15 December 2022
EMA/38803/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Calquence

International non-proprietary name: acalabrutinib

Procedure No. EMEA/H/C/005299/X/0009/G

Note

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

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Administrative information

Name of the medicinal product:	Calquence
MAH:	AstraZeneca AB 151 85 Sodertalje SWEDEN
Active substance:	Acalabrutinib maleate
International Non-proprietary Name	Acalabrutinib
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors, bruton's tyrosine kinase (btk) inhibitors (L01EL02)
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 as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.
Pharmaceutical form:	Film-coated tablet
Strength:	100 mg
Route of administration:	Oral use
Packaging:	blister (alu/alu)
Package sizes:	56 tablets, 60 tablets

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List of abbreviations

AE	adverse event
AI	Acceptable intake
ALT	alanine aminotransferase
AMT	acalabrutinib maleate film-coated tablet(s)
ARA	acid reducing agent
AST	aspartate aminotransferase
BCS	Biopharmaceutics Classification System
BMI	body mass index
BTK	Bruton tyrosine kinase
CHMP	Committee for Medicinal Products for Human use
CLL	chronic lymphocytic leukemia
Cmax	maximum plasma concentration
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
EC	European Commission
ECG	electrocardiogram
EU	European Union
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IMP	investigational medicinal product
IR	Infrared
LC-HRAMS	Liquid chromatography high resolution accurate-mass spectrometry
LDPE	Low density polyethylene
MAH	Marketing Authorisation holder
MedDRA	Medical Dictionary for Regulatory Authorities
MS	Mass Spectrometry
NCWP	Non-clinical working party
NMR	Nuclear magnetic resonance
NMT	Not more than
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PT	preferred term
QSAR	Qualitative structure activity relationship
QTPP	Quality target product profile
RH	Relative humidity

SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
UHPLC	Ultra-high performance liquid chromatography
ULN	upper limit of normal
UV	Ultraviolet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

AstraZeneca AB submitted on 11 October 2021 a group of variation(s) consisting of the following extension of the marketing authorisation and variation:

Extension application to introduce a new pharmaceutical form, film-coated tablet. The active substance in the new formulation, acalabrutinib maleate, is a free base equivalent of acalabrutinib, the active substance used in the hard capsules formulation.

Variation(s) requested		**Type**
A.6	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	IA

A.6 - To change the ATC Code of acalabrutinib from L01XE51 to L01EL02.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision, P/0408/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0408/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Željana Margan Koletić

The application was received by the EMA on	11 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 January 2022
<The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on>	10 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 February 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 April 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	19 May 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 June 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 July 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	21 July 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 June 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 November 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Calquence on	15 December 2022
The CHMP adopted a report on similarity of Calquence with Gazyvaro on (see Appendix on similarity)	15 December 2022

2. Scientific discussion

2.1. Problem statement

The current commercial formulation of acalabrutinib (Calquence) is presented as a 100 mg hard capsule for oral administration.

The purpose of this submission is to extend the current Marketing Authorisation to add a new pharmaceutical form of acalabrutinib maleate 100 mg (free base equivalent amount) in a film-coated tablet. The proposed clinical use for the tablet will be for the same indications which are currently approved for the 100 mg acalabrutinib capsule.

The aim of introducing the tablet, which has higher solubility over the full pH range compared to the approved capsule formulation, is to allow acalabrutinib to be co-administered with gastric acid reducing agents.

This submission is supported by one bioequivalence study (D8223C0013) and one study to evaluate bioavailability in addition to the effect of PPI and food on the tablet formulation (D8220C00018).

2.2. About the product

Acalabrutinib (ACP-196), is a highly selective, potent, orally bioavailable, covalent inhibitor of BTK. Acalabrutinib forms a covalent bond with Cys481 in the BTK adenosine triphosphate (ATP) pocket, permanently inactivating the enzyme and resulting in the inhibition of proliferation and survival signals in malignant B cells. Acalabrutinib has an active metabolite, ACP-5862, that is also a covalent inhibitor of BTK. Biochemical profiling showed that the pharmacological activity and kinase selectivity profile for ACP-5862 was comparable to that of acalabrutinib.

Calquence is currently commercially available as an immediate release capsule comprising 100 mg of the acalabrutinib free base. The current label for this product restricts its administration with acid reducing agents (ARAs), including the recommendation that patients avoid co-administration with proton-pump inhibitors (PPIs) and that dosing should be staggered with H2 receptor antagonists and antacids. These label restrictions are related to the low drug solubility above pH 4.

A 100 mg acalabrutinib maleate film-coated tablet (free base equivalent), which show complete drug dissolution regardless of pH conditions in the gastrointestinal tract has therefore been developed. Acalabrutinib maleate film-coated tablet dosed at 100 mg in acidic stomach conditions is shown to supersaturate in neutral intestinal conditions and allow acalabrutinib to be co-administered with ARAs. Hence, removal of the recommendations to avoid concomitant PPI use or to stagger dosing with H2 receptor antagonists and antacids from the product labelling are proposed for the tablet formulation.

2.3. Type of Application and aspects on development

No prior Scientific Advice has been sought from the CHMP for the proposed line extension application.

2.4. Quality aspects

2.4.1. Introduction

The finished product presentation applied for in this line extension is presented as film-coated tablets containing acalabrutinib maleate hydrate equivalent to 100 mg of acalabrutinib as active substance.

Other ingredients are:

Tablet core: mannitol (E421), microcrystalline cellulose (E460), low-substituted hydroxypropylcellulose (E463) and sodium stearyl fumarate.

Tablet coating: Hypromellose (E464), copovidone, titanium dioxide (E171), macrogol, medium-chain triglycerides, iron oxide yellow (E172) and iron oxide red (E172).

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

2.4.2. Active Substance

General information

The film coated tablets applied for in this line extension contain the maleate hydrate form of the active substance, in contrast to the approved hard capsules which contain the unsolvated free base form.

