear PK across a dose range of 75 to 250 mg. Population PK modelling suggests that the PK of acalabrutinib and ACP-5862 is similar across patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including, CLL), the geometric mean steady state daily area under the plasma concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) for acalabrutinib were 1679 ng•h/mL and 438 ng/mL, respectively, and for ACP-5862 were 4166 ng•h/mL and 446 ng/mL, respectively.

Absorption

The time to peak plasma concentrations (T_{max}) was 0.5-1.5 hours for acalabrutinib, and 1.0 hour for ACP-5862. The absolute bioavailability of Calquence was 25%.

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 69% and T_{max} was delayed 1-2 hours.

Distribution

Reversible binding to human plasma protein was 99.4% for acalabrutinib and 98.8% 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.

Biotransformation/Metabolism

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

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

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

Interactions with transport proteins

In vitro studies indicate that acalabrutinib and ACP-5862 are P-gp and BCRP substrates. Co-administration with BCRP inhibitors is however unlikely to result in clinically relevant drug interactions. Co-administration with an OATP1B1/1B3 inhibitor (600 mg rifampin, single dose) resulted in an increase in acalabrutinib C_{max} and AUC by 1.2-fold and 1.4-fold (N=24, healthy subjects), respectively, which is not clinically relevant.

Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 and MATE2-K at clinically relevant concentrations. Acalabrutinib may inhibit intestinal BCRP, while ACP-5862 may inhibit MATE1 at clinically relevant concentrations (see section 4.5). Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 1 to 2 hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was approximately 7 hours.

The mean apparent oral clearance (CL/F) was 134 L/hr for acalabrutinib and 22 L/hr for ACP-5862 in patients with B-cell malignancies.

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.

Special populations

Based on population PK analysis, age (> 18 years of age), sex, race (Caucasian, African American) and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862.

Paediatric population

No pharmacokinetic studies were performed with Calquence in patients under 18 years of age.

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/1.73 m^2) or renal impairment requiring dialysis. Patients with creatinine levels greater than 2.5 times the institutional ULN were not included in the clinical studies (see section 4.2).

Hepatic impairment

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

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Genotoxicity/Mutagenicity/Phototoxicity

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.

Based on phototoxicity assays using 3T3 cell line *in vitro*, acalabrutinib is considered to have a low risk for phototoxicity in humans.

Repeat-dose toxicity

In rats, microscopic findings of minimal to mild severity were observed in the pancreas (haemorrhage/pigment/inflammation/fibrosis in islets) at all dose levels. Non-adverse findings of minimal to mild severity in the kidneys (tubular basophilia, tubular regeneration, and inflammation) were observed in studies of up to 6-month duration with a No Observed Adverse Effect level (NOAEL) of 30 mg/kg/day in rats. The mean exposures (AUC) at the NOAEL in male and female rats correspond to 0.6x and 1x, respectively, the clinical exposure at the recommended dose of 100 mg twice daily, respectively. The Lowest Adverse Observed Effect Level (LOAEL) at which reversible renal (moderate tubular degeneration) and liver (individual hepatocyte necrosis) findings were observed in the chronic rat study was 100 mg/kg/day and provided an exposure margin 4.2-times greater than the clinical exposure at the recommended dose of 100 mg twice daily. In studies of 9 months duration in dogs, the NOAEL was 10 mg/kg/day corresponding to an exposure 3-times the clinical AUC at the recommended clinical dose. Minimal tubular degeneration in kidney, slight decreases in spleen weights and transient minimal to mild decreases in red cell mass and increases in ALT and ALP were observed at 30 mg/kg/day (9-times the clinical AUC) in dogs. Cardiac toxicities in rats (myocardial haemorrhage, inflammation, necrosis) and dogs (perivascular/vascular inflammation) were observed only in animals that died during studies at doses above the maximum tolerated dose (MTD). The exposures in rats and dogs with cardiac findings was at least 6.8-times and 25-times the clinical AUC, respectively. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the MTD.

Reproductive toxicology

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

No effects on embryofoetal development and survival were observed in pregnant rats, at exposures approximately 9-times the AUC in patients at the recommended dose of 100 mg twice daily. In two rat reproductive studies, dystocia (prolonged/difficult labour) was observed at exposures >2.3-times the clinical exposure at 100 mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma. Acalabrutinib and its active metabolite were present in the milk of lactating rats.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Colloidal anhydrous silica
Partially pregelatinised maize starch
Magnesium stearate (E470b)
Sodium starch glycollate

Capsule shell

Gelatine
Titanium dioxide (E171)
Yellow iron oxide (E172)
Indigo carmine (E132)

Printing ink

Shellac
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blisters, with sun/moon symbols, containing 6 or 8 hard capsules. Cartons of 56 or 60 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1479/001
EU/1/20/1479/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 November 2020
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Calquence 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of acalabrutinib (as acalabrutinib maleate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Orange, 7.5 x 13 mm, oval, biconvex tablet, debossed with 'ACA 100' on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT).

Calquence as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) not previously treated with a BTK inhibitor.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose of Calquence in monotherapy or in combination with other medicinal products is 100 mg acalabrutinib twice daily (equivalent to a total daily dose of 200 mg).

Calquence dose interval is approximately 12 hours.

For the combination regimens, refer to the prescribing information of each of the medicinal product for their dosing information (for details of the combination regimens, see section 5.1).

Calquence in monotherapy or in combination with obinutuzumab

Treatment with Calquence in monotherapy or in combination with obinutuzumab should be continued until disease progression or unacceptable toxicity.

Calquence in combination with venetoclax with or without obinutuzumab

Treatment with Calquence in combination with venetoclax with or without obinutuzumab, should continue until disease progression, unacceptable toxicity or completion of 14 cycles of treatment (each cycle is 28 days).

Calquence should be administered on Day 1 of Cycle 1 for a total of 14 cycles. Venetoclax should be administered on Day 1 of Cycle 3 for a total of 12 cycles, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg.

If Calquence is given in combination with venetoclax and obinutuzumab, obinutuzumab should be administered at 100 mg on Day 1 of Cycle 2, followed by 900 mg which may be administered on Day 1 or 2. Administer obinutuzumab at 1 000 mg on Day 8 and 15 of Cycle 2, followed by 1 000 mg on Day 1 of Cycles 3 to 7. Obinutuzumab is administered for a total of 6 cycles.

Calquence in combination with bendamustine and rituximab

Calquence should be administered on Day 1 on Cycle 1 (each cycle is 28 days) until disease progression or unacceptable toxicity. Bendamustine should be administered at 90 mg/m^2 on Days 1 and 2 of each cycle for a total of 6 cycles. Rituximab should be administered at 375 mg/m^2 on Day 1 each cycle for a total of 6 cycles. Patients achieving a response (partial response [PR] or complete response [CR]) after the first 6 cycles, may receive maintenance rituximab at 375 mg/m^2 on Day 1 of every other cycle for a maximum of 12 additional doses, starting on Cycle 8 up to Cycle 30.

<u>Dose adjustments</u>

Adverse reactions

Recommended dose modifications of Calquence for Grade ≥ 3 adverse reactions in patients receiving Calquence monotherapy, Calquence in combination with obinutuzumab and Calquence in combination with venetoclax with or without obinutuzumab are provided in Table 1.

Recommended dose modifications for Grade ≥ 3 adverse reactions in patients receiving Calquence in combination with bendamustine and rituximab are provided in Table 2.

Table 1. Recommended dose adjustments for adverse reactions*

Adverse reaction	**Adverse reaction occurrence**	**Dose modification** (Starting dose = 100 mg approximately every 12 hours)
.Grade 3 thrombocytopenia with bleeding .Grade 4 thrombocytopenia .Grade 4 neutropenia lasting longer than 7 days .Grade 3 or greater non-haematological toxicities	First and second	Interrupt Calquence. Once toxicity has resolved to Grade 1 or baseline, Calquence may be resumed at 100 mg 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 100 mg once daily.
	Fourth	Discontinue Calquence.

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Table 2. Recommended dose adjustments for Grade ≥ 3 adverse reactions* in patients receiving Calquence in combination with bendamustine and rituximab

Adverse reaction	**Bendamustine dose modification†**	**Calquence dose modification**
Neutropenia	If Grade 3 or Grade 4 neutropenia‡: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	If Grade 4 neutropenia lasting longer than 7 days then interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd adverse reaction occurrence).¶ Discontinue Calquence at 4th adverse reaction occurrence.
Thrombocytopenia	If Grade 3 or Grade 4 thrombocytopenia: Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	If Grade 3 thrombocytopenia with significant bleeding or Grade 4 then interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd occurrence).¶ Discontinue Calquence at 3rd adverse reaction occurrence for thrombocytopenia with significant bleeding. Discontinue Calquence at 4th adverse reaction occurrence.

Adverse reaction	Bendamustine dose modification†	Calquence dose modification
Other hematologic Grade 4§ or unmanageable Grade 3 toxicity	Interrupt bendamustine. Once toxicity has resolved to Grade ≤ 2 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	Interrupt Calquence. Once toxicity has resolved to Grade ≤ 2 or baseline level, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd and 3rd adverse reaction occurrence).¶ Discontinue Calquence at 4th adverse reaction occurrence.
Grade 3 or greater non-hematologic toxicities	Interrupt bendamustine. Once toxicity has resolved to Grade 1 or baseline level, bendamustine may be resumed at 70 mg/m^2. Discontinue bendamustine if additional dose reduction is required.	Interrupt Calquence. Once toxicity has resolved to Grade 2 or baseline, Calquence may be resumed at starting dose (1st adverse reaction occurrence) or at a reduced frequency of 100 mg once daily (2nd adverse reaction occurrence).¶ Discontinue Calquence at 3rd adverse reaction occurrence.

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

†For any toxicities not listed in this table refer to the bendamustine local prescribing information.

‡Consider use of myeloid growth factors before bendamustine dose modifications.

§Grade 4 lymphopenia is an expected outcome for treatment with bendamustine and rituximab. Dose modification due to lymphopenia is expected only if considered clinically important by investigators e.g. associated recurrent infections.

¶Dose may be re-escalated at the discretion of the physician if patient tolerates a reduced dose for ≥ 4 weeks.

Refer to the prescribing information of each of the medicinal products used in combination with Calquence for additional information for management of toxicities.

Interactions

Recommendations regarding use of Calquence with CYP3A inhibitors or inducers are provided in Table 3 (see section 4.5).

Table 3. Use with CYP3A inhibitors or inducers

	Co-administered medicinal product	Recommended Calquence use
CYP3A inhibitors	Strong CYP3A inhibitor	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	No dose adjustment. Monitor patients closely for adverse reactions if taking moderate CYP3A inhibitors.
	Mild CYP3A inhibitor	No dose adjustment.

CYP3A inducers	Strong CYP3A inducer	Avoid concomitant use.

Acalabrutinib tablets can be co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids), unlike acalabrutinib capsules which show impaired uptake when given with acid reducing agents (see section 4.5).

Missed dose

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

Special populations

Elderly

No dose adjustment is required for elderly patients (aged ≥ 65 years) (see section 5.2).

Renal impairment

No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in Calquence clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained, and serum creatinine levels monitored periodically. Calquence should be administered to patients with severe renal impairment (< 30 mL/min creatinine clearance) only if the benefit outweighs the risk and these patients should be monitored closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Hepatic impairment

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). However, patients with moderate hepatic impairment should be closely monitored for signs of toxicity. It is not recommended to use Calquence in patients with severe hepatic impairment (Child-Pugh C or total bilirubin > 3-times ULN and any AST) (see section 5.2).

Severe cardiac disease

Patients with severe cardiovascular disease were excluded from Calquence clinical studies.

Paediatric population

The safety and efficacy of Calquence in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration

Calquence is for oral use. The tablets should be swallowed whole with water at approximately the same time each day, with or without food (see section 4.5). The tablets should not be chewed, crushed, dissolved or divided.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haemorrhage

Major haemorrhagic events including central nervous system and gastrointestinal haemorrhage, some with fatal outcome, have occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. These events have occurred in patients both with and without thrombocytopenia. Overall, the bleeding events were less severe events including bruising and petechiae (see section 4.8).

The mechanism for the bleeding events is not well understood.

Patients receiving antithrombotic agents may be at increased risk of haemorrhage. Caution should be used with antithrombotic agents and additional monitoring considered for signs of bleeding when concomitant use is medically necessary. Warfarin or other vitamin K antagonists should not be administered concomitantly with Calquence.