The chemical name of acalabrutinib maleate is 4-{8-amino-3-[(2*S*)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-*N*-(pyridine-2-yl)benzamide (2*Z*)-2-butenedioic acid hydrate (1:1:1) corresponding to the molecular formula $C_{26}H_{23}N_7O_2.C_4H_4O_4.H_20$. It has a relative molecular mass of 599.59 g/mol (salt/hydrate form) and the following structure:

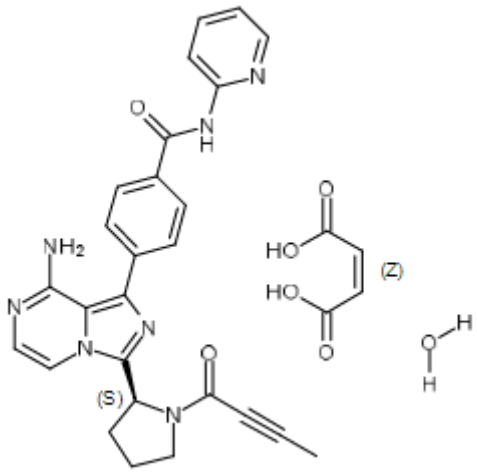


Figure 1: active substance structure

The chemical structure of acalabrutinib maleate hydrate was inferred from the route of synthesis and elucidated by a combination of mass spectrometry (MS), ^1H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), elemental analysis, and ultraviolet spectroscopy (UV). Acalabrutinib maleate hydrate has one chiral centre in the (*S*)-configuration as confirmed by single crystal X-ray diffraction (XRD).

The solid-state properties of the active substance were measured by differential scanning calorimetry and thermogravimetric analysis. Acalabrutinib maleate is a slightly hygroscopic, white to pale brown crystalline powder. It exhibits pH-dependent solubility in aqueous media with greater solubility at acidic pH. Extensive polymorph screening demonstrated that the monohydrate is the thermodynamically stable form under ambient conditions. The proposed commercial manufacturing process consistently produces the monohydrate form.

Manufacture, characterisation and process controls

The manufacturing process of acalabrutinib maleate hydrate up to the acalabrutinib stage remains the same as the previously approved process. The process parameters, specifications and control strategy also remain essentially unchanged from the approved acalabrutinib file. The details for the salt formation step are considered adequate.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials, reagents, solvents and auxiliary materials have been presented and are found acceptable.

Potential and actual impurities were well discussed with regards to their origin and characterised. There are no new impurities as compared with the free base.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

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

Specification

The active substance specification includes tests for appearance, identity (FT-IR), assay (HPLC), impurities (HPLC), residual solvents (GC) and particle size distribution (laser diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The limits for particle size are set in line with the clinical batches.

The absence of tests for water content, elemental impurities, some residual solvents used early in the process, residue of ignition/sulphated ash, polymorphism and microbial testing has been acceptably justified by the applicant.

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

Batch analysis data from 13 acalabrutinib maleate batches, pilot to production scale, from the proposed commercial manufacturer are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term and intermediate conditions (25 ºC / 60% RH and 30 °C / 75% RH respectively) and for up to 6 months under accelerated

conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: description, assay, organic impurities, enantiomeric purity, polymorphic identity, particle size, water content and microbiological purity. No significant changes to any of the studied attributes were observed.

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

Stability data generated for acalabrutinib maleate drug substance when stored in an open container under storage conditions up to and including 70 °C / 75% RH and 80 °C / 50% RH show no significant change in description, organic impurities, enantiomeric purity or polymorphic identity. This data confirms that acalabrutinib maleate drug substance is stable when exposed to high humidity and temperature.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months stored below 30 °C in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as oval, biconvex, film-coated tablets containing acalabrutinib maleate equivalent to 100 mg acalabrutinib free base, and measuring approximately 7.5×13 mm. The tablets are debossed with 'ACA 100' on one side and are plain on the reverse. The composition of Calquence film-coated tablets was presented.

Formulation development was performed to meet the criteria described in the Quality Target Product Profile (QTPP): an oral immediate release film-coated tablet containing acalabrutinib able to meet the clinical need, quality and pharmacopoeial requirements including purity, and free from microbial contamination. Acalabrutinib free base is used in the already-approved capsules but suffers from low solubility above pH 4. As a result, the SmPC currently restricts administration of Calquence capsules with acid-reducing agents such as proton pump inhibitors, antacids and H^2-antagonists. Oncology patients are likely to take an average of five medications concomitantly, including acid reducing agents. Therefore, an acalabrutinib formulation was sought which allows sufficient solubility to be maintained above pH 4. A screen of different salts identified acalabrutinib maleate as a salt which exhibits higher solubility above pH 4.

Acalabrutinib maleate is considered to be a BCS class 2 drug (high permeability and low solubility). Acalabrutinib maleate film-coated tablet dissolution is complete across the physiological pH range and is faster than the dissolution observed from acalabrutinib capsules. No precipitation of acalabrutinib was observed upon changing the pH of a solution of the film-coated tablet from acidic to neutral under biorelevant conditions.

Acalabrutinib maleate was found to be compatible with a range of commonly used excipients for the development of solid oral dosage forms, including diluents, binders, disintegrants and lubricants. All the excipients ultimately chosen are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

Several prototype tablets were made using different formulations including direct compression. Dry granulation by roller compaction was selected as the commercial manufacturing process in order to maximise the drug load in the formulation over what was considered achievable by direct compression. This allows production of a smaller dosage form for the same active substance content and thus, improved acceptability for patients taking multiple medicines.

Development of the dissolution method considered the clinical setting, i.e. the need for tablets to dissolve in the stomach at low pH or at higher pH when co-administered with proton pump inhibitors. Compendial apparatus and conditions are otherwise used (paddles, 75 rpm). The method was shown to discriminate between batches manufactured with active substance batches of differing particle size distributions and batches manufactured with meaningful changes in process parameters. It can also distinguish between capsules and tablets. Tablets and capsules were found to be bioequivalent in a clinical study conducted under appropriate conditions.