Consider the benefit-risk of withholding Calquence for at least 3 days pre- and post-surgery.

Infections

Serious infections (bacterial, viral or fungal), including fatal events, have occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. These infections predominantly occurred in the absence of neutropenia, with neutropenic infection reported in 10.1% of patients receiving monotherapy and 26.8% in patients receiving combination therapy. Infections due to hepatitis B virus (HBV) and herpes zoster virus (HZV) reactivation, aspergillosis and progressive multifocal leukoencephalopathy (PML) have occurred (see section 4.8).

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.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anaemia and thrombocytopenia, occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. Monitor complete blood counts as medically indicated (see section 4.8).

Second primary malignancies

Second primary malignancies, including skin and non-skin cancers, occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. Skin cancers were commonly reported. Monitor patients for the appearance of skin cancers and advise protection from sun exposure (see section 4.8).

Atrial fibrillation

Atrial fibrillation/flutter occurred in patients with haematologic malignancies treated with Calquence monotherapy and in combination with other medicinal products. Monitor for symptoms (e.g., palpitations, dizziness, syncope, chest pain, dyspnoea) of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated (see sections 4.5 and 4.2). In patients who develop atrial fibrillation on therapy with Calquence, a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk for thromboembolic disease, tightly controlled treatment with anticoagulants and alternative treatment options to Calquence should be considered.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with Calquence therapy. Patients considered at risk for TLS (e.g., presence of bulky disease at baseline) should be assessed for possible risk of TLS and closely monitored as clinically indicated.

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD)/pneumonitis has been reported in patients treated with Calquence in combination with bendamustine and rituximab in MCL. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. cough, dyspnea or hypoxia) and manage ILD/pneumonitis as clinically indicated.

Other medicinal products

Co-administration of strong CYP3A inhibitors with Calquence may lead to increased acalabrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A inducers may lead to decreased acalabrutinib exposure and consequently a risk for lack of efficacy. Concomitant use with strong CYP3A inhibitors should be avoided. If these inhibitors will be used

short-term (such as anti-infectives for up to seven days), treatment with Calquence should be interrupted. Patients should be closely monitored for signs of toxicity if a moderate CYP3A inhibitor is used (see sections 4.2 and 4.5). Concomitant use with strong CYP3A4 inducers should be avoided due to risk for lack of efficacy.

Calquence contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Acalabrutinib and its active metabolite are primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4), and both substances are substrates for P-gp and breast cancer resistance protein (BCRP).

Active substances that may increase acalabrutinib plasma concentrations

CYP3A/P-gp inhibitors

Co-administration with a strong CYP3A/P-gp inhibitor (200 mg itraconazole once daily for 5 days) increased acalabrutinib C_{max} and AUC by 3.9-fold and 5.0-fold in healthy subjects (N=17), respectively.

Concomitant use with strong CYP3A/P-gp inhibitors should be avoided. If the strong CYP3A/*P-gp* inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole) will be used short-term, treatment with Calquence should be interrupted (see section 4.2).

Co-administration with moderate CYP3A inhibitors (400 mg fluconazole as single dose or 200 mg isavuconazole as repeated dose for 5 days) in healthy subjects increased acalabrutinib C_{max} and AUC by 1.4-fold to 2-fold while the active metabolite ACP-5862 C_{max} and AUC was decreased by 0.65-fold to 0.88-fold relative to when acalabrutinib was dosed alone. No dose adjustment is required in combination with moderate CYP3A inhibitors. Monitor patients closely for adverse reactions (see Section 4.2).

Active substances that may decrease acalabrutinib plasma concentrations

CYP3A inducers

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

Concomitant use with strong inducers of CYP3A activity (e.g., phenytoin, rifampicin, carbamazepine) should be avoided. Concomitant treatment with St. John's wort, which may unpredictably decrease acalabrutinib plasma concentrations, should be avoided.

Gastric acid reducing medicinal products

No clinically significant differences in acalabrutinib pharmacokinetics were observed when a 100 mg acalabrutinib tablet was used concomitantly with a proton pump inhibitor (rabeprazole 20 mg twice daily for 3 days). Acalabrutinib tablets can be co-administered with gastric acid reducing agents (proton pump

inhibitors, H2-receptor antagonists, antacids), unlike acalabrutinib capsules which show impaired uptake when given with acid reducing agents.

Active substances whose plasma concentrations may be altered by Calquence

CYP3A substrates

Based on *in vitro* data, it cannot be excluded that acalabrutinib is an inhibitor of CYP3A4 at the intestinal level and may increase the exposure of CYP3A4 substrates sensitive to gut CYP3A metabolism. Caution should be exercised if co-administering acalabrutinib with CYP3A4 substrates with narrow therapeutic range administered orally (e.g., cyclosporine, ergotamine, pimozide).

Effect of acalabrutinib on CYP1A2 substrates

In vitro studies indicate that acalabrutinib induces CYP1A2. Co-administration of acalabrutinib with CYP1A2 substrates (e.g., theophylline, caffeine) may decrease their exposure.

Effects of acalabrutinib and its active metabolite, ACP-5862, on medicinal product transport systems

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP (see section 5.2). To minimise the potential for an interaction in the Gastrointestinal (GI) tract, oral narrow therapeutic range BCRP substrates such as methotrexate should be taken at least 6 hours before or after acalabrutinib.

ACP-5862 may increase exposure to co-administered MATE1 substrates (e.g., metformin) by inhibition of MATE1 (see section 5.2). Patients taking concomitant medicinal products with disposition dependent upon MATE1 (e.g., metformin) should be monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving Calquence.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Calquence.

Pregnancy

There are no or limited amount of data from the use of acalabrutinib in pregnant women. Based on findings from animal studies, there may be a risk to the foetus from exposure to acalabrutinib during pregnancy. Dystocia (difficult or prolonged labour) was observed in the rat and administration to pregnant rabbits was associated with reduced foetal growth (see section 5.3).
Calquence should not be used during pregnancy unless the clinical condition of the woman requires treatment with acalabrutinib.

Breast-feeding

It is not known whether acalabrutinib is excreted in human milk. There are no data on the effect of acalabrutinib on the breast-fed child or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. A risk to the breast-fed child cannot be excluded. Breast-feeding

mothers are advised not to breast-feed during treatment with Calquence and for 2 days after receiving the last dose.

Fertility

There are no data on the effect of Calquence on human fertility. In a non-clinical study of acalabrutinib in male and female rats, no adverse effects on fertility parameters were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Calquence has no or negligible influence on the ability to drive and use machines. However, during treatment with acalabrutinib, fatigue and dizziness have been reported and patients who experience these symptoms should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Calquence monotherapy

Of the 1 478 patients treated with Calquence monotherapy, the most common (≥ 20%) adverse drug reactions (ADRs) of any grade were infection, diarrhoea, headache, musculoskeletal pain, bruising, cough, arthralgia, fatigue, nausea and rash. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were infection, leukopenia, neutropenia, anaemia, second primary malignancy, and thrombocytopenia.

Calquence in combination with obinutuzumab

Of the 223 patients treated with Calquence in combination with obinutuzumab, the most common (≥ 20%) ADRs of any grade were infection, musculoskeletal pain, diarrhoea, headache, leukopenia, neutropenia, cough, fatigue, arthralgia, nausea, dizziness, and constipation. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were leukopenia, neutropenia, infection, thrombocytopenia and anaemia.

Calquence in combination with venetoclax

Of the 291 patients treated with Calquence in combination with venetoclax, the most common (≥ 20%) ADRs of any grade were infections, neutropenia, headache, bruising, diarrhoea and musculoskeletal pain. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reaction was neutropenia.

Calquence in combination with venetoclax and obinutuzumab

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, the most common (≥ 20%) ADRs of any grade were infections, neutropenia, headache, bruising, diarrhoea, nausea and musculoskeletal pain. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were neutropenia and thrombocytopenia.

Calquence in combination with bendamustine and rituximab

Of the 297 patients treated with Calquence in combination with bendamustine and rituximab, the most common (≥ 20%) ADRs of any grade were neutropenia, nausea, rash, diarrhoea, musculoskeletal pain,

headache, fatigue, vomiting, constipation, anaemia and thrombocytopenia. The most commonly reported (≥ 5%) Grade ≥ 3 adverse drug reactions were neutropenia, rash, thrombocytopenia, anaemia, pneumonia, second primary malignancies, hypertension and second primary malignancies excluding non-melanoma skin.

Tabulated list of adverse reactions

The below tables present adverse drug reactions (ADRs) identified in clinical studies with patients receiving Calquence monotherapy or combination therapy for haematological malignancies. The median duration of Calquence monotherapy treatment across the pooled dataset was 38.2 months. The median duration of Calquence treatment in patients treated with Calquence in combination with bendamustine and rituximab was 28.6 months. The median duration of Calquence treatment in patients treated with Calquence in combination with venetoclax with or without obinutuzumab was 12.9 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 defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib monotherapy (N=1 478)

MedDRA SOC	MedDRA Term	All Grades (%)	Grade ≥ 3* (%)
Infections and infestations	Upper respiratory tract infection	Very common (25.8)	1.2
	Pneumonia	Very common (15.8)	8.7
	Sinusitis	Very common (11.4)	0.4
	Urinary tract infection	Common (9.9)	1.8
	Bronchitis	Common (9.7)	0.6
	Herpes viral infections†	Common (9.1)	0.9
	Nasopharyngitis	Common (8.3)	0
	Aspergillus infections†	Uncommon (0.7)	0.6
	Hepatitis B reactivation	Uncommon (0.4)	0.3
Neoplasms benign, malignant and unspecified	Second Primary Malignancy (SPM)† Non-melanoma skin malignancy† SPM excluding non-melanoma skin†	Very common (17.6) Common (9.9) Common (9.7)	6.7 1.4 5.5
Blood and lymphatic system disorders	Neutropenia†	Very common (19.4)	17.5
	Anaemia†	Very common (17.1)	9.5

MedDRA SOC	MedDRA Term	All Grades (%)	Grade ≥ 3* (%)
	Thrombocytopenia†	Very common (11.5)	6.2
	Lymphocytosis	Uncommon (0.5)	0.3
Metabolism and nutrition disorders	Tumour Lysis Syndrome	Uncommon (0.5)	0.4
Nervous system disorders	Headache	Very common (36.5)	1.2
	Dizziness	Very common (13.9)	0.1
Cardiac disorders	Atrial fibrillation/Flutter†	Common (7.4)	2.3
Vascular disorders	Bruising† Contusion Petechiae Ecchymoses	Very common (30.9) Very common (20.7) Common (8.9) Common (5.7)	0 0 0 0
	Haemorrhage/haematoma† Gastrointestinal haemorrhage Intracranial haemorrhage	Very common (16.3) Uncommon (0.9) Uncommon (0.1)	3.2 0.7 0.1
	Hypertension†	Very common (11.9)	4.9
	Epistaxis	Common (8.0)	0.3
Gastrointestinal disorders	Diarrhoea	Very common (36.7)	2.6
	Nausea	Very common (21.8)	0.8
	Constipation	Very common (15.2)	0.1
	Abdominal pain†	Very common (14.5)	1.2
	Vomiting	Very common (14.0)	0.7
Skin and subcutaneous tissue disorders	Rash†	Very common (20.3)	0.9
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain†	Very common (31.9)	1.8
	Arthralgia	Very common (24.0)	0.9
General disorders and administration site conditions	Fatigue	Very common (23.6)	2.0
	Asthenia	Common (7.0)	0.9
Investigations§ (Findings based on test results)	Haemoglobin decreased±	Very common (47.4)	10.8
	Absolute neutrophil count decreased±	Very common (43.9)	24.0
	Platelets decreased±	Very common (36.9)	9.5

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

†Includes multiple ADR term.
‡Represents the incidence of laboratory findings, not of reported adverse events.
§Presented as CTCAE grade values.

Table 5. Adverse drug reactions* of patients with haematological malignancies treated with acalabrutinib combination therapy (N=1 095)

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Infections and infestations								
Upper respiratory tract infection	Very common (31.4)	1.8	Very common (18.2)	0.3	Common (8.2)	0.3	Common (6.3)	0
Sinusitis	Very common (15.2)	0.4	Common (6.4)	0	Common (2.7)	0	Common (2.5)	0
Nasopharyngitis	Very common (13.5)	0.4	Common (5.4)	0	Common (1.4)	0	Common (1.1)	0
Urinary tract infection	Very common (13)	0.9	Very common (11.1)	1.7	Common (3.1)	0	Common (6.0)	0.4
Pneumonia	Very common (10.8)	5.4	Very common (16.2)	8.8	Common (3.8)	1.4	Common (5.3)	3.9
Bronchitis	Common (9.9)	0	Common (6.4)	0.3	Common (2.1)	0	Common (2.5)	0
Herpes viral infections†	Common (6.7)	1.3	Very common (12.8)	1.0	Common (4.8)	0	Common (3.5)	0.4
Progressive multifocal leukoencephalopathy	Uncommon (0.4)	0.4	Not known	0	Not known	0	Not known	0
Hepatitis B reactivation	Uncommon (0.9)	0.1	Common (1.3)	0.3	Not known	0	Not known	0
Aspergillus infections†	Not known	0	Uncommon (0.3)	0.3	Not known	0	Uncommon (0.4)	0.4

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Neoplasms benign, malignant and unspecified								
Second primary malignancy†(SPM)	Very common (13)	4.0	Very common (17.8)	7.4	Common (5.2)	1.7	Common (4.2)	1.8
Non-melanoma skin malignancy†	Common (7.6)	0.4	Very common (11.1)	2.0	Common (3.1)	0	Common (1.8)	0.4
SPM excluding non-melanoma skin†	Common (6.3)	3.6	Common (9.8)	5.4	Common (2.7)	1.7	Common (2.5)	1.4
Blood and lymphatic system disorders								
Neutropenia†	Very common (31.8)	30	Very common (54.9)	50.2	Very Common (37.1)	32.3	Very Common (50.4)	46.1
Thrombocytopenia†	Very common (13.9)	9	Very common (22.9)	9.8	Common (5.8)	2.1	Very Common (12.3)	9.2
Anaemia†	Very common (11.7)	5.8	Very common (24.2)	9.4	Common (6.9)	3.8	Common (4.6)	2.1
Lymphocytosis	Uncommon (0.4)	0.4	Uncommon (0.7)	0	Not known	0	Uncommon (0.7)	0.4
Metabolism and nutrition disorders								
Tumour lysis syndrome	Common (1.8)	1.3	Common (1.3)	1.3	Uncommon (0.3)	0.3	Uncommon (0.4)	0.4
Nervous system disorders								
Headache	Very common (43)	0.9	Very common (30.3)	1.3	Very Common (35.1)	1.4	Very Common (28.2)	0.4
Dizziness	Very common (23.8)	0	Very common (14.5)	0.7	Common (5.5)	0	Common (6.7)	0
Cardiac disorders								
Atrial fibrillation/flutter†	Common (3.1)	0.9	Common (6.7)	4.0	Uncommon (0.7)	0.3	Common (2.1)	0.7

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Vascular disorders								
Bruising†	Very common (38.6)	0	Very common (14.1)	0.3	Very common (20.6)	0	Very common (21.8)	0
Contusion	Very common (27.4)	0	Very common (11.1)	0	Very common (14.1)	0	Very common (16.2)	0
Petechiae	Very common (11.2)	0	Common (2.0)	0	Common (4.8)	0	Common (5.3)	0
Ecchymoses	Common (3.1)	0	Common (3.0)	0.3	Common (2.7)	0	Common (3.9)	0
Haemorrhage/haematoma†	Very common (17.5)	1.3	Very common (15.5)	1.0	Common (8.9)	0.7	Common (8.5)	1.1
Gastrointestinal haemorrhage	Common (3.6)	0.9	Uncommon (0.3)	0	Uncommon (0.7)	0.3	Not known	0
Intracranial haemorrhage	Uncommon (0.9)	0	Not known	0	Not known	0	Not known	0
Hypertension†	Very common (13.5)	3.6	Very common (12.5)	5.7	Common (4.1)	2.7	Common (3.9)	2.1
Epistaxis	Common (8.5)	0	Common (2.7)	0	Common (1.7)	0	Common (4.2)	0
Respiratory, thoracic and mediastinal disorders								
Pneumonitis±	-	-	Common (2.4)	0.3	-	-	-	-
Gastrointestinal disorders								
Diarrhoea	Very common (43.9)	4.5	Very common (37.4)	3.0	Very common (32.6)	1.7	Very common (36.3)	1.4
Nausea	Very common (26.9)	0	Very common (42.8)	1.3	Very common (14.8)	0	Very common (21.8)	0.7

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Constipation	Very common (20.2)	0	Very common (24.6)	1.0	Common (6.5)	0.3	Common (8.1)	0
Vomiting	Very common (19.3)	0.9	Very common (25.6)	0.7	Common (5.5)	0	Common (6.7)	0
Abdominal pain†	Very common (14.8)	1.3	Very common (12.1)	2.0	Common (7.9)	1.0	Common (8.1)	0.7
Skin and subcutaneous tissue disorders								
Rash†	Very common (30.9)	1.8	Very common (39.1)	9.8	Very common (12.0)	0.3	Very common (16.2)	1.1
Musculoskeletal and connective tissue disorders								
Musculoskeletal pain†	Very common (44.8)	2.2	Very common (34.3)	3.7	Very common (24.1)	0.7	Very common (21.8)	1.1
Arthralgia	Very common (26.9)	1.3	Very common (17.5)	0.7	Very common (12.7)	1.0	Very common (10.9)	0.4
General disorders and administration site conditions								
Fatigue	Very common (30.5)	1.8	Very common (29.3)	2.7	Very common (14.8)	0.3	Very common (14.4)	0
Asthenia	Common (7.6)	0.4	Very common (10.4)	1.0	Common (4.1)	0	Common (3.2)	0
Investigations¶								
Absolute neutrophil count decreased§	Very common (57.4)	35	Very common (76.8)	56.6	Very common (78.0)	38.1	Very common (81.7)	53.5
Platelets decreased§	Very common (46.2)	10.8	Very common (69.4)	17.8	Very common (42.6)	5.2	Very common (54.9)	13.7
Haemoglobin decreased§	Very common (43.9)	9	Very common (79.5)	10.8	Very common (34.7)	6.5	Very common (45.8)	3.5
Alanine aminotransferase increased‡	-	-	Common (9.1)	4.4	-	-	-	-

	Calquence + Obinutuzumab N=223		Calquence + BR N=297		Calquence + venetoclax N=291		Calquence + venetoclax + obinutuzumab N=284	
MedDRA SOC and MedDRA Term	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**	**All Grades (%)**	**Grade ≥ 3* (%)**
Aspartate aminotransferase increased‡	-	-	Common (8.1)	3.0	-	-	-	-

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Includes multiple ADR term.
‡One event with fatal outcome was reported.
§Represents the incidence of laboratory findings, not of reported adverse events.
¶Presented as CTCAE grade values.
‡Adverse reaction only for the Calquence + BR arm in the ECHO study.

Description of selected adverse reactions

Serious infections when treating patients with Calquence in combination with venetoclax with or without obinutuzumab

Of the 291 patients treated with Calquence in combination with venetoclax, severe (Grade ≥ 3) infections were reported in 12.4% of the patients (most frequently reported COVID-19 or COVID-19 pneumonia). Fatal infections occurred in 3.1% of patients (most frequently reported COVID-19 or COVID-19 pneumonia).

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, severe (Grade ≥ 3) infections were reported in 23.6% of the patients (most frequently reported COVID-19 or COVID-19 pneumonia). Fatal infections occurred in 5.6% of patients (most frequently reported COVID-19 or COVID-19 pneumonia).

Discontinuation and dose reduction due to adverse reactions

Of the 1 478 patients treated with Calquence monotherapy, discontinuation due to adverse reactions were reported in 14.6% of the patients. These main adverse reactions included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 5.9% of patients. These main adverse reactions included hepatitis B reactivation, sepsis, and diarrhoea.

Of the 223 patients treated with Calquence in combination with obinutuzumab, discontinuation of Calquence due to adverse reactions were reported in 10.8% of the patients. These main adverse reactions included pneumonia, thrombocytopenia and diarrhoea. Dose reductions due to adverse reactions were reported in 6.7% of patients. These main adverse reactions included neutropenia, diarrhoea and vomiting.

Of the 291 patients treated with Calquence in combination with venetoclax, discontinuation of Calquence due to adverse reactions were reported in 7.6% of the patients and dose reduction of Calquence due to adverse reactions were reported in 5.8% of patients. These main adverse reactions leading to discontinuation included COVID-19 pneumonia and COVID-19 and the adverse reaction leading to dose reduction was neutropenia.

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, discontinuation of Calquence due to adverse reactions were reported in 13.7% of the patients and dose reductions of Calquence due to adverse reactions were reported in 6.3% of patients. These main adverse reactions leading to discontinuation included COVID-19 pneumonia and COVID-19 and the adverse reaction leading to dose reduction was neutropenia.

Of the 297 patients treated with Calquence in combination with bendamustine and rituximab, discontinuation of Calquence due to adverse reactions were reported in 42.8% of the patients. These main adverse reactions included COVID-19, COVID-19 pneumonia, neutropenia and pneumonia. Dose reductions due to adverse reactions were reported in 10.1% of patients. These main adverse reactions included neutropenia and nausea.

Elderly

Of the 1 478 patients in clinical studies of Calquence monotherapy, 42% were greater than 65 years and less than 75 years of age and 20.6% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Of the 223 patients in clinical studies of Calquence in combination of obinutuzumab, 47% were greater than 65 years and less than 75 years of age and 26% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Of the 291 patients treated with Calquence in combination with venetoclax, 28.9% were greater than 65 years and less than 75 years of age and 4.5% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Of the 284 patients treated with Calquence in combination with venetoclax and obinutuzumab, 24% were greater than 65 years and less than 75 years of age and 6.3% were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EL02.

Mechanism of action

Acalabrutinib is a selective 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 with minimal off-target interactions.

Pharmacodynamic effects

In patients with B-cell malignancies dosed with acalabrutinib 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

The effect of acalabrutinib on the QTc interval was evaluated in 46 healthy male and female subjects in a randomised, double-blind thorough QT study with placebo and positive controls. At a supratherapeutic dose, 4-times the maximum recommended dose, Calquence did not prolong the QT/QTc interval to any clinically relevant extent (e.g., not greater than or equal to 10 ms) (see sections 4.4, 4.8 and 5.3).

Clinical efficacy and safety

Patients with previously untreated CLL

Calquence monotherapy or in combination with obinutuzumab

The safety and efficacy of Calquence monotherapy or in combination with obinutuzumab in previously untreated CLL were evaluated in a randomised, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. 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, were included in ELEVATE-TN, 27.9% patients had a CrCl of < 60 mL/min. Of the patients who were < 65 years of age, 16.1% had a median CIRS-G score of 8. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.

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

- 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 1 000 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 1 000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days.
- Calquence monotherapy: Calquence 100 mg was administered twice daily until disease progression or unacceptable toxicity.
- Obinutuzumab plus chlorambucil (GClb): Obinutuzumab and chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1 000 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 1 000 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. Table 6 summarises the baseline demographics and disease characteristics of the study population.

Table 6. Baseline patient characteristics in (ELEVATE-TN) patients with previously untreated CLL

Characteristic	**Calquence plus obinutuzumab N=179**	**Calquence monotherapy N=179**	**Obinutuzumab plus chlorambucil N=177**
Age, years; median (range)	70 (41-88)	70 (44-87)	71 (46-91)
Male; %	62	62	59.9
Caucasian; %	91.6	95	93.2
ECOG performance status 0-1; %	94.4	92.2	94.4
Median time from diagnosis (months)	30.5	24.4	30.7
Bulky disease with nodes ≥ 5 cm; %	25.7	38	31.1
Cytogenetics/FISH Category; %			
17p deletion	9.5	8.9	9
11q deletion	17.3	17.3	18.6
TP53 mutation	11.7	10.6	11.9
Unmutated IGHV	57.5	66.5	65.5
Complex karyotype (≥ 3 abnormalities)	16.2	17.3	18.1
Rai stage; %			
0	1.7	0	0.6
I	30.2	26.8	28.2
II	20.1	24.6	27.1
III	26.8	27.9	22.6
IV	21.2	20.7	21.5

The primary endpoint was progression-free survival (PFS) of Calquence+G arm versus GClb arm 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. Efficacy results are presented in Table 7.