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

Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: conventional mixing, dry granulation, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive productions scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description, identification (UHPLC, UV), assay (UHPLC), degradation products (UHPLC), related substances (ACP-7341, LC-HRAMS), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.) and microbiological quality (Ph. Eur.).

The impurities are adequately qualified at the specified limits.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities and no significant risk was identified. Batch analysis data on 4 pilot scale batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was well below 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that no elemental impurity controls are needed.

The applicant submitted a risk evaluation on the potential presence of nitrosamines in the finished product. Both active substance and finished product manufacturing processes were considered, along with raw materials and packaging. ACP-1049 is an impurity in the active substance and a finished product degradant and contains a secondary amine susceptible to nitrosation in the presence of adventitious nitrite. Therefore, the CHMP requested the applicant to conduct confirmatory testing for the respective nitrosamine impurity using a suitably sensitive analytical method as a major objection. The results indicate the impurity is present. An acceptable intake (AI) was derived and the impurity is

now controlled in line with this limit. The limit is adequately justified, and the major objection is considered resolved.

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

Batch analysis results are provided for 5 pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data from 3 pilot scale batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH), 18 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

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

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

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

Based on available stability data, the proposed shelf-life of 2 years without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The film-coated tablets, subject of this line extension, contain a different salt form of the active substance compared to the approved capsules. This allows dissolution at higher pH and means the label restrictions associated with the capsules are not necessary for the tablets. Bioequivalence between the two formulations has been demonstrated.

During the procedure, a new nitrosamine impurity (ACP-7341) was identified in the finished product. The MAH developed a suitably sensitive analytical method and provided batch data which complies with the AI. The control strategy is considered to be acceptable.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The full nonclinical safety profile of acalabrutinib has been discussed in detail in the original marketing application for Calquence. Additional toxicology studies have been submitted with this application to support the use of acalabrutinib maleate tablet in the proposed indications. These studies were conducted to qualify a degradation product in acalabrutinib maleate drug product and to assess the mutagenic potential of two theoretical N-nitrosamine impurities.

2.5.2. Pharmacology

No new pharmacology studies were submitted with this application.

2.5.3. Pharmacokinetics

No new pharmacokinetics studies were submitted with this application.

2.5.4. Toxicology

2.5.4.1. Studies on impurities

ACP-6169

A 1 month repeat dose study in the rat was conducted to qualify ACP-6169, a degradation product in the acalabrutinib maleate drug product.

Four groups of Han Wistar rats, each consisting of 10 males and 10 females (main study) and 3 males and 3 females (toxicokinetics), were given acalabrutinib maleate or acalabrutinib free-base orally, once daily, at a dose level of 100 mg/kg/day for 28 days.

Acalabrutinib maleate-related and acalabrutinib free base-related, non-adverse pancreas microscopic findings were noted in male rats only at 100 mg/kg/day and were characterised by minimal

(acalabrutinib maleate) or mild to moderate (acalabrutinib free base) pancreatic islet haemorrhage/inflammation/fibrosis/intrahistiocytic pigment. There was no difference in the nature of the pancreas microscopic findings between acalabrutinib maleate and acalabrutinib free base.

For all other parameters, there were no test item related changes considered to be related to administration of acalabrutinib maleate or acalabrutinib free base.

ACP-7341 and ACP-7512

ACP-7341 and ACP-7512 are two theoretical N-nitrosamine impurities that may be present in acalabrutinib maleate drug substance. The potential mutagenicity of these theoretical N-nitrosamines was evaluated in Ames test. The design of Ames tests for these impurities was optimised to increase the detection of the potential mutagenic/carcinogenic activity of N-nitrosamines. As such, potential mutagenicity of these N-nitrosamines was evaluated in the presence of rat and hamster metabolic activators (S9-mix). Mutagenicity of ACP-7512 was assessed in the presence of hamster and rat S9 mix in a single Ames assay. The same strategy was used for mutagenicity evaluation of ACP-7341, however assessments in the presence of hamster and rat S9 mix were conducted in two separate Ames assays.

ACP-7341

ACP-7341 is a nitrosamine that theoretically could be formed from the known impurity ACP-1049

ACP-7341 was tested for mutagenic activity using genetically modified Salmonella typhimurium LT2 bacteria of strains TA1535, TA1537, TA98 and TA100, and Escherichia coli WP2 strain uvrA/pKM101 as indicator organisms in the presence of a hamster liver S9-based metabolic activation system (S9 mix).

Preliminary assessments of solubility were not conducted as part of this study as ACP-7341 had been tested in a previous study in which dimethyl formamide (DMF) was found to be suitable. DMF was therefore used throughout this study as the solvent for the test item.

The dose range used was 1.6 to 5000 µg per plate. For comparison with the in-house historical control database, concurrent dimethyl sulphoxide (DMSO) controls were also tested.

No significant increase in numbers of revertant (histidine/tryptophan-independent) colonies was seen after treatment with ACP-7341 with any of the five indicator strains in the presence of hamster liver S9 mix.

It was concluded that ACP-7341 was not mutagenic when tested under the conditions used in this assay.

ACP 7512

ACP-7512 is a nitrosamine that theoretically could be formed from the known impurity ACP-5516.

ACP-7512 was tested for mutagenic activity using genetically modified Salmonella typhimurium LT2 bacteria of strains TA1535, TA1537, TA98 and TA100, and Escherichia coli WP2 strain uvrA/pKM101 as indicator organisms.

Preliminary assessments of solubility were conducted. As dimethyl formamide was found to be suitable, this was used throughout this study as the solvent for the test item.

The test item dose range used was 0.5 to 5000 µg per plate. In addition to solvent (dimethyl formamide) controls, for comparison with the in-house historical control database, concurrent dimethyl sulphoxide controls were tested.