Table 7. Efficacy results per IRC Assessments in (ELEVATE-TN) patients with CLL

	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)
PD, n (%)	9 (5)	20 (11.2)	82 (46.3)
Death events (%)	5 (2.8)	6 (3.4)	11 (6.2)
Median (95% CI), months	NR	NR (34.2, NR)	22.6 (20.2, 27.6)

	Calquence plus obinutuzumab N=179	Calquence monotherapy N=179	Obinutuzumab plus chlorambucil N=177
HR† (95% CI)	0.10 (0.06, 0.17)	0.20 (0.13, 0.30)	-
P-value	< 0.0001	< 0.0001	-
24 months estimate, % (95% CI)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)
Overall Survival[a]			
Death events (%)	9 (5)	11 (6.1)	17 (9.6)
Hazard Ratio (95% CI) †	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	-
Best overall response rate* (CR + CRi + nPR + PR)			
ORR, n (%) (95% CI)	168 (93.9) (89.3, 96.5)	153 (85.5) (79.6, 89.9)	139 (78.5) (71.9, 83.9)
P-value	< 0.0001	0.0763	-
CR, n (%)	23 (12.8)	1 (0.6)	8 (4.5)
CRi, n (%)	1 (0.6)	0	0
nPR, n (%)	1 (0.6)	2 (1.1)	3 (1.7)
PR, n (%)	143 (79.9)	150 (83.8)	128 (72.3)

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
[a] Median OS not reached for both arms.

PFS results for Calquence with or without obinutuzumab were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation or unmutated IGHV), the PFS HRs of Calquence with or without obinutuzumab versus obinutuzumab plus chlorambucil was 0.08 [95% CI (0.04, 0.15)] and 0.13 [95% CI (0.08, 0.21)], respectively.

Table 8. Subgroup analysis of PFS (Study ELEVATE-TN)

	Calquence monotherapy			Calquence+G		
	N	**Hazard Ratio**	**95% CI**	**N**	**Hazard Ratio**	**95% CI**
All subjects	179	0.20	(0.13, 0.30)	179	0.10	(0.06, 0.17)
Del 17P						
Yes	19	0.20	(0.06, 0.64)	21	0.13	(0.04, 0.46)
No	160	0.20	(0.12, 0.31)	158	0.09	(0.05, 0.17)

	Calquence monotherapy			Calquence+G		
	N	**Hazard Ratio**	**95% CI**	**N**	**Hazard Ratio**	**95% CI**
TP53 mutation Yes No	 19 160	 0.15 0.20	 (0.05, 0.46) (0.12, 0.32)	 21 158	 0.04 0.11	 (0.01, 0.22) (0.06, 0.20)
Del 17P or/and TP53 mutation Yes No	 23 156	 0.23 0.19	 (0.09, 0.61) (0.11, 0.31)	 25 154	 0.10 0.10	 (0.03, 0.34) (0.05, 0.18)
IGHV mutation Mutated Unmutated	 58 119	 0.69 0.11	 (0.31, 1.56) (0.07, 0.19)	 74 103	 0.15 0.08	 (0.04, 0.52) (0.04, 0.16)
Del 11q Yes No	 31 148	 0.07 0.26	 (0.02, 0.22) (0.16, 0.41)	 31 148	 0.09 0.10	 (0.03, 0.26) (0.05, 0.20)
Complex Karyotype Yes No	 31 117	 0.10 0.27	 (0.03, 0.33) (0.16, 0.46)	 29 126	 0.09 0.11	 (0.03, 0.29) (0.05, 0.21)

With long term data, the median follow-up was 58.2 months for Calquence+G arm, 58.1 months for Calquence arm and 58.2 months for the GClb arm. The median investigator assessed PFS for Calquence+G and Calquence monotherapy was not reached; and was 27.8 months in GClb arm. At the time of most recent data cut off, a total of 72 patients (40.7%) originally randomised to the GClb arm crossed over to Calquence monotherapy. The median overall survival had not been reached in any arm with a total of 76 deaths: 18 (10.1%) in the Calquence+G arm, 30 (16.8%) in the Calquence monotherapy arm, and 28 (15.8%) in the GClb arm.

Table 9. Efficacy Results per INV assessment in (ELEVATE-TN) Patients with CLL

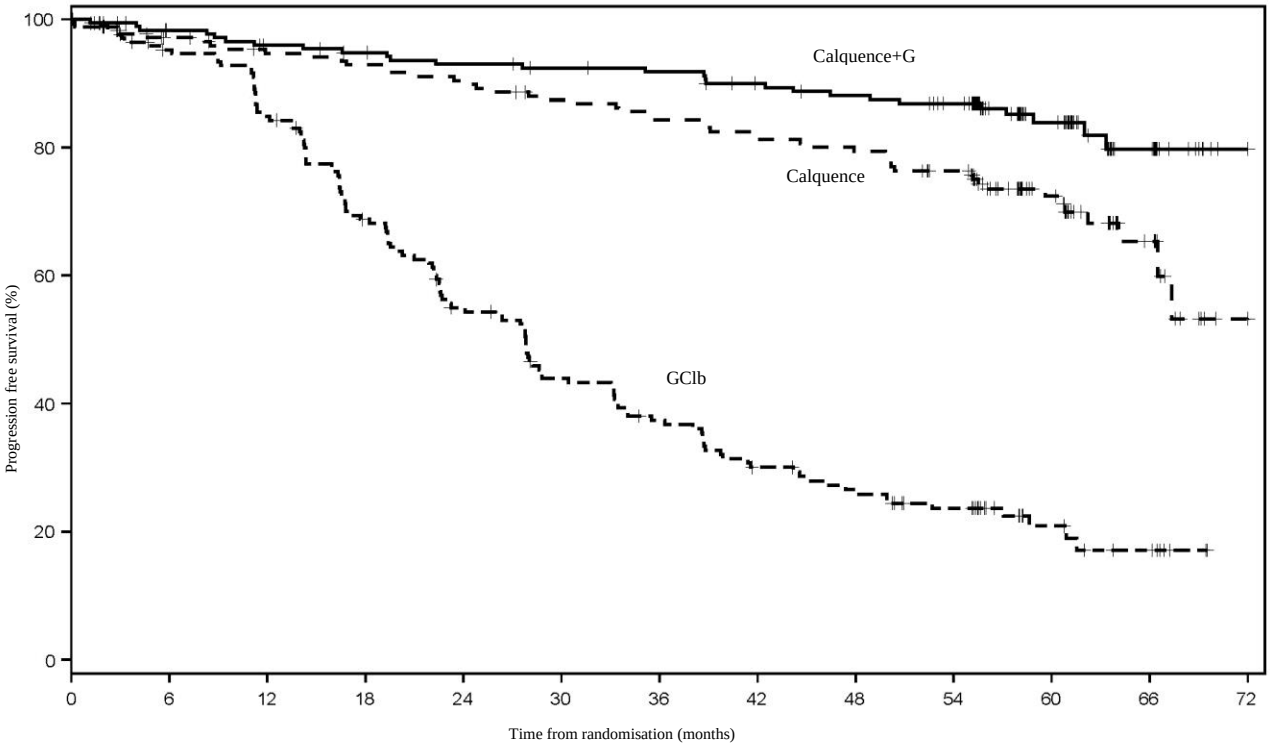
	Calquence plus obinutuzumab N=179	Calquence monotherapy N=179	Obinutuzumab plus Chlorambucil N=177
Progression-free survival			
Number of events (%)	27 (15.1)	50 (27.9)	124 (70.1)
PD, n (%)	14 (7.8)	30 (16.8)	112 (63.3)
Death events (%)	13 (7.3)	20 (11.2)	12 (6.8)
Median (95% CI), months*	NR	NR (66.5, NR)	27.8 (22.6, 33.2)
HR† (95% CI)	0.11 (0.07, 0.16)	0.21 (0.15, 0.30)	-
Overall survival			
Death events (%)	18 (10.1)	30 (16.8)	28 (15.8)
Hazard Ratio (95% CI) †	0.55 (0.30, 0.99)	0.98 (0.58, 1.64)	-

CI=confidence interval; HR=hazard ratio; NR=not reached

* 95% confidence interval based on Kaplan-Meier estimation.

†Estimate based on stratified Cox-Proportional-Hazards model for Hazard Ratio (95% CI) stratified by 17p deletion status (yes vs no).

Figure 1. Kaplan-Meier Curve of INV-Assessed PFS in (ELEVATE-TN) Patients with CLL (ITT Population)



Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	70
Calquence	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	120	93	63	39	22	6	1
Calquence+G	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	133	99	65	39	27	7	1
GClb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	40	38	31	30	20	13	8	7	2	0

Patients with previously untreated CLL – Fixed duration therapy

Calquence in combination with venetoclax with or without obinutuzumab

The safety and efficacy of Calquence in combination with venetoclax with or without obinutuzumab in previously untreated CLL was evaluated in a randomised, multi-centre, open-label Phase 3 study (AMPLIFY) of 867 patients. Patients received Calquence plus venetoclax, Calquence plus venetoclax and obinutuzumab, or Investigator's choice of chemoimmunotherapy, either FCR (fludarabine plus cyclophosphamide plus rituximab) or BR (bendamustine plus rituximab). AMPLIFY included patients previously untreated for CLL without del(17p) or TP53 mutation that were 18 years of age and older. The trial allowed patients to receive antithrombotic agents except warfarin and other vitamin K antagonists.

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

- Calquence plus venetoclax (AV): Calquence 100 mg was administered twice daily starting on Cycle 1 Day 1 for a total of 14 cycles or until disease progression or unacceptable toxicity. On Cycle 3 Day 1 patients started the venetoclax 5-week dose-titration schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles. Each cycle was 28 days.

- Calquence plus venetoclax plus obinutuzumab (AVO): Calquence 100 mg was administered twice daily starting on Cycle 1 Day 1 for a total of 14 cycles or until disease progression or unacceptable toxicity. On Cycle 3 Day 1 patients started the venetoclax 5-week dose-titration schedule, starting at 20 mg and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Venetoclax was administered for a total of 12 cycles. Obinutuzumab 1 000 mg was administered on Day 1 or Day 1 and 2 (100 mg on Day 1 and 900 mg on Day 1 or 2), 8 and 15 of Cycle 2 followed by 1 000 mg on Day 1 of Cycles 3-7. Each cycle was 28 days.

- Investigator's choice of chemoimmunotherapy (FCR/BR):
    - Fludarabine plus cyclophosphamyde plus rituximab (FCR): Fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) were administered on Days 1-3 up to a maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on Day 1 Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.
    - Bendamustine plus rituximab (BR): Bendamustine 90 mg/m^2 was administered on Days 1 and 2 up to maximum of 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 on Day 1 Cycle 1 and 500 mg/m^2 on Day 1 of Cycles 2 up to 6. Each cycle was 28 days.

Patients were stratified by age (> 65 years or ≤ 65 years), IGHV mutational status (mutated versus unmutated), Rai stage (high risk [≥ 3] versus non-high risk) and geographic region (North America and Western Europe versus other). Table 10 summarises the baseline demographics and disease characteristics of the study population.

Table 10. Baseline Patient Characteristics in (AMPLIFY) Patients with Previously Untreated CLL

Characteristic	AV N=291	AVO N=286	FCR/BR N=290
Age, years; median (range)	61 (31-84)	61 (29-81)	61 (26-86)
Male; %	61.2	69.2	63.1
Caucasian; %	91.1	86.7	86.9
ECOG performance status 0-1; %	90.0	95.1	90.3
Median time from diagnosis to randomization (months)	28.5	26.1	29.6
Bulky disease with nodes ≥ 5 cm; %	38.8	35.0	42.8
Cytogenetics/FISH Category; %			
11q deletion	17.5	19.6	15.9
Complex karyotype (≥ 3 abnormalities)	15.5	16.1	14.5
Unmutated IGHV; %	57.4	59.1	59.3
Rai stage; %			
0	1.0	0.3	1.4
I	16.2	21.3	21.4
II	35.7	37.8	33.4
III	23.7	17.8	20.3
IV	23.4	22.7	23.4

The primary endpoint was IRC-assessed PFS for AV versus Investigator's choice of chemoimmunotherapy (FCR/BR) arm as assessed by IWCLL 2018 criteria. Additional efficacy endpoints were IRC-assessed PFS of AVO versus Investigator's choice (FCR/BR) arm and OS in both AV arm vs. Investigator's choice (FCR/BR) arm and AVO vs. Investigator's choice (FCR/BR) arm.