There was no evidence of cytotoxicity. The maximum dose level scored for numbers of revertant colonies was 5000 µg per plate.

No significant increase in numbers of revertant (histidine/tryptophan-independent) colonies was seen after treatment with ACP-7512 for any of the five indicator strains in the presence of either rat or hamster liver S9 mix or in the absence of S9 mix.

It was concluded that ACP-7512 was not mutagenic when tested under the conditions used in this assay.

Proposal for an AI for ACP-7341

The MAH chose to propose an AI based on a read-across strategy and to implement Quality control to meet this limit. N-nitrosopyrrolidine was selected for the read-across, as it is the only molecule to contain the same nitrosamine structural moiety as ACP-7341 and with carcinogenicity data available.

2.5.5. Ecotoxicity/environmental risk assessment

Based on the Environmental Risk Assessment for acalabrutinib previously submitted to support the initial Market Authorisation Application for Calquence (Procedure Number EMEA/H/C/005299/0000) which was approved on 05 November 2020 acalabrutinib is not expected to pose a risk to the environment. The changes described in this submission have no effect on environmental exposure. Therefore, in accordance with the European Medicines Agency guidance, EMEA/CHMP/SWP/4447/00 corr2 (CHMP 2006), a revised ERA for acalabrutinib was not submitted with this application.

2.5.6. Discussion on non-clinical aspects

A 1 month repeat dose study in the rat was conducted to qualify ACP-6169, a degradation product in the acalabrutinib maleate drug product. With a NOAEL of 100 mg/kg, the maximum level of ACP-6169 qualified by this study is 1.5% at a clinical dose of 200 mg per day.

ACP-7341 and ACP-7512 were identified as two nitrosamines which theoretically could be present as drug substance impurities. The MAH performed Ames assays with these nitrosamines, in both cases with a negative outcome. As a consequence of these negative assays, in line with ICH M7 both were defined as class 5 and no further control measure or testing was considered necessary by the MAH.

As a consensus on the appropriate conditions for the Ames assay for nitrosamines has not yet been reached, this position was not accepted by the CHMP. Further *in vitro or in vivo* mutagenicity evaluation was not pursued, due to the lack of an agreed position on appropriate assays for this purpose.

The MAH chose to propose an AI based on a read-across strategy and to implement Quality control to meet this limit. N-nitrosopyrrolidine was selected for the read-across, as it is the only molecule to contain the same nitrosamine structural moiety as ACP-7341 and with carcinogenicity data available.

Based on the read-across-strategy, a limit for the nitrosamine ACP-7341 was proposed by the NCWP OEG on nitrosamines and the proposal as agreed by the CHMP. The MAH also accepted the limit and updated relevant sections of Module 3 accordingly.

2.5.7. Conclusion on the non-clinical aspects

There are no objections to an approval of this extension from a nonclinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Summary of Clinical Studies to Support the Safety of AMT

Study	Study design	Subject population	Safety variables	Number of subjects (randomized)	Treatment duration
D8220C00018 (ACE-HV-115) A 2-Part, Phase I, Open-label, Single-dose, Sequential Randomized Crossover Study of New Acalabrutinib Maleate Tablet in Healthy Subjects to Evaluate Relative Bioavailability, Proton Pump Inhibitor (Rabeprazole) Effect, Food Effect and Particle Size Effect	2-part, open-label, sequential Randomized Crossover	Healthy subjects	AEs; vital signs; clinical laboratory test results; ECGs; physical examination	54	Part 1: Each subject received 3 of 4 treatments (single doses), each separated by a washout period of at least 7 days. Part 2: Each subject received 4 treatments (single doses), each separated by a washout period of at least 3 days.
D8223C00013 A Phase I, Open-Label, Randomized, 2-Treatment, 2-Period, Crossover Study in Healthy Subjects to Assess the Bioequivalence of Acalabrutinib Tablet and Acalabrutinib Capsule	Open-label, randomized, 2-treatment, 2-period, Crossover	Healthy subjects	AEs; vital signs; clinical laboratory test results; ECGs; physical examination	66	Each subject received 2 treatments (single doses), each separated by a washout period of at least 5 days.

AE = adverse event; AMT = acalabrutinib maleate film-coated tablet(s); ECG = electrocardiogram.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Calquence capsules containing the active substance as a free base, and the free base has a low solubility at a pH above 4. Therefore, the bioavailability of acalabrutinib is decreased at higher stomach pH, and there are restriction in the use of gastric acid reducing agents (proton pump inhibitors should be avoided and H2-receptor antagonists or antacids must be administered at least 2 hours after Calquence according to the SmPC section 4.2).

The current application is a line extension to the approved capsules and is a tablet formulation containing the maleate salt of acalabrutinib. The maleate salt has a higher solubility over the full pH range, and the aim was to develop a formulation that can be co-administered with gastric acid reducing agents.

Pharmacokinetics were used to bridge the clinical efficacy and safety data for the approved capsules to the new tablet maleate formulation. This was done through a bioequivalence study comparing the tablet to the capsule in fasting state **(D8223C0013)**. In addition, the food effect and the effect of PPI (rabeprazole) of the new formulation was characterised in a multi-arm single dose study **(D8220C00018).**

Samples from both studies were analysed for the content of acalabrutinib as well as ACP-5862 at using an HPLC-MS/MS method using isotope-labeled acalabrutinib or ACP-5862 as internal control (Method ID ACACHPP). The linear range was 1-1000 ng/mL for actabrutinib and 5-5000 ng/ml for ACP-5862.

Study D8220C00018 was a 2-Part, phase I, open-label, single-dose, sequential randomized crossover study of new acalabrutinib maleate tablet in healthy subjects to evaluate relative bioavailability, proton pump inhibitor (rabeprazole) effect, food effect and particle size effect (not discussed further as this was not part of the current line extension application). The study was performed between June 2020 and January 2021.

Study D8223C00013 was a phase I, open-label, randomized, 2-treatment, 2-period, crossover study in healthy subjects to assess the bioequivalence of acalabrutinib tablet and acalabrutinib capsule. The study was performed was performed between February-May2021.

Bioequivalence

In study D8223C00013, 66 healthy male and female subjects (50-100 kg) were included, and 64 completed the study (two discontinuations occurred, one subject was lost to follow-up, one withdrew consent). The subjects were administered acalabrutinib capsule 100 mg (reference;) or acalabrutinib maleate tablet 100 mg (test;) after an overnight fast. The wash-out time between treatments was at least 5 days. 16 PK samples were taken in each period (pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 48 h post-dose). In addition, blood sampling for PD (BTK receptor occupancy) was performed predose, 4 and 12 h post dose as an exploratory endpoint). Primary endpoints were AUCinf, AUClast and Cmax.

Bioequivalence of acalabrutinib was shown both with regards to Cmax (T/R ratio 1.00; 90% CI 0.91-1.11) and AUCt (T/R ratio 0.99; 90% CI 0.94-1.04). The parameters for the metabolite ACP-5862 as well as AUCinf were within standard bioequivalence limits. (**Table *1***).

Table 1. Pharmacokinetic parameters and assessment of bioequivalence in study D8223C00013

Analyte	Parameter (unit)	Treatment	N	n	Geometric LSM	95%CI	Pairwise Comparison (A/B)			
							Ratio (%)	90%CI	Intra-CV%	Inter-CV%
Acalabrutinib	Cmax (ng/mL)	A	65		535.4	(475.4, 603.0)				
		B	63	63	533.5	(473.2, 601.5)	100.36	(90.78, 110.96)	34.64	35.62
	AUCinf (h·ng/mL)	A	65		566.1	(517.3, 619.4)				
		B	63	63	574.3	(524.7, 628.7)	98.56	(93.44, 103.96)	17.97	32.72
	AUClast (h·ng/mL)	A	65		561.9	(513.3, 615.0)				
		B	63	63	568.8	(519.4, 622.9)	98.78	(93.61, 104.24)	18.12	32.85
ACP-5862	Cmax (ng/mL)	A	65		476.3	(434.7, 521.8)				
		B	63	63	459.4	(418.9, 503.8)	103.68	(95.70, 112.32)	27.35	25.98
	AUCinf (h·ng/mL)	A	65		1490	(1387, 1601)				
		B	63	63	1468	(1366, 1577)	101.54	(98.23, 104.96)	10.99	27.30
	AUClast (h·ng/mL)	A	65		1398	(1298, 1507)				
		B	63	63	1374	(1275, 1481)	101.76	(98.16, 105.48)	12.04	28.34

Treatment A: Acalabrutinib maleate tablet, 100 mg, fasted state; Treatment B: Acalabrutinib capsule, 100 mg, fasted state.
Only the subjects with valid PK parameter in both treatments are included for statistical analysis.
Result based on linear mixed effect ANOVA of log-transformed PK parameter with sequence, period, treatment as fixed effect, and subject nested within sequence as random effect.
Geometric mean ratio and corresponding 90% CI are back-transformed and presented as percentages. Geometric LS mean and corresponding 95% CI are also back transformed.
ANOVA, analysis of variance; CI, confidence interval; LSM, least-squares mean; N, number of subjects in the PK analysis set; n, number of subjects included in the statistical comparison analysis; PK, pharmacokinetic.

Similar target occupancy was observed in both groups.

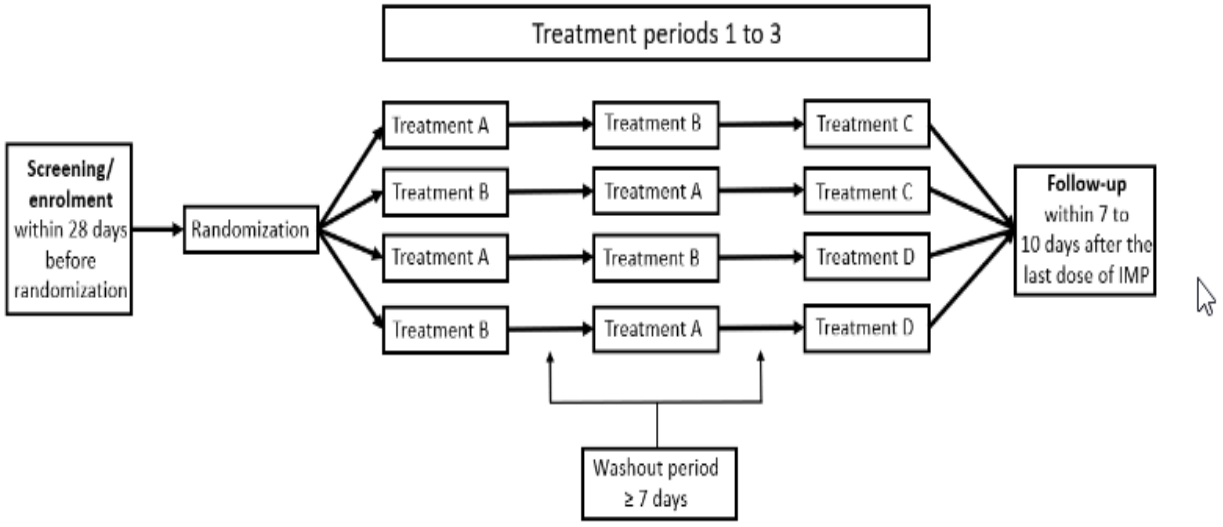
Influence of food

The effect of a high fat breakfast on the bioavailability of the test tablet was assessed.

Part 1 of the study had 4 armed and studied both test and reference in the fasting state, test with food and test with rabeprazole (

Figure *2*). 30 healthy male and female subjects (50-100 kg) were included, and 29 completed the study (one withdrew from the study). The subjects were administered acalabrutinib capsule 100 mg (reference) or acalabrutinib maleate tablet 100 mg (test).