Efficacy results are presented in Table 11. The Kaplan-Meier curve for IRC-PFS is shown in Figure 2.

Table 11. Efficacy results in (AMPLIFY) patients with previously untreated CLL

	AV N=291	AVO N=286	FCR/BR[a] N=290
Progression-free survival[*]			
Number of events (%)	89 (30.6)	56 (19.6)	95 (32.8)
PD, n (%)	77 (26.5)	23 (8.0)	66 (22.8)
Death events (%)	12 (4.1)	33 (11.5)	29 (10.0)
Median (95% CI), months	NC (51.1, NC)	NC (NC, NC)	47.6 (43.3, NC)
HR[†] (95% CI)	0.65 (0.49, 0.87)	0.42 (0.30, 0.59)	-
P-value	0.0038	<0.0001	-
Overall Survival[b]			
Death events (%)	23 (7.9)	37 (12.9)	44 (15.2)
HR[†] (95% CI)	0.42 (0.25, 0.70)[c]	0.75 (0.48, 1.16)	-

NC= Not calculable; CI= Confidence interval; PD= Progressive disease.

[*]Per IRC assessment.

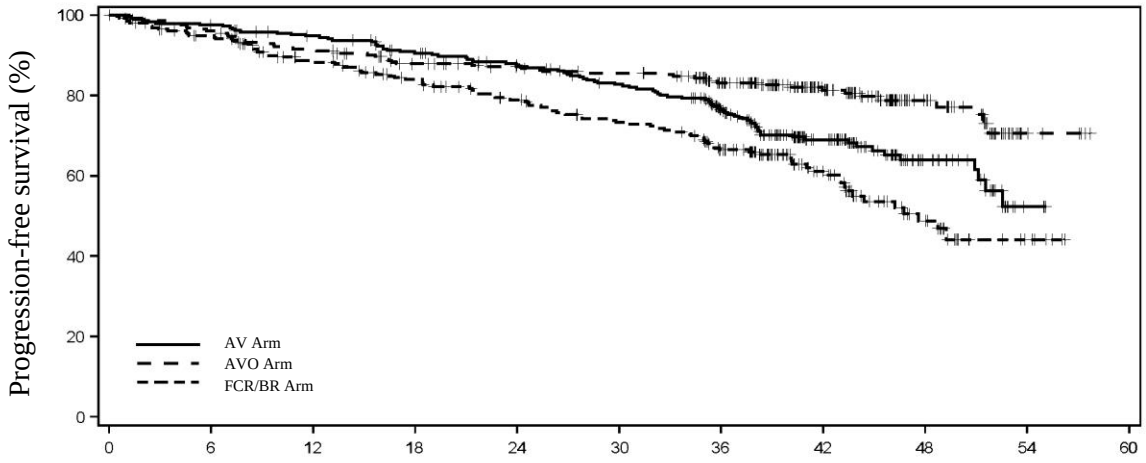
[†]Based on stratified Cox-Proportional-Hazards model.

[a]Per Investigator's choice 143 patients were planned to receive FCR and 147 patients were planned to receive BR.

[b]OS data at additional 6 months follow-up from PFS interim analysis.

[c]The p-value is not significant after adjusting for multiplicity.

Figure 2. Kaplan-Meier Curve of IRC-Assessed PFS in (AMPLIFY) patients with CLL (ITT Population)



Patients at risk											
AV Arm	291	282	269	251	237	219	177	102	35	3	0
AVO Arm	286	272	258	237	225	219	191	116	51	7	0
FCR/BR Arm	290	236	208	189	170	154	127	66	28	6	0

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 not including BCL-2 inhibitors or B-cell receptor inhibitors. Patients received Calquence monotherapy or investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab. The study allowed patients to receive antithrombotic agents. Patients who required anticoagulation with warfarin or equivalent vitamin K antagonists were excluded.

Patients were randomised 1:1 to receive either:

- Calquence 100 mg twice daily until disease progression or unacceptable toxicity, or
- Investigator's choice:
  - Idelalisib 150 mg twice daily in combination with rituximab 375 mg/m2 IV on Day 1 of the first cycle, followed by 500 mg/m2 IV every 2 weeks for 4 doses, then every 4 weeks for 3 doses for a total of 8 infusions
  - 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. Table 12 summarizes the baseline demographics and disease characteristics of the study population.

Table 12. Baseline patient characteristics in (ASCEND) patients with CLL

Characteristic	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Age, years; median (range)	68 (32-89)	67 (34-90)
Male; %	69.7	64.5
Caucasian; %	93.5	91.0
ECOG performance status; %		
0	37.4	35.5
1	50.3	51.0
2	12.3	13.5
Median time from diagnosis (months)	85.3	79.0
Bulky disease with nodes ≥ 5 cm; %	49.0	48.4
Median number of prior CLL therapies (range)	1 (1-8)	2 (1-10)
Number of Prior CLL Therapies; %		
1	52.9	43.2
2	25.8	29.7
3	11.0	15.5
≥ 4	10.3	11.6
Cytogenetics/FISH Category; %		
17p deletion	18.1	13.5
11q deletion	25.2	28.4
TP53 mutation	25.2	21.9
Unmutated IGHV	76.1	80.6
Complex karyotype (≥3 abnormalities)	32.3	29.7
Rai Stage; %		
0	1.3	2.6
I	25.2	20.6
II	31.6	34.8
III	13.5	11.6
IV	28.4	29.7

The primary endpoint was PFS as assessed by IRC IWCLL 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 16.1 months, PFS indicated a 69% statistically significant reduction in the risk of death or progression for patients in the Calquence arm. Efficacy results are presented in Table 13. The Kaplan-Meier curve for PFS is shown in Figure 3.

Table 13. Efficacy results per IRC Assessments in (ASCEND) patients with CLL

	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Progression-free survival*		
Number of events (%)	27 (17.4)	68 (43.9)
PD, n (%)	19 (12.3)	59 (38.1)

	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155
Death events (%)	8 (5.2)	9 (5.8)
Median (95% CI), months	NR	16.5 (14.0, 17.1)
HR† (95% CI)	0.31 (0.20, 0.49)	
P-value	< 0.0001	
15 months estimate, % (95% CI)	82.6 (75.0, 88.1)	54.9 (45.4, 63.5)
Overall survival[a]		
Death events (%)	15 (9.7)	18(11.6)
Hazard Ratio (95% CI) †	0.84 (0.42, 1.66)	-
Best overall response rate* (CR + CRi + nPR + PR)**		
ORR, n (%) (95% CI)	126 (81.3) (74.4, 86.6)	117 (75.5) (68.1, 81.6)
P-value	0.2248	-
CR, n (%)	0	2 (1.3)
PR, n (%)	126 (81.3)	115 (74.2)
Duration of Response (DoR)		
Median (95% CI), months	NR	13.6 (11.9,NR)

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; PD=progressive disease

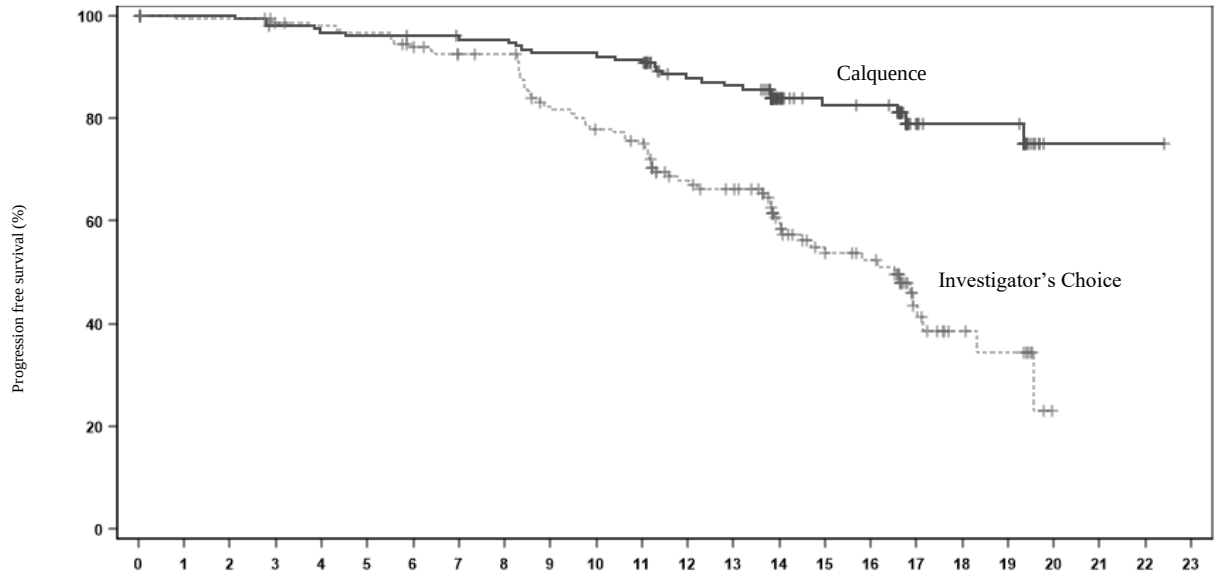
*Per IRC assessment.

[a] Median OS not reached for both arms. P<0.6089 for OS.

**CRi and nPR have values of 0.

†Based on stratified Cox-Proportional-Hazards model.

Figure 3. Kaplan-Meier curve of IRC-assessed PFS in (ASCEND) patients with CLL (ITT Population)



Number of patients at risk																								
Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Calquence	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
Investigator's Choice	155	150	150	146	144	142	136	130	129	112	105	101	82	77	56	44	39	18	10	8	0			

PFS results for Calquence were consistent across subgroups, including high risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation and unmutated IGHV), the PFS HR was 0.27 [95% CI (0.17, 0.44)].

Table 14. Subgroup analysis of IRC-assessed PFS (Study ASCEND)

	Calquence monotherapy		
	N	**Hazard Ratio**	**95% CI**
All subjects	155	0.30	(0.19, 0.48)
Del 17P Yes No	 28 127	 0.21 0.33	(0.07, 0.68) (0.21, 0.54)
TP53 mutation Yes No	 39 113	 0.24 0.33	(0.11, 0.56) (0.20, 0.57)
Del 17P or TP53 mutation Yes No	 45 108	 0.21 0.36	(0.09, 0.48) (0.21, 0.61)
IGHV mutation Mutated Unmutated	 33 118	 0.32 0.32	(0.11, 0.94) (0.19, 0.52)
Del 11q Yes No	 39 116	 0.28 0.31	(0.11, 0.70) (0.19, 0.53)
Complex Karyotype Yes No	 50 97	 0.32 0.23	(0.16, 0.63) (0.12, 0.44)

At final analysis, with a median follow-up of 46.5 months for Calquence and 45.3 months for the IR/BR, a 72% reduction in risk of investigator-assessed disease progression or death was observed for patients in the Calquence arm. The median investigator assessed PFS was not reached in Calquence and was 16.8 months in IR/BR. Efficacy results per Investigator Assessments (INV) are presented in Table 15. The Kaplan-Meier curve for INV assessed PFS is shown in Figure 4.