Figure 2. Study design of study D8220C00018. Treatment A-reference, fasting state, B-test, fasting state, C-test, fed state, D- test together with rabetprazol



Subjects were randomized to one of 4 treatment sequences in a 4-sequence, 4-treatment, 3-period crossover: ABC, BAC, ABD, or BAD.
Treatment A = 100 mg acalabrutinib capsule, fasted state;
Treatment B = 100 mg acalabrutinib maleate tablet (Variant 1), fasted state;
Treatment C = 100 mg acalabrutinib maleate tablet (Variant 1), fed state;
Treatment D = 20 mg rabeprazole QD (fasted) at 2 hours before administration of 100 mg acalabrutinib maleate tablet (Variant 1) and following prior administration of 20 mg rabeprazole BID (with meals) on Days -3, -2, and -1.

In period A and B, the reference and test product, respectively, was administered after an overnight fast.

In period C the test product was administered 30 minutes after start of a standardised, high-calorie, high-fat FDA breakfast.

In period D, the test product was administered together with rabeprazole 20 mg administered on day -3, -2 and -1 BID (with food), as well as 2 h before aclabrutinib administration (fasting)(See also interaction with PPI belowO.

The wash-out time between treatments was at least 7 days. 15 PK samples were taken in each period (pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h post-dose). In addition, blood sampling for PD (BTK receptor occupancy) was performed predose, 4, 12 and 24 h h post dose as an exploratory endpoint). Primary endpoints were AUCinf, AUClast and Cmax of aclabrutinib.

The Cmax was lower when the tablet was administered with food (Cmax ratio 0.46), whereas the total exposure (AUCinf) remained unchanged (fed/fasting AUC ratio 0.98; 90% CI 0.88-1.10) (

Table *2*). Tmax was longer with food, the median tmax under fed conditions was 2.00 h, range 0.25-4.00 whereas the corresponding tmax under fasting conditions was 0.73 (0.25-1.53).

Table 2. Pharmacokinetic results of the food effect assessment in study 8220C00018.

Analyte	Parameter (Unit)	Treatment	N	n	Geometric LSM	95% CI	Pairwise Comparison (C/B)	
							Ratio (%)	90% CI
Acala-brutinib	Cmax (ng/mL)	B	29		555.4	(446.2, 691.4)		
		C	14	14	255.6	(205.3, 318.1)	46.01	(35.92, 58.95)
	AUCinf (h·ng/mL)	B	29		541.2	(483.0, 606.5)		
		C	14	14	528.7	(471.9, 592.5)	97.69	(87.19, 109.5)
	AUClast (h·ng/mL)	B	29		538.2	(480.0, 603.4)		
		C	14	14	525.7	(468.9, 589.4)	97.69	(87.18, 109.5)
ACP-5862	Cmax (ng/mL)	B	29		560.6	(469.4, 669.5)		
		C	14	14	358.4	(300.1, 428.1)	63.94	(54.15, 75.49)
	AUCinf (h·ng/mL)	B	29		1617	(1470, 1778)		
		C	14	14	1644	(1495, 1809)	101.7	(96.90, 106.7)
	AUClast (h·ng/mL)	B	29		1531	(1387, 1691)		
		C	14	14	1532	(1388, 1692)	100.1	(95.47, 104.9)

B: 100 mg acalabrutinib maleate tablet (Variant 1), fasted state; C: 100 mg acalabrutinib maleate tablet (Variant 1), fed state.

Interaction with PPI

In **study 8220C00018** the effect of rabeprazole on the bioavailability of the test tablet was also assessed.

When the acalabrutinib maleate tablet was administered with rabeprazole, Cmax of acalabrutinib was lower (24% lower geometric mean) and AUCinf was higher (17% higher geometric mean) (

Table 3). Tmax was similar with rabeprazol, the median tmax with PPI was 1.01 h, range 0.23-3.00 whereas the corresponding tmax under fasting conditions was 0.73 (0.25-1.53).

Similar target occupancy was observed in both periods, after 24 hours the mean target occupancy (SD) in the rabeprazole period was 89.9%% (4.9) and the corresponding occupancy without PPI was 89.6% (9.5)

Table 3. Pharmacokinetic results of the assessment of the effect of rabeprazole in study 8220C00018.

Analyte	Parameter (Unit)	Treatment	N	n	Geometric LSM	95% CI	Pairwise Comparison (D/B)	
							Ratio (%)	90% CI
Acala-brutinib	Cmax (ng/mL)	B	29		486.9	(338.2, 700.9)		
		D	14	14	371.9	(258.3, 535.5)	76.39	(54.88, 106.3)
	AUCinf (h·ng/mL)	B	29		591.1	(466.9, 748.4)		
		D	14	14	694.1	(548.2, 878.7)	117.4	(105.4, 130.8)
	AUClast (h·ng/mL)	B	29		587.8	(462.6, 746.9)		
		D	14	14	669.7	(527.0, 850.9)	113.9	(101.4, 128.0)
ACP-5862	Cmax (ng/mL)	B	29		523.6	(390.7, 701.9)		
		D	14	14	365.3	(272.5, 489.6)	69.76	(51.31, 94.86)
	AUCinf (h·ng/mL)	B	29		1770	(1491, 2101)		
		D	14	14	1783	(1502, 2117)	100.7	(93.26, 108.8)
	AUClast (h·ng/mL)	B	29		1666	(1397, 1985)		
		D	14	14	1656	(1389, 1973)	99.40	(90.81, 108.8)

B: 100 mg acalabrutinib maleate tablet (Variant 1), fasted state; D: 20 mg rabeprazole QD (fasted) at 2 hours before administration of 100 mg acalabrutinib maleate tablet (Variant 1) and following prior administration of 20 mg rabeprazole BID (with meals) on Days -3, -2, and -1.

2.6.3. Discussion on clinical pharmacology

The pharmacokinetic study package performed by the applicant is considered adequate. Since only one strength is available and the capsule can be administered regardless of food, a single dose bioequivalence study in fasting condition is considered appropriate to bridge the clinical data of the approved formulation to the new tablet formulation. In addition, as the new formulation contains a salt formulation with a different sensitivity to pH, a characterisation of the effect of PPI and food on the new formulation is also requested. In general, it is enough to measure parent compound as it is the most sensitive entity to detect differences in absorption.

The study design of the bioequivalence study was considered adequate. Given the short half-life of acalabrutinib (1-2 h) the sampling time as well as wash-out time was sufficient. Bioequivalence was shown under fasting conditions, and thus the clinical efficacy and safety of the capsule can be bridged to the new tablet formulation.

A high fat meal made absorption of acalabrutinib from the tablet slower (longer tmax) and decreased Cmax with 54%. The exposure remained unchanged. These results are similar to those reported for the approved capsule (69% decrease in Cmax) and it is agreed that also the new formulation can be taken regardless of food.

Rabeprazol was chosen as PPI to increase gastric pH in the DDI study, whereas omeprazole had been used in the studies of the approved capsule formulation. The MAH justifies the use of rabeprazole instead of omeprazole with a quicker onset of action reported for rabeprazole (maximum effect after 3 days instead of 5 days for omeprazole) and that rabeprazole is less sensitive to CYP2C19 genotype due to a lower fraction CYP metabolism. This is considered acceptable. According to the SmPC of rabeprazole maximum effect on gastric pH is reached within 3 days and the dose is 20 mg BID is used for the eradication of H pylori (20 mg daily for gastric ulcer). The dosing regimen of rabeprazole chosen thus appears adequate.

A small effect of rabeprazole was observed on the absorption of acalabrutinib from the tablet. The applicant provided a discussion about the potential mechanism(s) behind the increased bioavailability of acalabrutinib with rabeprazole, suggesting a potential effect of CYP3A4 inhibition caused by rabeprazole together with a potential effect of PPIs increasing gastric retention and thus increasing the time of acalabrutinib in the absorption window. Although the exact mechanisms behind the small effects seen on acalabrutinib absorption in the study is unclear, it is agreed with the MAH that the slightly lower Cmax and higher AUC is unlikely to be of clinical significance and that, unlike the approved capsule, the new tablet can be administered with acid reducing agents. Therefore, the proposed wording in Section 4.2 of the SmPC, that unlike the capsules, there are no restrictions in the co-administration of acalabrutinib tablets with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids).

At the request of the CHMP and in order to further highlight the differences between the formulations when co-administered with PPIs, the MAH has added additional warnings in Sections 4.5 and 5.2 of the SmPC.

2.6.4. Conclusions on clinical pharmacology

There are no objections to approval of this line extension from a clinical pharmacology point of view.

2.6.5. Clinical efficacy

No new data were submitted.

2.6.6. Clinical safety

2.6.6.1. Patient exposure

Safety data on single doses in healthy subjects is provided from 30+24 subjects in the relative bioavailability study D8220C00018 and from 66 subjects in the bioequivalence study D8223C00013.

2.6.6.2. Adverse events

Most AEs were of mild grade 1 in both studies and overall in line with the previously observed safety profile for the currently approved capsule. The number of subjects experiencing at least one AE in Study D8220C00018 was 9 (30.0%) and 8 (33.3%) subjects in Parts 1 and 2, respectively, and in Study D8223C00013 was 11 (16.7%) subjects.

In Study D8220C00018 Part 1, 3 subjects experienced moderate AEs (headache in 2 [6.7%] subjects and rash pruritic in 1 [3.3%] subject); all AEs reported in Part 2 were mild in intensity. In Study D8223C00013, 1 subject (1.5%) experienced a Grade 2 (moderate) AE (dizziness). No Grade 3 or higher AEs were reported in either study.

2.6.6.3. Serious adverse events, deaths, and other significant events

No subject in either study reported a fatal or serious AE.

2.6.6.4. Laboratory findings

Elevations of alanine aminotransferase (ALT) were reported in Study D8220C00018 in which one subject discontinued treatment due to a non-serious AE of increased ALT. The event was mild in intensity and resolved.

In addition, 5 subjects had elevated ALT values in study D8220C00018. The onset of increased ALT occurred within 6-14 days after the first treatment with acalabrutinib, were mild in intensity, and resolved within 5-14 days after onset with the exception of one subject who had a slightly elevated but stable ALT at the last follow-up sample.

2.6.6.5. In vitro biomarker test for patient selection for safety

N/A

2.6.6.6. Safety in special populations

N/A

2.6.6.7. Immunological events

N/A

2.6.6.8. Safety related to drug-drug interactions and other interactions

Please refer to separate Pharmacokinetics section.

2.6.6.9. Discontinuation due to adverse events

Two subjects discontinued the IMP due to an AE, in both subjects a non-serious AE.

One subject discontinued IMP due to a rash pruritic which was moderate in intensity, resolved, and not considered related to the IMP by the investigator.

One subject discontinued IMP due to a non-serious AE of increased ALT with onset 6 days after first treatment which was mild in intensity, resolved within 23 days, and was considered related to the IMP by the investigator.

2.6.6.10. Post marketing experience

No new data on safety has been reported.

2.6.7. Discussion on clinical safety

Safety data is provided from two studies on single doses in healthy subjects.

Most of the reported AEs were of mild grade. No Grade 3 or higher AEs were reported. Overall, the safety profile is considered to be in line with previously observed safety profile for the acalabrutinib capsule. No new safety concerns were raised.

Laboratory findings of increased ALT were observed in a number of subjects and one subject discontinued treatment due to a non-serious AE of increased ALT. The event was mild in intensity and

resolved. From this data, no new safety concern is raised with regard to hepatotoxicity. However, it is noted that in a separate procedure an update of the RMP is proposed to include hepatotoxicity as an important potential risk of acalabrutinib. Furthermore, an in-depth analysis of hepatotoxicity events is requested as part of the PSUSA procedure.