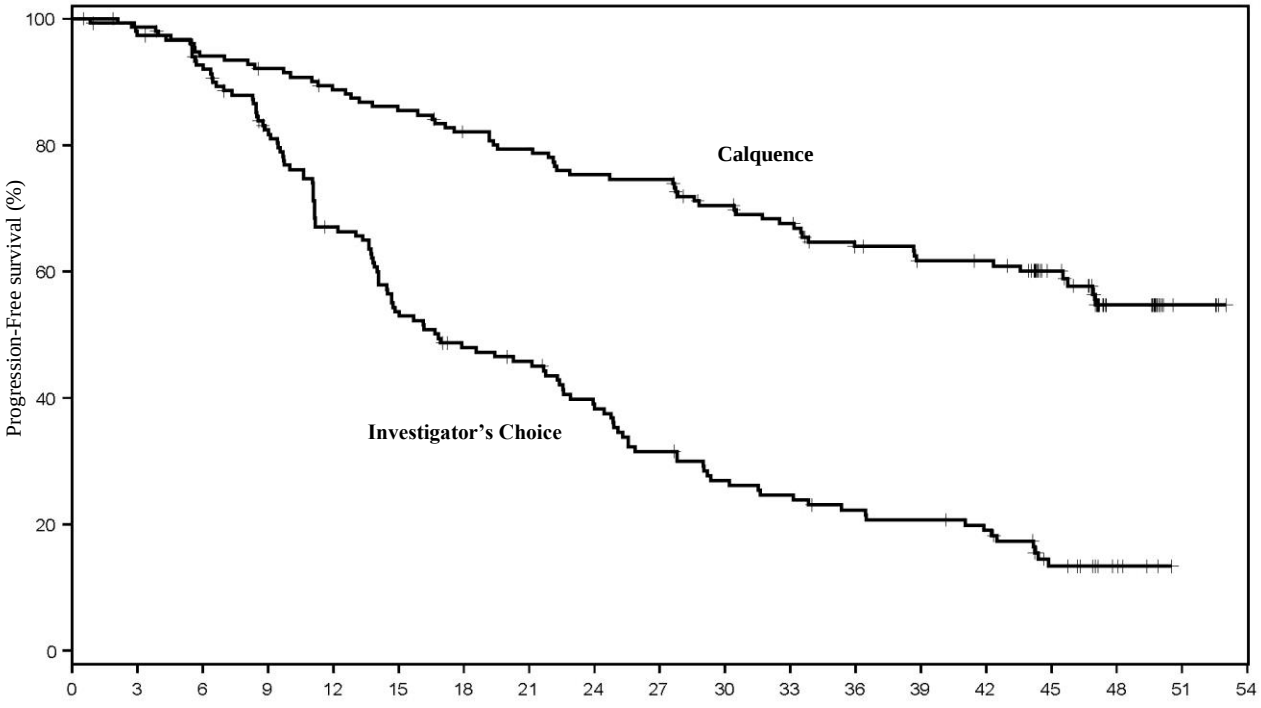
Table 15. Efficacy results at final analysis per INV assessments in (ASCEND) patients with CLL

	Calquence monotherapy N=155	**Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155**
Progression-free survival*		
Number of events (%)	62 (40.0)	119 (76.8)
PD, n (%)	43 (27.7)	102 (65.8)
Death events (%)	19 (12.3)	17 (11.0)
Median (95% CI), months	NR	16.8 (14.1, 22.5)
HR† (95% CI)	0.28 (0.20, 0.38)	
Overall survival[a]		
Death events (%)	41 (26.5)	54 (34.8)
Hazard Ratio (95% CI) †	0.69 (0.46, 1.04)	-

	Calquence monotherapy N=155	Investigator's choice of idelalisib + rituximab or bendamustine + rituximab N=155

CI=confidence interval; HR=hazard ratio; NR=not reached; PD=progressive disease
*Per INV assessment.
[a] Median OS not reached for both arms P=0.0783 for OS.
†Based on stratified Cox-Proportional-Hazards model.

Figure 4. Kaplan-Meier curve of INV-assessed PFS at final analysis in (ASCEND) patients with CLL



Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Calquence	155	151	143	139	133	128	121	117	111	110	100	94	85	80	79	52	21	4	0
Investigator's Choice	155	147	138	118	95	76	66	62	52	42	35	32	28	26	23	12	5	0	

Investigator assessed PFS results at final analysis for Calquence were consistent across subgroups, including high risk features and were consistent with the primary analysis.

Patients with previously untreated MCL

The safety and efficacy of Calquence in patients with previously untreated MCL was evaluated in ECHO, a randomised, double-blind, placebo-controlled, multi-centre, phase 3 study. ECHO included 598 patients 65 years of age and older with confirmed MCL that was previously untreated.
Patients were randomised in 1:1 ratio in 2 arms to receive:

- Calquence plus bendamustine and rituximab (Calquence + BR) arm: Calquence 100 mg was administered twice daily from Day 1 of Cycle 1, continuously. Bendamustine, 90 mg/m^2, was intravenously administered over 30 minutes on Days 1 and 2 of each of six 28-day cycles; and rituximab, 375 mg/m^2, was intravenously administered on Day 1 of each cycle of six 28-day

cycles. Calquence + BR was administered for a maximum of 6 treatment cycles (induction treatment).

- Placebo plus bendamustine and rituximab (Placebo + BR) arm: Placebo was administered twice daily from Day 1 of Cycle 1, continuously. Bendamustine, 90 mg/m^2, was intravenously administered over 30 minutes on Days 1 and 2 of each of six 28-day cycles; and rituximab, 375 mg/m^2, was intravenously administered on Day 1 of each cycle of six 28-day cycles. Placebo + BR was administered for a maximum of 6 treatment cycles (induction treatment).

Calquence or placebo was administered continuously until disease progression or unacceptable toxicity. After the induction treatment, patients who were achieving a response (PR or CR) received rituximab maintenance at 375 mg/m^2 on Day 1 of every other cycle for maximum of 12 additional doses up to Cycle 30. Patients randomised to placebo + BR arm who had confirmed PD were eligible to cross over to Calquence monotherapy at 100 mg twice daily dose until their second disease progression or unacceptable toxicity.

Patient randomisation was stratified by geographic region (North America versus Western Europe versus Other) and simplified MIPI (Mantle Cell Lymphoma International Prognostic Index) score (0-3 versus 4-5 versus 6-11).

The median age was 71 years (65-86), 70.7% were males, 78.3% were Caucasians, 93.1% had an ECOG performance status of 0-1. The simplified MIPI score was low (0-3) in 33.1%, intermediate (4-5) in 42.8% and high (6-11) in 24.1% of patients. A total of 37.7% of patients had tumour bulk ≥ 5 cm and 86% had Ann Arbor stage IV disease. Aggressive variants of MCL such as blastoid and pleomorphic forms were seen in 7.7% and 5.5% of patients respectively. A total of 47.8% patients had Ki-67 score of ≥ 30%. The baseline characteristics were similar for both arms.

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per 2014 Lugano Classification for non-Hodgkin's lymphoma (NHL) in subjects with previously untreated MCL. Additionally, overall response rate (ORR) was also assessed by an IRC.

IRC-assessed PFS was assessed at a median follow-up of 49.8 months.

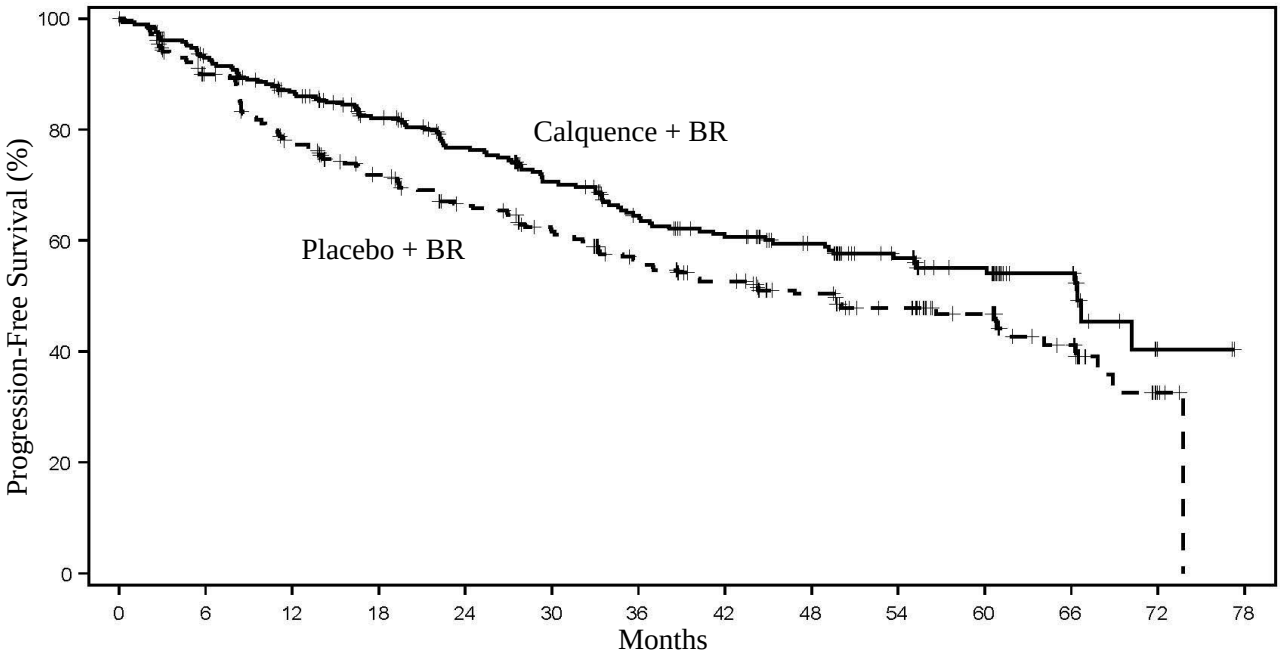
With an additional 6 months of follow-up from the primary PFS analysis, and a median follow-up of 63.0 months, the median overall survival had not been reached in either arm. There were a total of 218 deaths: 105 (35.1%) in the Calquence + BR arm and 113 (37.8%) in the placebo + BR arm. Efficacy results are presented in Table 16. The Kaplan-Meier curves for PFS are shown in Figure 5.

Table 16. Efficacy Results in Patients with previously untreated MCL in ECHO

	Calquence + BR N=299	**Placebo + BR N=299**
IRC-assessed PFS		
Median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
HR (95% CI) (stratified)*	0.73 (0.57, 0.94)	
p-value‡	0.0160	
IRC-assessed ORR		
CR + PR n (%)	272 (91.0)	263 (88.0)
95% CI	87.3,93.8	83.9, 91.3
CR n (%)	199 (66.6)	160 (53.5)
PR n (%)	73 (24.4)	103 (34.4)
p-value	0.2196	-

HR = hazard ratio, CR = complete response, PR = partial response, NE = not evaluable
*Stratified by randomisation stratification factors: Geographic Regions (North American, Western Europe, Other) and simplified MIPI Score (Low risk [0 to 3], Intermediate risk [4 to 5], High Risk [6 to 11]) as collected via IXRS. Estimated based on stratified Cox Proportional Hazards model for hazard ratio (95% CI).
‡ Estimated based on stratified log-rank test for p-value.

Figure 5. Kaplan-Meier Curve of IRC-Assessed PFS in patients with previously untreated MCL (ECHO)



Number of patients at risk

Calquence + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

Patients with MCL who received at least one prior therapy

The safety and efficacy of CALQUENCE in MCL were evaluated in an open-label, multi-centre, single-arm Phase 2 study (ACE-LY-004) of 124 previously treated patients. All patients received CALQUENCE 100 mg orally twice daily until disease progression or unacceptable toxicity. The trial did not include patients who received prior treatment with either BTK or BCL-2 inhibitors. The primary endpoint was investigator-assessed overall response rate (ORR) per the Lugano classification for non-Hodgkin's lymphoma (NHL). Duration of Response (DoR) was an additional outcome measure. Efficacy results at final (54 months) analysis are presented in Table 17.

At final analysis, the median age was 68 (range 42 to 90) years, 79.8% were male and 74.2% were Caucasian. At baseline, 92.8% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46.3 months and the median number of prior treatments was 2 (range 1 to 5), including 17.7% with prior stem cell transplant. The most common prior regimens were CHOP-based (51.6%) and ARA-C (33.9%). At baseline, 37.1% of patients had at least one tumour with a longest diameter ≥ 5 cm, 72.6% had extra nodal involvement including 50.8% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 43.5% and high in 16.9% of patients.

Table 17. ORR and DOR in (ACE-LY-004) Patients with MCL at 54 months final analysis

	Investigator Assessment at 54 months **N=124** **n (%) (95% CI[*])**
Overall Response Rate (ORR)	
Overall Response Rate	101 (81.5%) (73.5, 87.9)
Complete Response	59 (47.6%) (38.5, 56.7)
Partial Response	42 (33.9%) (25.6, 42.9)
Non-Evaluable[†]	3 (2.4%) (0.5, 6.9)
Duration of Response (DoR)	
Median (months)	28.6 (17.5, 39.1)

CI=Confidence Interval
[*]95% exact binomial confidence interval.
[†]Includes subjects without any adequate post-baseline disease assessment.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Calquence in all subsets of the paediatric population for the treatment of mature B-cell neoplasms (for information on paediatric use, see section 4.2).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of acalabrutinib and its active metabolite, ACP-5862, were studied in healthy subjects and in patients with B-cell malignancies. Acalabrutinib exhibits dose-proportionality, and both acalabrutinib and ACP-5862 exhibit almost linear PK across a dose range of 75 to 250 mg. Population PK modelling suggests that the PK of acalabrutinib and ACP-5862 is similar across patients with different B-cell malignancies. At the recommended dose of 100 mg twice daily in patients with B-cell malignancies (including, CLL), the geometric mean steady state daily area under the plasma concentration over time curve (AUC_{24h}) and maximum plasma concentration (C_{max}) for acalabrutinib were 1679 ng•h/mL and 438 ng/mL, respectively, and for ACP-5862 were 4166 ng•h/mL and 446 ng/mL, respectively.