From a general safety perspective, the informative value of these data on single-dose administration in healthy individuals is limited. From a comparative perspective, the investigation of the proposed new tablet formulation compared with the capsule, in studies D8220C00018 and D8223C00013, does not suggest an inferior safety profile of the new tablet formulation.

During a time period, both the capsule and tablet formulation of acalabrutinib will be available on the market. Considering the fact that concomitant use of proton pump inhibitors should only be used with the tablets but not with acalabrutinib tablets, there is a potential risk of medication error when both formulations are available on the market at the same time.

The Applicant has described the following measures taken to reduce the risk for medication error:

- Swift transition to the tablet formulation, to minimise the time of access to both formulations
- Provision of information about the switch plan to physicians, pharmacists, and patients
- Independent SmPCs and PLs with different administration instructions for each formulation
- Packaging designed to differentiate between the two formulations
- Routine pharmacovigilance and assessment of medication errors routinely in the PBRER

The above measures were considered sufficient to minimise the potential for medication errors.

2.6.8. Conclusions on clinical safety

In terms of safety, no obvious differences between the formulations are noted.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of Safety Concerns

Important Identified Risks	Haemorrhage with or without association with thrombocytopenia Serious infections with or without association with neutropenia Second primary malignancy Atrial fibrillation/flutter
Important Potential Risks	Cerebrovascular events
Missing Information	Long-term safety Use in patients with moderate to severe cardiac impairment

2.7.2. Pharmacovigilance plan

On-going and planned additional pharmacovigilance activities

Study & Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Study D8220C00008 is a Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with CLL On-going	The primary objective of this study is to evaluate the safety and tolerability of CALQUENCE monotherapy in approximately 600 subjects with TN or R/R CLL who may receive CALQUENCE for 48 cycles of study treatment (28 days per cycle).	Long term safety and SPM	Interim report	30/08/2021
			Final report	31/01/2026
Cohort to Study D8220C00008 is a Phase 3b, multicentre, open-label, single-arm study of CALQUENCE (ACP-196) in subjects with CLL Planned	The primary objective of the cohort is to evaluate the safety of CALQUENCE in patients with moderate to severe cardiac impairment	Moderate and severe cardiac impairment	Protocol amendment submission	30/09/2020
Study ACE-CL-007 and Study ACE-CL-309 Ongoing (both studies not classified as PASS)	The primary objective of these studies is to evaluate the efficacy and safety of CALQUENCE in treatment naive CLL patients (as monotherapy or combination therapy with obinutuzumab) and in relapsed/refractory CLL patients (as monotherapy)	Long Term Safety and SPM	Final report	For study ACE-CL-007 by Q3/2022 For study ACE-CL-309 by Q4/2021

2.7.3. Risk minimisation measures

Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures
Haemorrhage with or without association with thrombocytopenia	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8
Serious infections with or without association with neutropenia	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8
Atrial fibrillation/flutter	**Routine risk minimisation measures**: SmPC section(s) 4.4 and 4.8
Cerebrovascular events	None
Long-term safety	None
Use in patients with moderate to severe cardiac impairment	None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.Product information

2.8.3. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Calquence 100 mg hard capsule. The bridging report submitted by the MAH has been found acceptable.

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Calquence (acalabrutinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The purpose of this submission is to extend the current MA to add a new pharmaceutical form of acalabrutinib (100 mg acalabrutinib maleate film-coated tablet). The proposed clinical use for the tablet will be for the same indications which are currently approved for the 100 mg acalabrutinib capsule.

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3.1.2. Available therapies and unmet medical need

Not relevant for this application.

3.1.3. Main clinical studies

The main clinical studies are the bioequivalence study D8223C0013, and study D8220C00018 to evaluate bioavailability in addition to the effect of PPI and food on the tablet formulation. Both studies were Phase I, open-label, randomized studies.

The applied tablet formulation was compared to the previously approved capsule formulation, in healthy subjects (n = 120 in total).

3.2. Favourable effects

The aim of introducing the tablet formulation, which has higher solubility over the full pH range compared to the approved capsule formulation, is to allow acalabrutinib to be co-administered with gastric acid reducing agents and by that benefit patients by enabling a less complex situation regarding multiple medications and interactions.

Bioequivalence was demonstrated with regards to Cmax and AUC in study D8223C0013 comparing 100 mg tablet with 100 mg capsule formulation under fasting conditions, and similar target occupancy was observed.

A slightly lower Cmax and higher AUC was observed from the tablet formulation in combination with PPI rabeprazole, but these findings are considered unlikely to be of clinical significance, and allow the new tablet formulation to be co-administered with acid reducing agents.

3.3. Uncertainties and limitations about favourable effects

There are no remaining uncertainties or limitations with the tablet formulation that have an impact on the benefit-risk balance.

3.4. Unfavourable effects

From a general safety perspective the informative value of these data on single-dose administration in healthy individuals is limited. From a comparative perspective, the investigation of the proposed new tablet formulation compared with the capsule, in studies D8220C00018 and D8223C00013, does not suggest an inferior safety profile of the new tablet formulation. In terms of safety, no obvious differences between the formulations are noted.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefits of the new tablet formulations are acknowledged.

3.7.2. Balance of benefits and risks

The B/R is considered positive.

3.8. Conclusions

The overall benefit/risk balance of Calquence is positive, subject to the conditions stated in section Recommendations.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Calquence is not similar to Gazyvaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Calquence 100 mg film-coated tablets is favourable in the

following indications:

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

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

The CHMP therefore recommends the extension of the marketing authorisation for Calquence subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with 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.

In addition, CHMP did recommend the variation to the term of the marketing authorisation, concerning the following change:

Variations requested		**Type**	**Annexes affected**
A.6	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	Type IA	I

To change the ATC Code of acalabrutinib from L01XE51 to L01EL02.