Calquence tablets and Calquence capsules have been demonstrated to be bioequivalent. Calquence tablets contain acalabrutinib maleate, a salt form of acalabrutinib that shows higher solubility at high pH than the acalabrutinib base, which is the active content of Calquence capsules. Calquence tablets thus have a better absorption when combined with acid reducing agents.

Absorption

The time to peak plasma concentrations (T_{max}) was 0.2-3.0 hours for acalabrutinib, and 0.5-4.0 hours for ACP-5862. The absolute bioavailability of Calquence was 25%.

Effect of food on acalabrutinib

In healthy subjects, administration of a single 100 mg dose of acalabrutinib tablet 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 54% and T_{max} was delayed 1-2 hours.

Distribution

Reversible binding to human plasma protein was 99.4% for acalabrutinib and 98.8% 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.

Biotransformation/Metabolism

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

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

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

Interactions with transport proteins

In vitro studies indicate that acalabrutinib and ACP-5862 are P-gp and BCRP substrates. Co-administration with BCRP inhibitors is however unlikely to result in clinically relevant drug interactions. Co-administration with an OATP1B1/1B3 inhibitor (600 mg rifampin, single dose) resulted in an increase in acalabrutinib C_{max} and AUC by 1.2-fold and 1.4-fold (N=24, healthy subjects), respectively, which is not clinically relevant.

Acalabrutinib and ACP-5862 do not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 and MATE2-K at clinically relevant concentrations. Acalabrutinib may inhibit intestinal BCRP, while ACP-5862 may inhibit MATE1 at clinically relevant concentrations (see section 4.5). Acalabrutinib does not inhibit MATE1, while ACP-5862 does not inhibit BCRP at clinically relevant concentrations.

Elimination

Following a single oral dose of 100 mg acalabrutinib tablet, the geometric mean terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 1.4 hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was 6.6 hours.

The mean apparent oral clearance (CL/F) was 134 L/hr for acalabrutinib and 22 L/hr for ACP-5862 in patients with B-cell malignancies.

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.

Special populations

Based on population PK analysis, age (>18 years of age), sex, race (Caucasian, African American) and body weight did not have clinically meaningful effects on the PK of acalabrutinib and its active metabolite, ACP-5862.

Paediatric population

No pharmacokinetic studies were performed with Calquence in patients under 18 years of age.

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 studies (see section 4.2).

Hepatic impairment

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

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with acalabrutinib.

Genotoxicity/Mutagenicity/Phototoxicity

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.

Based on phototoxicity assays using 3T3 cell line *in vitro*, acalabrutinib is considered to have a low risk for phototoxicity in humans.

Repeat-dose toxicity

In rats, microscopic findings of minimal to mild severity were observed in the pancreas (haemorrhage/pigment/inflammation/fibrosis in islets) at all dose levels. Non-adverse findings of minimal to mild severity in the kidneys (tubular basophilia, tubular regeneration, and inflammation) were observed in studies of up to 6-month duration with a No Observed Adverse Effect level (NOAEL) of 30 mg/kg/day in rats. The mean exposures (AUC) at the NOAEL in male and female rats correspond to 0.6x and 1x, respectively, the clinical exposure at the recommended dose of 100 mg twice daily, respectively. The Lowest Adverse Observed Effect Level (LOAEL) at which reversible renal (moderate tubular degeneration) and liver (individual hepatocyte necrosis) findings were observed in the chronic rat study was 100 mg/kg/day and provided an exposure margin 4.2-times greater than the clinical exposure at the recommended dose of 100 mg twice daily. In studies of 9 months duration in dogs, the NOAEL was 10 mg/kg/day corresponding to an exposure 3-times the clinical AUC at the recommended clinical dose. Minimal tubular degeneration in kidney, slight decreases in spleen weights and transient minimal to mild decreases in red cell mass and increases in ALT and ALP were observed at 30 mg/kg/day (9-times the clinical AUC) in dogs. Cardiac toxicities in rats (myocardial haemorrhage, inflammation, necrosis) and dogs (perivascular/vascular inflammation) were observed only in animals that died during studies at doses above the maximum tolerated dose (MTD). The exposures in rats and dogs with cardiac findings was at least 6.8-times and 25-times the clinical AUC, respectively. Reversibility for the heart findings could not be assessed as these findings were only observed at doses above the MTD.

Reproductive toxicology

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

No effects on embryofoetal development and survival were observed in pregnant rats, at exposures approximately 9-times the AUC in patients at the recommended dose of 100 mg twice daily. In two rat reproductive studies, dystocia (prolonged/difficult labour) was observed at exposures > 2.3-times the clinical exposure at 100 mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in foetal rat plasma. Acalabrutinib and its active metabolite were present in the milk of lactating rats.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)
Microcrystalline cellulose (E460)
Low-substituted hydroxypropyl cellulose (E463)
Sodium stearyl fumarate

Tablet coating

Hypromellose (E464)
Copovidone
Titanium dioxide (E171)
Macrogol
Medium-chain triglycerides
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blister packs, with sun/moon symbols, containing 8 or 10 film-coated tablets. Cartons of 56 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1479/003
EU/1/20/1479/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 November 2020
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 100 MG CAPSULE

1. NAME OF THE MEDICINAL PRODUCT

Calquence 100 mg hard capsules
acalabrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg of acalabrutinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
56 hard capsules
60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1479/001 56 hard capsules
EU/1/20/1479/002 60 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

calquence

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 100 MG CAPSULE

1. NAME OF THE MEDICINAL PRODUCT

CALQUENCE 100 mg capsules
acalabrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Sun/Moon symbol

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 100 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

Calquence 100 mg film-coated tablets
acalabrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of acalabrutinib (as acalabrutinib maleate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
56 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1479/003 56 film-coated tablets
EU/1/20/1479/004 60 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

calquence

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 100 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

CALQUENCE 100 mg tablets
acalabrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Sun/Moon symbol

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Calquence 100 mg hard capsules
acalabrutinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Calquence is and what it is used for
2. What you need to know before you take Calquence
3. How to take Calquence
4. Possible side effects
5. How to store Calquence
6. Contents of the pack and other information

1. What Calquence is and what it is used for

What Calquence is
- Calquence contains the active substance acalabrutinib.
- It belongs to a group of medicines called Bruton tyrosine kinase (BTK) inhibitors.

What Calquence is used for
Calquence is used to treat adults with chronic lymphocytic leukaemia (CLL).

CLL is a cancer of white blood cells called B-lymphocytes (or B-cells). These cells are part of the immune system (the body's defences).

Calquence is used to treat adults with mantle cell lymphoma (MCL).

MCL is a type of blood cancer affecting the lymph nodes.

How Calquence works
Calquence works by blocking BTK, a protein in the body that helps these cancer cells grow and survive. By blocking BTK, Calquence helps to kill and can reduce the number of cancer cells which can slow down the worsening of the disease.

If you have any questions about how Calquence works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Calquence

Do not take Calquence if:
- you are allergic to acalabrutinib or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist or nurse before taking Calquence.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Calquence if you:
- have ever had unusual bruising or bleeding or are on any medicines that increase your risk of bleeding (see section 4 'Possible side effects').
- have an infection (see section 4 "Possible side effects')
- have recently had an operation or are about to have one. Your doctor may stop treatment with Calquence before and after a medical, surgical or dental procedure.
- have ever had hepatitis B (a liver infection) – this is because Calquence could cause hepatitis B to become active again and so that your doctor will look out for signs of this infection coming back (see section 4 'Possible side effects').
- have or ever had irregular heart beat (see section 4 'Possible side effects').

Talk to your doctor if you develop a new lesion or any change in the appearance of an area on the skin as you are at a high risk of developing skin cancer, see section 4. Use sun protection and make regular skin examination.

Your doctor will check your blood cell counts as needed during treatment.

Children and adolescents
Do not give this medicine to children or adolescents aged less than 18 years. This is because it has not been studied in this age group.

Other medicines and Calquence
Tell your doctor, pharmacist or nurse if you are taking or have recently taken or might take any other medicines, especially if you take any of the following:

- antibiotics for bacterial infections – such as clarithromycin
- medicines for fungal infections – such as posaconazole, itraconazole, voriconazole
- ketoconazole – a medicine for Cushing's syndrome (a condition in which the body produces too much of the hormone cortisol)
- medicines for HIV infections – such as indinavir and ritonavir
- medicines for hepatitis C – such as telaprevir
- rifampicin – an antibiotic for bacterial infections (tuberculosis)
- ergotamine – a medicine for migraines
- conivaptan – a medicine for low blood sodium
- metformin – a medicine for high blood sugars
- cyclosporine – a medicine to prevent organ rejection
- medicines for fits (seizures) or epilepsy – such as carbamazepine and phenytoin
- pimozide – a medicine used for Tourette (condition which causes uncontrolled movements and outbursts of words and sounds)
- St. John's wort – an herbal medicine for depression
- theophylline – a medicine used for wheezing, shortness of breath, and chest tightness
- medicines for reducing stomach acid:

- antacids – such as calcium carbonate. Take Calquence2 hours before or 2 hours after you take these medicines.
- histamine-2 receptor blockers – such as ranitidine and famotidine. Take Calquence 2 hours before or 10 hours after you take these medicines.
- proton pump inhibitors – such as omeprazole. Avoid taking these medicines while you are taking Calquence.

- methotrexate – a medicine for diseases such as rheumatoid arthritis, psoriasis and ulcerative colitis, which are caused by the immune system working incorrectly.
  - This medicine should be taken at least 6 hours before or after Calquence.

Medicines that increase your risk of bleeding
Calquence may make you bleed more easily. Tell your doctor, pharmacist, or nurse if you take other medicines that increase your risk of bleeding:
- Antiplatelets (medicines that act against blood clotting) such as acetylsalicylic acid and clopidogrel.
- Anticoagulants (blood thinners) such as warfarin or enoxaparin.

Pregnancy
Talk to your doctor before taking Calquence if you are pregnant, think you may be pregnant, or are planning on having a baby. This is because Calquence may harm your unborn baby.

Breast-feeding
Do not breast-feed during treatment with Calquence and for 2 days after your last dose of Calquence. It is not known if Calquence passes into your breast milk.

Driving and using machines
Calquence is unlikely to affect the ability to drive and use machines. However, if you feel dizzy, weak or tired while taking Calquence, you must not drive or use machines.

Calquence contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to take Calquence

Calquence will only be prescribed to you by a doctor with experience in the use of medicines for cancer. Always take Calquence exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Depending on your type of cancer, Calquence may be given in combination with other anticancer medicines.

How much to take
- The usual dose is one capsule (100 mg) twice a day. Take doses about 12 hours apart.

How to take
- Swallow the capsule whole with water at about the same time each day.
- Do not chew, dissolve or open the capsules as this may change how quickly the medicine gets into your body.
- You can take Calquence with food or between meals.

- You can check when you last took a capsule of Calquence by looking on the blister. Pictures on the blister will help you to take your dose at the right time — the sun for the morning dose and the moon for the evening dose.

If you take more Calquence than you should
If you have taken more Calquence than you should, see a doctor or go to the nearest hospital straight away. Take the capsules and this leaflet with you.

If you forget to take a dose
- If less than 3 hours have passed after your usual time for taking a dose, take the missed dose right away. Take the next dose at your usual time.
- If more than 3 hours have passed after your usual time for taking a dose, skip the missed dose. Take the next dose at your usual time.
- Do not take a double dose of Calquence to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Calquence and contact a doctor or go to your nearest emergency department immediately if you experience any of the following symptoms:

Very common serious side effects (may affect more than 1 in 10 people):
- Bleeding in different sites, including skin, gut and brain. Symptoms may be black stools or stools with blood, pink or brown urine, nosebleeds, bruising, unexpected bleeding, vomiting or coughing up blood, dizziness, weakness, confusion.
- Infections. Signs may include fever, chills, feeling weak or confused, cough, shortness of breath [Pneumonia, a **very common side effect** (may affect more than 1 in 10 people) or Aspergillus infections, an **uncommon side effect** (may affect up to 1 in 100 people)].

Common serious side effects (may affect up to 1 in 10 people):
- fast heart rate, missed heart beats, weak or uneven pulse, dizziness, feeling faint, chest discomfort or shortness of breath (signs of heart rhythm problems known as atrial fibrillation and atrial flutter).
- fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, or muscle or joint pain. This can be symptoms of tumour lysis syndrome (TLS) – a condition caused by the fast breakdown of cancer cells.

Other side effects:

Very common (may affect more than 1 in 10 people)**:**
- muscle or joint pain
- headache
- rash
- feeling tired (fatigue), weakness or lack of energy
- feeling sick to your stomach (nausea),vomiting, stomach pain, constipation (infrequent or hard to pass stool), diarrhoea (frequent or loose stools)
- decreased number of red blood cells, decreased number of neutrophils (a type of white blood cells) or decreased number of cells that help blood clot (platelets)

- high blood pressure
- dizziness
- headache, pressure in the eyes, nose or cheek area (sinusitis)
- sore throat and runny nose (nasopharyngitis)
- upper respiratory tract infection
- urinary tract infection (pain or burning feeling when passing urine).
- new cancers, including cancers of the skin, may happen during treatment with Calquence (see Section 2 'What you need to know before you take Calquence')
- herpes

Common (may affect up to 1 in 10 people):
- increased levels of the liver enzymes (aspartate aminotransferase and alanine aminotransferase) in blood tests [when used in combination with certain medicines to treat mantle cell lymphoma (MCL)].
- bronchitis
- fever, chills, weakness, confusion, being sick and yellowing of the skin or eyeballs (jaundice) – these may be signs of hepatitis B (a liver infection) becoming active again.
- inflammation of the lungs (pneumonitis)

Uncommon side effects (may affect up to 1 in 100 people):
- memory loss, trouble thinking, difficulty walking or sight loss – these may be signs of a serious brain infection (Progressive Multifocal Leukoencephalopathy or PML).
- lymphocytosis (a higher than normal amount of lymphocytes, a type of white blood cells, in the blood).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Calquence

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister foil and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Calquence contains
The active substance is acalabrutinib. Each hard capsule contains 100 mg of acalabrutinib.

The other ingredients are:

- Capsule content: microcrystalline cellulose, colloidal anhydrous silica, partially pregelatinised maize starch , magnesium stearate (E470b) and sodium starch glycollate (see section 2 “Calquence contains sodium”).
- Capsule shell: gelatine, titanium dioxide (E171), yellow iron oxide (E172) and indigo carmine (E132).
- Printing ink: shellac, black iron oxide (E172), propylene glycol (E1520) and ammonium hydroxide.

What Calquence looks like and contents of the pack
Calquence is a 20 mm hard gelatine capsule with a yellow body and blue cap, marked with “ACA 100 mg” in black.

Calquence is supplied in aluminium blisters containing either 6 or 8 hard capsules. Each carton contains either 56 or 60 hard capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tel: +46 8 553 26 000

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Package leaflet: Information for the patient

Calquence 100 mg film-coated tablets
acalabrutinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Calquence is and what it is used for
2. What you need to know before you take Calquence
3. How to take Calquence
4. Possible side effects
5. How to store Calquence
6. Contents of the pack and other information

1. What Calquence is and what it is used for

What Calquence is
- Calquence contains the active substance acalabrutinib.
- It belongs to a group of medicines called Bruton tyrosine kinase (BTK) inhibitors.

What Calquence is used for
Calquence is used to treat adults with chronic lymphocytic leukaemia (CLL).

CLL is a cancer of white blood cells called B-lymphocytes (or B-cells). These cells are part of the immune system (the body's defences).

Calquence is used to treat adults with mantle cell lymphoma (MCL).

MCL is a type of blood cancer affecting the lymph nodes.

How Calquence works
Calquence works by blocking BTK, a protein in the body that helps these cancer cells grow and survive. By blocking BTK, Calquence helps to kill and can reduce the number of cancer cells which can slow down the worsening of the disease.

If you have any questions about how Calquence works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Calquence

Do not take Calquence if:
- you are allergic to acalabrutinib or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist or nurse before taking Calquence.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Calquence if you:
- have ever had unusual bruising or bleeding or are on any medicines that increase your risk of bleeding (see section 4 'Possible side effects').
- have an infection (see section 4 'Possible side effects')
- have recently had an operation or are about to have one. Your doctor may stop treatment with Calquence before and after a medical, surgical or dental procedure.
- have ever had hepatitis B (a liver infection) – this is because Calquence could cause hepatitis B to become active again and so that your doctor will look out for signs of this infection coming back (see section 4 'Possible side effects').
- have or ever had irregular heart beat (see section 4 'Possible side effects').

Talk to your doctor if you develop a new lesion or any change in the appearance of an area on the skin as you are at a high risk of developing skin cancer, see section 4. Use sun protection and make regular skin examination.

Your doctor will check your blood cell counts as needed during treatment.

Children and adolescents
Do not give this medicine to children or adolescents aged less than 18 years. This is because it has not been studied in this age group.

Other medicines and Calquence
Tell your doctor, pharmacist or nurse if you are taking or have recently taken or might take any other medicines, especially if you take any of the following:

- antibiotics for bacterial infections – such as clarithromycin
- medicines for fungal infections – such as posaconazole, itraconazole, voriconazole
- ketoconazole – a medicine for Cushing's syndrome (a condition in which the body produces too much of the hormone cortisol)
- medicines for HIV infections – such as indinavir and ritonavir
- medicines for hepatitis C – such as telaprevir
- rifampicin – an antibiotic for bacterial infections (tuberculosis)
- ergotamine – a medicine for migraines
- conivaptan – a medicine for low blood sodium
- metformin – a medicine for high blood sugars
- cyclosporine – a medicine to prevent organ rejection
- medicines for fits (seizures) or epilepsy – such as carbamazepine and phenytoin
- pimozide – a medicine used for Tourette (condition which causes uncontrolled movements and outbursts of words and sounds)
- St. John's wort – an herbal medicine for depression
- theophylline – a medicine used for wheezing, shortness of breath, and chest tightness

- methotrexate – a medicine for diseases such as rheumatoid arthritis, psoriasis and ulcerative colitis, which are caused by the immune system working incorrectly.
    - This medicine should be taken at least 6 hours before or after Calquence.

You can take stomach acid reducing medicines such as antacids (calcium carbonate), histamine-2 receptor blockers (ranitidine and famotidine) and proton pump inhibitors (omeprazole) with Calquence tablets.

Medicines that increase your risk of bleeding
Calquence may make you bleed more easily. Tell your doctor, pharmacist, or nurse if you take other medicines that increase your risk of bleeding:
- Antiplatelets (medicines that act against blood clotting) such as acetylsalicylic acid and clopidogrel.
- Anticoagulants (blood thinners) such as warfarin or enoxaparin.

Pregnancy
Talk to your doctor before taking Calquence if you are pregnant, think you may be pregnant, or are planning on having a baby. This is because Calquence may harm your unborn baby.

Breast-feeding
Do not breast-feed during treatment with Calquence and for 2 days after your last dose of Calquence. It is not known if Calquence passes into your breast milk.

Driving and using machines
Calquence is unlikely to affect the ability to drive and use machines. However, if you feel dizzy, weak or tired while taking Calquence, you must not drive or use machines.

Calquence contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to take Calquence

Calquence will only be prescribed to you by a doctor with experience in the use of medicines for cancer. Always take Calquence exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Depending on your type of cancer, Calquence may be given in combination with other anticancer medicines.

How much to take
- The usual dose is one tablet (100 mg) twice a day. Take doses about 12 hours apart.

How to take
- Swallow the tablet whole with water at about the same time each day.
- Do not chew, crush, dissolve or divide the tablets.
- You can take Calquence with food or between meals.
- You can check when you last took a tablet of Calquence by looking on the blister. Pictures on the blister will help you to take your dose at the right time — the sun for the morning dose and the moon for the evening dose.

If you take more Calquence than you should
If you have taken more Calquence than you should, see a doctor or go to the nearest hospital straight away. Take the tablets and this leaflet with you.

If you forget to take a dose
- If less than 3 hours have passed after your usual time for taking a dose, take the missed dose right away. Take the next dose at your usual time.
- If more than 3 hours have passed after your usual time for taking a dose, skip the missed dose. Take the next dose at your usual time.
- Do not take a double dose of Calquence to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Calquence and contact a doctor or go to your nearest emergency department immediately if you experience any of the following symptoms:

Very common serious side effects (may affect more than 1 in 10 people):
- Bleeding in different sites, including skin, gut and brain. Symptoms may be black stools or stools with blood, pink or brown urine, nosebleeds, bruising, unexpected bleeding, vomiting or coughing up blood, dizziness, weakness, confusion.
- Infections. Signs may include fever, chills, feeling weak or confused, cough, shortness of breath [Pneumonia, a **very common side effect** (may affect more than 1 in 10 people) or Aspergillus infections, an **uncommon side effect** (may affect up to 1 in 100 people)].

Common serious side effects (may affect up to 1 in 10 people):
- fast heart rate, missed heart beats, weak or uneven pulse, dizziness, feeling faint, chest discomfort or shortness of breath (signs of heart rhythm problems known as atrial fibrillation and atrial flutter).
- fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, or muscle or joint pain. This can be symptoms of tumor lysis syndrome (TLS) – a condition caused by the fast breakdown of cancer cells.

Other side effects:

Very common (may affect more than 1 in 10 people)**:**
- muscle or joint pain
- headache
- rash
- feeling tired (fatigue), weakness or lack of energy
- feeling sick to your stomach (nausea),vomiting, stomach pain, constipation (infrequent or hard to pass stool), diarrhoea (frequent or loose stools)
- decreased number of red blood cells, decreased number of neutrophils (a type of white blood cells) or decreased number of cells that help blood clot (platelets)
- high blood pressure
- dizziness
- headache, pressure in the eyes, nose or cheek area (sinusitis)
- sore throat and runny nose (nasopharyngitis)

- upper respiratory tract infection
- urinary tract infection (pain or burning feeling when passing urine)
- new cancers, including cancers of the skin, may happen during treatment with Calquence (see section 2 ‘What you need to know before you take Calquence’)
- herpes

Common (may affect up to 1 in 10 people):
- increased levels of the liver enzymes (aspartate aminotransferase and alanine aminotransferase) in blood tests [when used in combination with certain medicines to treat mantle cell lymphoma (MCL)].
- bronchitis
- fever, chills, weakness, confusion, being sick and yellowing of the skin or eyeballs (jaundice) – these may be signs of hepatitis B (a liver infection) becoming active again.
- inflammation of the lungs (pneumonitis)

Uncommon side effects (may affect up to 1 in 100 people):
- memory loss, trouble thinking, difficulty walking or sight loss – these may be signs of a serious brain infection (Progressive Multifocal Leukoencephalopathy or PML).
- lymphocytosis (a higher than normal amount of lymphocytes, a type of white blood cells, in the blood).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Calquence

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister foil and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Calquence contains
The active substance is acalabrutinib. Each film-coated tablet contains 100 mg of acalabrutinib (as acalabrutinib maleate).

The other ingredients are:
- Tablet core: mannitol (E421), microcrystalline cellulose (E460), low-substituted hydroxypropyl cellulose (E463) and sodium stearyl fumarate (see section 2 ‘Calquence contains sodium’).
- Tablet coating: hypromellose (E464), copovidone, titanium dioxide (E171), macrogol, medium-chain triglycerides, iron oxide yellow (E172) and iron oxide red (E172).

What Calquence looks like and contents of the pack
Calquence is an orange, 7.5 x 13 mm, oval, biconvex tablet, debossed with ‘ACA 100’ on one side and plain on the reverse.

Calquence is supplied in aluminium blisters containing either 8 or 10 film-coated tablets. On each blister there are sun/moon symbols to help you to take your dose at the right time — the sun for the morning dose and the moon for the evening dose. Both the sun and the moon blisters contain the same medicine. Each carton contains either 56 or 60 film-coated tablets.

Not all pack sizes may be marketed.

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Manufacturer
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu