EMA/616224/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Parsaclisib Incyte Biosciences Distribution B.V.

International non-proprietary name: parsaclisib

Procedure No. EMEA/H/C/005893/0000

Note

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

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
Akt	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
BOR	best overall response
BTK	Bruton's tyrosine kinase
CL/F	apparent clearance following oral dose administration
CMA	Conditional Marketink Autorisation
CMV	cytomegalovirus
COVID-19	coronavirus 2019
CR	complete response
CRR	complete response rate
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-drug interaction
DEA	differentially expressed analytes
DLBCL	Diffuse large B-cell lymphoma
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
ESMO	European Society for Medical Oncology
EU	European Union
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FAS	full analysis set
FL	Follicular Lymphoma
GVHD	Graft versus host disease
HRQoL	health-related quality of life
HSCT	hemapoietic stem-cell transplant
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	independent ethics committee
iNHL	indolent Non-Hodgkin Lymphoma
IRB	institutional review board
IRC	independent review committee
ITT	Intend to treat
KM	Kaplan-Meier
LBSI	laboratory parameters of special interest

LPLV	Last Patient Last visit
MAIC	Matching adjust indirect comparison
MALT	mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MTD	Maximum tolerated dose
MZL	marginal zone lymphoma
NA	not applicable
NCCN	National Comprehensive Cancer Network
NE	not estimable
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
P-Akt	phosphorylated Akt
PD	pharmacodynamic(s)
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PJP	Pneumocystis jirovecii pneumonia infection
PK	pharmacokinetic(s)
PO	Per os
PR	partial response
PT	preferred term
QD	once daily
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QW	once weekly
R/R MZL	relapsed/refractory marginal zone lymphoma
SAP	statistical analysis plan
SLR	systematic literature review
SMQ	Standardized MedDRA Queries
SOC	system organ class
STD	standard deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
Vz/F	apparent volume of distribution during terminal phase
WHO	World Health Organization

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for parsaclisib, an orphan medicinal product, in monotherapy for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL), is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (redacted from published report).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions (redacted from published report).

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Clinical-General

- The justification of the intended maintenance dose of 2.5mg QD. Missing PK data should be addressed, analysis of late-onset AEs is requested and the selection of the intended maintenance should be further justified based on data on early phase and pivotal studies;

Clinical-Conditional marketing authorization

- The justification of the requirement for a CMA: a) The applicant is requested to justify the major therapeutic advantage over existing therapies. b) The B/R is currently negative.

Clinical-Benefice/risk

- Single arm trials are not able to isolate the safety profile of an investigational agent. Given the known safety profile of the drug class, it is questionable whether a conclusion that benefits outweigh risks can be reach based on data from a single arm trial.;

Clinical-Efficacy

- The clarification in the wording of the indication which should specified that patients must have received at least 1 prior treatment including one anti-CD20 based therapy as required in the pivotal study. The indication is proposed to be reworded as follow:

"*TRADENAME as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have previously received at least one prior anti-CD20-based therapy*".

Quality

INCB055312 should be designated as starting material as it significantly contributes to the final active substance structure. Relevant information on this starting material (supplier details and overview of synthesis) should be provided in the dossier (MO);

- The submission of process validation data for commercial product launch and continuous process verification to validate process changes over the product lifecycle is expected for this submission (MO);

- The selection of the QC dissolution method is not regarded as adequate (MO);

NAS Assessment

- In order to fully justify that parsaclisib can be considered a new active substance, a more extensive discussion of all relevant aspects in accordance with the CHMP Reflection paper EMA/CHMP/QWP/104223/2015 should be provided (MO).

1.1. Questions to be posed to additional experts

N/A

1.2. Inspection issues

1.2.1. GMP inspection(s)

All sites involved in the manufacturing, quality control, batch release and packaging have been inspected by the relevant Competent Authorities. The manufacturing sites comply with European GMP.

1.2.2. GCP inspection

Not Applicable

1.3. New active substance status

Based on the review of the data, it is considered that the active substance parsaclisib (as hydrochloride) contained in the medicinal product Parsaclisib Incyte Biosciences Distribution B.V. could be qualified as a new active substance provided that satisfactory responses are given to the concerns (MO) as detailed in the List of Questions (removed from published report).

1.4. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is "in monotherapy for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL)".

2.1.2. Epidemiology and risk factors

According to the European Cancer Information System (ECIS), about 97,391 cases of NHL were newly diagnosed in the EU-28 in 2018. It can be estimated that about 8% of the NHL new cases would be MZL cases, in line with what is reported in literature (Bron et al 2014; Teixeira Mendes and Wotherspoon 2017). This results in an estimated incidence of 7,791 new MZL cases in 2018. A 10-year mean disease duration was determined, based on the Olszewski and Castillo analysis of the survival of patients with MZL (Olszewski and Castillo 2013). The Eurostat estimate was applied for the EU-28 population (512.7 million inhabitants). Based on this, the current prevalence of MZL in the EU can be estimated at approximatively 1.5 per 10,000 people.

The latest WHO lymphoma classification identifies the following 3 subtypes of MZL according to the involved site and characteristic molecular findings (Swerdlow et al 2016):

- Extranodal MZL (EMZL) of the mucosa-associated lymphoid tissue (MALT), which is the most common subtype, accounting for nearly 70% of all MZL.

- Splenic marginal zone lymphoma (SMZL) which represents about 20% of cases.

- Nodal MZL (NMZL) which represents approximately 10% of cases.

The average age at diagnosis is 60 years according to the lymphoma research foundation (2017) and it is slightly more common in women than in men. However, based on data from the US SEER-18 program from 2001-2017, incidence rates were slightly higher in men for SMZL and NMZL, but similar for EMZL (Cerhan and Habermann, 2021).

The strongest associations with MZL include Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis, immune thrombocytopenic purpura and autoimmune haemolytic anaemia. Several infectious agents are also known or suspected to cause MZL. Increasing evidence suggests that EMZL may be related to chronic immune reactions caused by bacterial (i.e. *Helicobacter pylori*-induced chronic gastritis and *Campylobacter psittaci*), viral (i.e. HCV infection), or autoimmune stimuli (i.e. history of Sjögren's syndrome) (Ambrosetti et al 2004; Ramos-Casals et al 2007).

2.1.3. Biologic features

Marginal zone B-cell lymphoma is a heterogeneous group of indolent B-cell lymphomas that originate from memory B lymphocytes normally present in a distinct micro-anatomic compartment called the "marginal zone" of the secondary lymphoid follicles (Zinzani 2012). Aberrant signal transduction via the PI3K pathway has been observed in malignant B-lymphocytes, agents that inhibit this signaling pathway, and particularly PI3Kδ.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Nodal MZL is a primary nodal lymphoma in the absence of previous or concurrent involvement of any extranodal site. The 5-year OS is 60% to 70% and the 5-year event-free survival approximately of 30%.

Splenic MZL grows in a marginal zone pattern in the spleen; the median OS is > 10 years.

Symptoms related to cytopenia, massive splenomegaly (left upper abdominal discomfort and early satiety resulting in weight loss), or bulky lymph node enlargement may be present at diagnosis in patients with splenic or nodal MZL or may arise during follow-up, as part of progressive disease.

Extranodal MZL differs from splenic and nodal MZL due in part to its involvement in epithelial tissues, including the stomach, lungs, salivary glands, small bowel, thyroid, and lachrymal glands.

The clinical findings and presenting symptoms of extranodal MZL are generally related to the primary location. The stomach is the most common site of localization, accounting for approximately one-third of cases of extranodal MZL (Zinzani 2012). Patients with gastric MZLs present with epigastric pain or other dyspeptic symptoms, weight loss, or gastrointestinal bleeding (Rossi, 2022). The average 5-year overall survival (OS) is more than 85% in most series.

There are no diagnostic biomarkers for MZLs, and they may be confused with other indolent B-cell lymphomas. A proper diagnosis of MZL can be established only after an extensive pathological workup and the integration of clinical, morphologic, phenotypic, cytogenetic, and molecular features.

The diagnosis of **nodal MZL** is based on evaluation of nodal biopsy in the context of the clinical presentation. A definitive diagnosis of **splenic MZL** relies on histologic evaluation of a splenic specimen However, splenectomy is not frequently performed for therapeutic purposes, which prompts the use of blood and bone marrow findings to indirectly establish the diagnosis of splenic MZL in patients with clinical splenomegaly (Rossi et al. 2022).

If **extranodal MZL** is suspected, clinicians should aim to obtain the largest biopsy specimen possible, since small specimens may not provide adequate tissue. Imaging can identify sites of extranodal MZL involvement and guide a diagnostic biopsy.

The stage of splenic and nodal MZLs is determined with the Lugano modifications of the Ann Arbor system. There is controversy over the best method for staging gastric MZLs. The most recent staging systems recommend endoscopy with multiple biopsy specimens from the stomach, duodenum, and gastroesophageal junction and from each site with an abnormal appearance (Rossi et al. 2022).

2.1.5. Management

Although outcomes are favorable for patients with MZL, advanced-stage disease remains incurable, and the relapsing nature of indolent lymphomas requires continued retreatment.

No treatment in EU has a specific indication in relapse or refractory MZL. Bendamustine is authorized in some European countries in indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen (i.e. refractory iNHL).

However, ESMO and NCCN recommendations for relapse/refractory MZL, in case systemic treatment is required, are preferably chemoimmunotherapy.

According to EMSO guideline, chemoimmunotherapy can be repeated after long initial remissions (≥24 months) and autologous transplantation may be considered in fit patients with clinically aggressive relapse. In other cases, an alternate chemoimmunotherapy regimen can be used.

According to NCCN guideline, the preferred regimens for second line and subsequent therapy are an anti-CD20 mAb (rituximab or obinutuzumab) in association with bendamustine, CHOP, CVP, lenalidomide, or ibrutinib monotherapy. In addition, PI3K inhibitors (copanlisib, duvelisib, idelalisib) are recommended after 2 prior therapies with the exception of umbralisib which is recommended after at least one prior anti-CD20 mAb based regimen. It should be noted that despite NCCN recommendations, the only PI3K authorized in MZL in the US is umbralisib whose B/R is currently under reassessment by the FDA due to a safety signal (increased risk of death) in an ongoing clinical trial in CLL.

2.2. About the product

Parsaclisib is an antineoplastic agent, next-generation PI3Kδ inhibitor, with approximately 20,000-fold selectivity over the other PI3K family members (PI3Kα, PI3Kβ, and PI3Kγ).

Class I PI3Ks catalyze the phosphorylation of phosphatidylinositol-4,5-bisphosphate, giving rise to phosphatidylinositol-3,4,5-trisphosphate, which functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion, and migration. PI3Kδ is the main isozyme responsible for the activation of the PI3K pathway in B-cell biology, functioning as a downstream mediator of the B-cell receptor (Shin et al 2020). Parsaclisib directly blocks PI3K signalling-mediated cell proliferation in normal and malignant B-cells and indirectly controls tumor growth by lessening immunosuppression through regulatory T-cell inhibition.

The applicant claimed an indication in monotherapy for the treatment of adult patients with relapsed or refractory marginal zone lymphoma at the recommended dose of 20 mg once daily for 8 weeks followed by 2.5 mg once daily. The treatment should be continued until disease progression or unacceptable toxicity.

2.3. The development programme/compliance with guidance/scientific advice

The main source of data for this application is provided by the results of the pivotal phase II clinical trial INCB 50465-204 (CITADEL-204) which is an ongoing, open-label study in subjects with relapse or refractory MZL, with or without prior exposure to a BTK inhibitor. Supportive data are provided by a phase 1/2 dose escalation study in subjects with previously treated B-cell malignancies, a systematic literature review (SLR) followed by a matching-adjusted indirect comparison (MAIC) and an ongoing phase 2 open label study in patients with relapse or refractory follicular lymphoma.

Scientific advices (SA) for parsaclisib were provided by the CHMP, in December 2018 (EMA/CHMP/SAWP/852274/2018), in September 2019 (EMA/CHMP/SAWP/493962/2019) and in November 2020 (EMA/CHMP/SAWP/582619/2020). The latter concerned in particular the proposed phase III study (INCB 50465-302) to evaluate the efficacy and safety of parsaclisib + an anti-CD20 mAb vs an anti-CD20 mAb alone in adult subjects with R/R iNHL, including R/R FL and R/R MZL (questions on population, comparator arm, endpoints, suitability for a CMA in R/R MZL were addressed).

While the proposed primary endpoint (PFS assessed by IRC) and the use of Lugano criteria were agreed, the CHMP reminded the applicant that "Recent EU regulatory precedent is noted for Revlimid, where both FL and MZL populations were enrolled in the AUGMENT study, total of 63 patients with MZL, yet a PFS benefit was not specifically demonstrated for the MZL subpopulation (EMA/CHMP/693880/2019). Therefore despite acknowledgements that similar treatment strategies may be used in the R/R setting for both diseases, an overall benefit for the ITT full population would not obviate the requirement to demonstrate benefit in MZL subgroup alone".

Further concerns regarding the comparator arm were expressed as an anti-CD20 mAb monotherapy is only recommended as a preferred option for elderly or infirm patients according to NCCN guidelines whereas the preferred regimen for MZL in R/R setting for second line or subsequent therapy are bendamustine + anti-CD20 mAb, Ibrutinib, R2, RCHOP or RCVP. Furthermore, ESMO Guidelines consider rituximab monotherapy in relapsed disease for *'symptomatic cases with low tumour burden'*. Moreover, if frail older patients are the target population to be enrolled, there is a significant concern for toxicity in the experimental arm with parsaclisib.

The concerns about the control arm and the population for the proposed confirmatory phase III study (CITADEL-204) in the context of the CMA have not been addressed by the applicant in this submission

2.4. General comments on compliance with GMP, GLP, GCP

<u>GCP aspects</u>

The applicant states that clinical studies included in this marketing application were performed in compliance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, Directive 2001/20/EC, and other applicable local ethical and legal requirements.

No issues have been identified at this time of the assessment

GLP aspects

The pivotal toxicology and safety pharmacology studies were conducted in accordance with GLP regulations and ICH guidelines, i.e. supported by an adequate quality assurance system including in study audits. No reasons to trigger a GLP inspection were observed. Some clarifications are requested to complete missing information in two study reports.

For study T13-07-05, a clarification is requested regarding the date of dosing administration indicated performed on 6th of August, 2013 (CTP p111) compared to date of formulations indicated as prepared on 7th of August 2013 (p67, p79, ..). For the same study T-13-07-05, the validation report for formulation analysis is mentioned as a draft report (p3). No information is submitted regarding the edition of a finalized version and particularly if modifications were done between draft and final versions. Data regarding the stability of the test item in the rat plasma (T13-07-05) and dog plasma (T13-07-04) from sampling to analysis were not indicated in the final report (**OC**).

Drug Substance:

A QP decalaration is provided by Incyte Biosciences Distribution B.V., Paasheuvelweg 25, 1105 BP Amsterdam, Netherlands dated 6 December 2021.

Drug product:

Appropriate GMP status of manufacturers listed in CTD module 3.2.P.3 is documented.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

The applicant plans to conduct a confirmatory phase 3, double blind, randomized, placebo controlled multicentre study (Study INCB 50465-302) in patients with R/R MZL in the same clinical setting than the pivotal phase 2 study for this application. This study is designed to evaluate the efficacy and safety of the combination of parsaclisib plus investigator's choice of either rituximab or obinutuzumab in participants with R/R FL and R/R MZL. The submission of clinical trial applications will be initiated in Europe in Q1 2022 and the LPLV is targeted for Q3-2031 with an interim CSR at Q3 2027.

- Unmet medical needs will be addressed, as patients with MZL commonly relapse after first line treatment, and current treatment recommendations are still not satisfactory as they are based

on evidence in other indolent subtypes, primarily FL. Furthermore, any treatment recommendations for R/R MZL treatment are supported by minimal to no data specific to the MZL patient population. Importantly, none of the medicinal products recommended for the treatment of patients with R/R MZL is specifically approved for this indication:

  - The anti-CD20 antibody rituximab is indicated for the treatment of follicular lymphoma
  - The alkylating agent bendamustine, carries a decentralized approval in some EU countries for the treatment of patients with indolent NHL after disease progression during or within six months of treatment with rituximab or rituximab-containing treatment. The approval of bendamustine was based on pivotal data primarily in patients with R/R FL.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Patients with R/R MZL have a high unmet medical need and only limited therapeutic options. All products in clinical use are not formally approved for the treatment of R/R MZL in the EU. According to the applicant, parsaclisib has an acceptable safety profile with adverse events expected for this class of compounds (PI3K inhibitors) and are clinically manageable. A CMA would allow patients with R/R MZL to have access to parsaclisib much sooner than the time when the drug could eventually be made available after submission of the Phase 3 data from the proposed confirmatory study

2.5.3. Marketing authorisation under exceptional circumstances

Not Applicable.

2.5.4. New active substance status

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

2.5.5. Orphan designation

Parsaclisib was designated as an orphan medicinal product EU/3/19/2185 on 25 July 2019 in the following condition: Treatment of marginal zone lymphoma. The applicant provided a copy of the Commission Decision on the designation as an orphan medicinal product.

2.5.6. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication

2.5.7. Information on paediatric requirements

Pursuant to Article 13 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-002696-PIP01-19 on the granting of a product-specific waiver on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as oral immediate release tablet containing 1 mg, 2.5 mg, 5 mg, 10 mg, or 20 mg of parsaclisib hydrochloride as active substance.

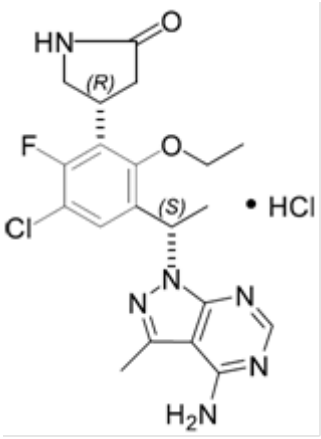
The product is available in copolymer PVC blister with an aluminium foil lidding film.

3.1.2. Active Substance

3.1.2.1. General Information

The drug substance (DS) is parsaclisib (INN) as hydrochloride.

Structural formula:



Molecular formula: $C_{20}H_{23}Cl_2FN_6O_2$ as HCl salt; $C_{20}H_{22}ClFN_6O_2$ as free base.

Relative molecular mass: 469.34 Da as HCl salt; 432.88 Da as free base.

Parsaclisib hydrochloride possesses two chiral centers. The drug substance exhibits polymorphism.

Parsaclisib hydrochloride is classified as a BCS class 3 compound based on the aqueous solubility (over a pH range of 1-8).

3.1.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Name and address of the facilities responsible for drug substance manufacture, testing, storage, and packaging are presented in the dossier.

However, information on intermediate manufacturers (if sourced from a third party) should be included in this section. A question in this regard was raised during the assessment.

GMP compliance for the drug substance sites is confirmed.

The proposed manufacturing process of parsaclisib hydrochloride drug substance is described and a synthesis scheme and a flow chart are provided in the dossier. IPCs with respective acceptance criteria and analytical method descriptions are listed. Information regarding critical process parameters,

production equipment, quantities of raw materials, yields, reaction conditions (e.g. temperatures) is presented. Manufacturers, synthetic route, specification, analytical methods, analytical method validation data, impurity profile and CoA are presented for the proposed starting materials (SM). For each key material, specifications, batch analytical data, description of the analytical methods and chromatograms are presented. Solvents and reagents used in the manufacture of parsaclisib hydrochloride drug substance are listed and specifications are presented. Specifications, analytical method descriptions, analytical method validation details, batch analysis data, and information on impurity profile, reprocessing/reworking and stability of the proposed intermediates are also presented. IPCs (including test description, acceptance criteria, and analytical method) are listed tabularly for each manufacturing step. However, during the assessment, a major objection was raised regarding designation of the starting materials and several other concerns regarding the drug substance manufacturing process were identified.

The drug substance is non-sterile. Accordingly, no process validation and/or evaluation data need to be submitted in the course of the MA application.

During development, two different synthetic processes (process 1 and process 2) have been used to manufacture parsaclisib hydrochloride drug substance. Process 1 was utilized for manufacture of parsaclisib hydrochloride drug substance at the early stage of development, including animal toxicology studies, the primary reference standard batches, and earlier cGMP batches for initial human clinical studies. Process 2 is the proposed commercial process.

Characterisation

DS structure has been elucidated applying standard methods. Reference standard batches tested were manufactured according to process 1. A question has been raised during the assessment whether the changes between process 1 and commercial process 2 have an impact on DS structure and whether the presented data are considered representative for the commercial DS.

A comprehensive discussion on actual and potential impurities is provided. Organic, inorganic impurities, residual solvents, genotoxic impurities, nitrosamine impurities of starting materials, key raw materials, intermediates, and final DS are addressed in the dossier (including reagents, solvents, catalysts, by-products and degradations products). Nevertheless, several questions were raised during the assessment.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The drug substance specifications are presented in the dossier. The set parameters and specified limits are mostly acceptable for the control of the drug substance (recommendations of Ph. Eur. monograph 2034 are followed). Nevertheless, during the assessment, several questions were raised.

Analytical procedures and reference standards

Analytical procedures are described in sufficient detail. Validation data have been presented. However, several questions were raised during the assessment. The reference standards are sufficiently qualified.

Batch analysis

Reported batch data demonstrate similar quality of pilot batches (used in clinical studies) and commercial batches (irrespective of manufacturer). All relevant parameters are tested and comply to acceptance criteria set. Commercial size batches (manufactured according to synthetic process 2) comply with the DS specification presented in section 3.2.S.4.1 of the eCTD Module 3. Overall, clinical batches (manufactured according to synthetic process 1 or 2) and primary stability batches (manufactured according to synthetic process 2) are considered representative for commercial DS (manufactured according to synthetic process 2). However, it is not clear from presented data in eCTD section 3.2.S.4.4 what manufacturer of SM has been involved in the production of various analytical batches. Clarification

in this regard and batch analysis results of the final drug substance obtained from all declared SM manufacturers that would confirm that the impurity profiles are similar, were requested during the assessment.

Container closure

The components of the container closure system (CCS) are listed: double PE bags (with plastic ties), with desiccant placed between the inner and outer bags, and between outer bag and HDPE drum (with lid). A specification for the primary packaging material (PE Bags) is provided. Compliance to Commission Directive 10/2011/EU has been presented for the PE resin. However, several issues were raised during the assessment.

3.1.2.4. Stability

Stability studies have been performed according to ICH recommendations on 3 "primary stability batches" (pilot scale process 2 batches that were further manufactured to the primary drug product stability lots) and 2 "supportive stability" batches (manufactured by process 1 and process 2) each under long-term and accelerated conditions, respectively.

The container closure system applied for stability studies consists of double polyethylene (PE) bags in an HDPE container with desiccant (as described in eCTD section 3.2.S.6).

A summary of the stress testing studies (i.e. acid, basic, oxidative, light, and heat stress testing) including treatment conditions and discussion of results have been presented tabularly.

Stress studies for DS in solution indicate that under acid or basic conditions degradants are formed.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Parsaclisib drug product is supplied as immediate release uncoated tablets for oral administration in strengths of 1 mg, 2.5 mg, 5 mg, 10 mg and 20 mg. Qualitative and quantitative compositions of the drug product are included in the dossier.

Description of the tablets, tabulated composition and a brief description of the container closure are given by the applicant.

A QTTP is defined and CQAs listed are considered to be critical for efficacy and safety of the commercial product at the same level as in clinical studies. During the assessment, several issues were raised concerning the QTTP, impurities formation in the context of the water level specified for the product, and the control of polymorphism.

For solubility and permeability, the substance is considered a BCS class III substance by the applicant and due to in vivo behaviour a class I in BDDCS. The drug substance is slightly hygroscopic. For formulation development, in clinical trials the same formulation as depicted in eCTD section 3.2.P.1 was used, with the exemption of differences in shape, debossing, and hardness. No 10 mg strength was used for clinical trials.

For the dissolution method development, data on all strengths but 10 mg are provided. Sink conditions are proven by calculation. However, during the assessment, a major objection was raised concerning the dissolution method.

For the control of elemental impurities, a control strategy along option 2b of ICH Q3D is conducted. The nitrosamine risk assessment evaluated the drug substance, excipients, manufacturing process, and container closure system. However, a question was raised during the assessment regarding the risk assessment and control strategy of elemental impurities.

Manufacturing process development covers data and changes from the clinical up to the commercial manufacturing process. Data are generated by DOE to bridge process inputs to quality attributes. Furthermore, the development of the control strategy is underlined. Blend uniformity and stratified content uniformity testing will be conducted during validation of the manufacturing process only. Several questions were raised during the assessment, concerning manufacturing process development. Development of container closure is sufficiently described. The heat seal lacquer conforms to the Council of Europe Resolution AP (2004) and (EU) No.10/2011. Chapters microbiological attributes and compatibility are acceptable.

3.1.3.2. Manufacture of the product and process controls

Manufacturers are correctly tabulated and batch formula for all strengths are given in the dossier. Appropriate GMP status of manufacturers listed in eCTD section 3.2.P.3 is provided.

Description and flow chart of the manufacturing process are depicted comprehensively and controls of critical steps and intermediates are covered by the information provided. No intermediates are defined for the drug product manufacturing process. Bulk holding times have not been defined by the applicant. A question in this regard has been raised during the assessment as such confirmation is needed for setting the start of shelf-life following CPMP/QWP/072/96 guideline.

For process validation, only a validation master plan is provided, but no validation report. The applicant suggests a Continuous Process Verification (CPV), which is as such acceptable. Nevertheless, during the assessment, a major objection was raised, requesting the submission of process validation data (which can in principle follow proposed stage 2 – PPQ) for commercial product launch.

Excipients used for drug product formulation are of compendial grade and their control is set accordingly. A request for submission of specifications for excipients as set by the applicant was raised during the assessment.

3.1.3.3. Product specification, analytical procedures, batch analysis

Regarding the specifications, all parameters expected for this type of product are listed. However, several issues regarding total impurities, description of the drug product and assay limits were raised during the assessment.

Description of analytical methods is comprehensive. For validation of analytical methods, assay and impurities method (HPLC) are covered by all parameters following ICH Q2. Concerning the HPLC method used for dissolution, the applicant was requested during the assessment to unambiguously demonstrate the specificity of the method.

Adequate batch data are included in the dossier. All values are well within limits set for the parameters. Limits for degradation products are found appropriately justified.

Documentation of reference standards is acceptable. Several issues concerning the container closure documentation were identified during the assessment.

3.1.3.4. Stability of the product

Available stability data are provided in the dossier, covering both long-term and accelerated conditions. Based on the presented data, the proposed drug product shelf life is not acceptable and questions were raised during the assessment. Photostability data comply with ICH Q1B and no special packaging considerations are required. Freeze-thaw experiments show no impact on the quality of the drug product.

3.1.3.5. Post approval change management protocol(s)

N/A

3.1.3.6. Adventitious agents

N/A

3.1.3.7. GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The proposed drug product is not acceptable from a quality point of view as several questions (including major objections) have been raised.

3.2. Non-clinical aspects

3.2.1. Introduction

To support the proposed treatment of adult patients with relapsed or refractory marginal zone lymphoma, studies were conducted to characterize the in vitro properties of parsaclisib, a novel, potent, and selective inhibitor of PI3Kδ. Its activity against and selectivity for Class I PI3K isoforms were first assessed with biochemical enzyme assays and then further evaluated with the PI3K isoform specific signaling assays in DLBCL, MCL, ALL and AML cells. Parsaclisib was evaluated in two murin model for haematological malignancy (Rec-1 xenograft model of MCL and Pfeiffer xenograft model of DLBCL). Parsaclisib was also evaluated in a standard safety pharmacology core battery studies according the relevant recommendations (ICH guideline S7). The pharmacokinetic profile of parsaclisib was extensively studied in vitro as well as in non-clinical species using Sprague-Dawley rats, beagle dogs and cynomolgus monkeys. Parsaclisib has been evaluated in nonclinical toxicology studies that meet requirements as defined in ICH S9. Repeat-dose toxicity studies included up to 6 months in duration in rats and up to 9 months in dogs. The potential genetic toxicity of parsaclisib was evaluated in a bacterial reverse mutation assay, in vitro chromosomal aberrations assay in human peripheral blood lymphocytes, and in vivo micronucleus study in rats. Potential embryofetal developmental toxicity was evaluated in rats and rabbits, and a fertility and early embryonic development study was conducted in rats. Phototoxicity was investigated in an in vitro neutral red uptake study in BALB/c 3T3 mouse fibroblasts. Starting materials, potential process impurities, and process intermediates were evaluated in silico for potential mutagenicity using QSAR software. All pivotal nonclinical studies were conducted according the GLP requirements.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

In vitro

Studies were conducted to characterize the in vitro properties of parsaclisib, a novel, potent, and selective inhibitor of PI3Kδ. Its activity against and selectivity for Class I PI3K isoforms were first assessed with biochemical enzyme assays and then further evaluated with the PI3K isoform specific signaling assays in cells. The cellular activity of INCB050465 against PI3Kδ function was extensively

investigated with assays measuring biological consequences of PI3Kδ inhibition in primary leukocytes from different species and in hematological tumor cell lines. In biochemical assay (INCYTE-IN VITRO-13.04.2), parsaclisib was a potent inhibitor of PI3Kδ (IC_{50} = 1 nM), with approximately 20000-fold selectivity for PI3Kα, PI3Kβ, PI3Kγ, and 57 other kinases. This inhibition of PI3Kδ is confirmed in cellular assay with similar IC_{50}. The compound was not active against PI3Kα- or PI3Kγ-mediated signaling in cells. However, parsaclisib showed modest activity (IC_{50} ~30-100 nM) in a PI3Kβ-specific signaling assay, suggesting > 30-fold selectivity over PI3Kβ versus PI3Kδ. Therefore, the high selectivity of parsaclisib for PI3Kδ claimed by the applicant is questionable. Indeed, the unbound Cmax value of 141 nM at the MRHD (maximum recommended human dose, 20 mg once daily) is 141-fold higher than IC_{50} values of PI3Kδ inhibition but also 1.4- to 4.7-fold higher than the IC_{50} values of PI3Kβ inhibition, thus MRHD could inhibited PI3Kδ and PI3Kβ-specific signalling pathways. The applicant should discuss this point and modify the SmPC section 5.1, subsection mechanism of action in order to reflect the inhibitor activity of PI3Kδ and PI3Kβ (**OC**).

Parsaclisib has potently inhibited human CD19+B cells proliferation induced by immune and inflammatory stimuli with an IC_{50} of 0.21 nM. As requested in the scientific advice (EMA/CHMP/SAWP/493962/2019), this applicant has submitted measurement of inhibitory activity of parsaclisib against rat and dog PI3Kδ kinase. Indeed, rat and dog cells were tested and the anti-proliferative effects in B cell was similar to human (IC_{50} = 1.19 nM, 1.72 nM, respectively). Animal exposure at all levels measured in pivotal studies exceeded the determined IC_{50}. Therefore, the two species used in pivotal safety studies could be considered as pharmacological species. Mouse cells were also tested and the anti-proliferative effects in B cell was similar to human (IC_{50} = 0.37 nM).

The impact on cell type other than B cells was evaluated in vitro. PI3Kδ is known to have a role in CD28 costimulation during mouse T cell activation and is known to be required for the differentiation of T cell to Th17, Th1 and Th2 cells. However, from *in vitro* study, it was shown that parsaclisib has a modest inhibition against CD-28-induced proliferation of human T cells (IC_{50} = 96nM) but not on anti-CD3 and CD28 dual activation (IC_{50} > 330 nM). Moreover, parsaclisib has an impact on T-cell function by inhibition of the production of IL17, IFNγ, and IL13 by naïve T cells cultured under Th17 th1 and TH2 differentiation conditions (IC_{50} = 0.90, 0.73 and 0.26 nM respectively).

The potent inhibitory activity of parsaclisib was tested on 19 cells lines from different human hematological malignancies. The results were shown that parsaclisib has an activity on DLBCL, MCL, ALL and AML cell lines but not on multiple myeloma cell lines, burkitt's lymphoma calls or on panel of non-B cell origins (including solid tumors). The PI3K signal pathway induce the activation of AKt than FOXO (a transcription factor) implicated in the cellular proliferation and cell function. The *in vitro* assay (Western blot) has shown that the inhibition of PI3K by parsaclisib has induced an inhibition of phosphorylation (and activation) of AKt and FOXO in 3 cells lines (Pfeiffer, SUHL5 and WSU-NHL) with dose-dependent manner. These results have demonstrated how parsaclisib conducted to the inhibition of proliferation of B cells by inhibition of PI3K and Akt pathways. In human whole blood to which a cell line was added (SU-HDL-5 cells), levels of pAkt were measured. An inhibition of Akt phosphorylation was observed by parsaclisib with an IC_{50} of 4nM. Although, parsaclisib was not tested in MZL cell lines (e.g. VL51) the results obtained with other haematological malignancies cell lines (in particular MCP cell lines, also an indolent lymphoma) could be considered relevant for the intended MZL indication.

In vivo

Parsaclisib was evaluated in two murin model for haematological malignancy (Rec-1 xenograft model of MCL and Pfeiffer xenograft model of DLBCL). Parsaclisib was not assessed in MZL model but MCL mice model (Rec-1 xenograft model) which will also represent an indolent lymphoma could be considered acceptable for this apllication. The second model, DLBCL mice model (aggressive lymphoma) could be considered as supportive data.

In the Rec-1 xenograft model of MCL, mice were treated twice daily at 0.1, 1 and 10mg/kg during 12 days, the inhibition of tumor growth by 23%, 59% and 73% was observed at 0.1, 1 and 10 mg/kg respectively. Statically significant inhibition was observed at dose levels ≥ 1 mg/kg/d.

In Pfeiffer xenograft model of DLBCL, three experiments were performed, the activity was evaluated by the capacity to inhibit growth tumor and the pAKt level was measured reflected the inhibition of PI3k. In the first experiment, parsaclisib was administrated twice daily at 0.3, 1, 3 and 10 mg/kg during 14 days (10 females). A decrease of the tumor volume was observed with increasing dose (by 22% 24% 36 % and 58% respectively) but only treatment with 10 mg/kg showed a statistically significant inhibition. A decrease of pAKt levels ≥ 1 mg/kg were observed (4%, 25% and 30% at 1, 3, and 10 mg/kg). It is unclear if this diminution is statistically significant. Plasma concentrations were measured. All exposure were above IC_{50} during the measured interval (15h postdose) and exposure after dose administrations ≥ 1 mg/kg/d were above IC_{90} for 10h post-dose.

In a second experiment, mice were treated twice daily at 0.1,1 and 10 mg/kg BID during 14 days, the inhibition of tumor growth was observed by 30, 57 and 52% with increasing dose. Treatment with 1 and 10 mg/kg showed a statistically significant inhibition. The observed response was not dose-dependent, indeed a slightly higher response was observed after administration of 1 mg/kg parsaclisib than after 10 mg/kg/d. Exposure after dose administrations ≥ 1 mg/kg/d were above IC_{90} for 8h post-dose. In the third experiment, mice were treated once at 0.1,1 and 10 and 30 mg/kg. A statistically significant decrease in pAKT (Ser473) levels was observed at 10 mg/kg (30%) and 30 mg/kg (32%).

To summarize, in the Rec-1 xenograft model of MCL, statically significant inhibition of the tumor volume was observed at dose levels ≥ 1 mg/kg/d. In Pfeiffer xenograft model of DLBCL, the three experiment performed showed disparate results in terms of dose-dependency (tumor volume diminution) and statistically significance (pAKT levels). Indeed, it is unclear if 1 mg/kg or 10 mg/kg was the minimal effective dose in this model. The applicant should discus this point and explain which dose is selected to achieve the minimal PD effect in MZL indication (**OC**).

3.2.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamics were conducted to evaluate the potential inhibition on several receptors, enzymes or ion channels. Parsaclisib showed no cross reactivity against a panels of 70 receptors, ion channels, transporters and enzymes at 0.1 and 1.0 µM. Moreover, two in vitro kinase assays screen were performed including 55 and 192 kinases and parsaclisib demonstrated no significant inhibition (< 30% inhibition) at 100 nM. To conclude, based on the *in vitro* results provided, no secondary pharmacodynamic action is expected at MHRD. The applicant´s conclusions are acceptable.

3.2.2.3. Safety pharmacology programme

Parsaclisib was also evaluated in a safety pharmacology core battery studies at doses up to 100 mg/kg: CNS and respiratory studies in the rat, a cardiovascular study in telemeterized conscious dogs, and in an *in vitro* hERG channel assay. These studies were conducted in accordance with ICH S7A. There were no adverse effect observed on any vital functions. Only non-adverse findings on respiratory and CV functions. A non-adverse higher pulse pressure (7.2%) was observe in male dogs at 15 mg/kg. A non-adverse lower respiratory frequency (up to 20.9%) in rats at 100 mg/kg and non-adverse lower tidal volume (up to 8.5%) and non-adverse lower minute volume (up to 17.5%) following doses of 30 and 100 mg/kg. As the respiratory changes were considered parsaclisib-related, the applicant should clarify the long-term effect of parsaclisib on the respiratory frequency and minute volume (**OC**). A statistically significant inhibition of hERG channel was observed and the IC_{50} was determined at 188 µM which is approximately 1300-fold higher than unbound steady state Cmax after clinical dose of 20 mg (141 nM unbound, according values mentioned in the SmPC section 5.2). Therefore, parsaclisib is not expected

to cause any effect on ventricular repolarization via hERG inhibition. The studies are well described in the RMP Part II: Module SII and in the SmPC section 5.3.

However, the applicant has not followed the non-clinical advice given in 2019 (EMA/CHMP/SAWP/493962/2019). The CHMP was requested to discuss whether parsaclisib has the potential to induce Torsades de Pointes cardiac arrhythmias via an inhibition of cardiac potassium currents (IKr, IKs) and an increase of the cardiac late sodium current. Indeed, it was highlighted that recently, an inhibition of the phosphoinositide 3-kinase (PI3K) signalling pathway has been identified as a potential cause of drug-induced long QT syndrome via an inhibition of cardiac potassium currents (IKr, IKs) and an increase of the cardiac late sodium current (Lu et al. 2012, Yang et al. 2014; reviews in Ballou et al. 2015, Cohen et al. 2017). The applicant need to clarify this point (**OC**).

3.2.2.4. Pharmacodynamic drug interactions

There were no nonclinical pharmacodynamic drug interaction studies conducted.

3.2.3. Pharmacokinetics

The pharmacokinetic profile of parsaclisib was extensively studied *in vitro* as well as in non-clinical species using Sprague-Dawley rats, beagle dogs and cynomolgus monkeys. Toxicokinetic data were generated in rats (up to 6 months), dogs (up to 9 months) and rabbits (EFD). The distribution was determined via quantitative whole-body autoradiography (QWBA) and a study to determine the distribution of parsaclisib into brain and cerebrospinal fluid (CSF) was conducted in rats. The excretion mass balance of ^{14}C-parsaclisib was determined in rats, dogs and humans. The metabolism of parsaclisib was characterized using *in vitro* methods and from *in vivo* samples across nonclinical species and humans. The tissue distribution of ^{14}C-parsaclisib was determined in non-pigmented and pigmented rats. In addition, the following ADME studies were conducted: permeability and efflux in Caco-2 cells, *in vitro* studies to access interactions with drug transporters and CYPs, protein binding, and metabolism studies by CYPs.

The used analysis methods were adequately validated.

Absorption

In vitro permeability for parsaclisib was low, with transporter studies suggesting efflux via P-gp. Following single oral administration, parsaclisib was rapidly absorbed with Tmax values of 0.3h (rat), 0.4h (dog) to 2.5h (monkey). The bioavailability of parsaclisib was complete in dogs (100%), and high in monkeys (79%) and rats (74%). Following repeated oral administration, TK analysis showed that parsaclisib was rapidly absorbed in rats and dogs, half-life values were generally independent of dose and day with an approximate value of 2 and 4 h for most dose groups in rats and dogs. In rats, the mean Cmax and AUC values in females were higher than corresponding values in males (higher metabolism in males, see below), while there were minimal or no sex differences in dogs. The mean Cmax and AUC values increased with dose, but not always in a dose proportional manner. After multiple dosing, there is no significant accumulation.

Distribution

The plasma protein binding was moderate to high and not affected by varying concentrations of parsaclisib. For rats and beagle dogs, the average *ex vivo* fractions unbound were 16.5% and 3.5%, respectively, while for human plasma and serum, the average *in vitro* fraction unbound was 7.4%. Blood partitioning data indicate minor to no preferential partitioning of parsaclisib-derived radioactivity into blood cells of rats, dogs, and humans. Parsaclisib was widely distributed after a single oral dose of 14C-parsaclisib in rats. Maximum tissue concentrations were generally observed at 1 h post-dose.

Concentrations in all groups declined with time and radioactivity was generally not detectable by 168 h after administration. There is comparable distribution and tissue concentrations in non-pigmented and pigmented rats, except for ocular tissues. Indeed, parsaclisib was largely distributed in uveal tract in male and female pigmented rats. Moreover, parsaclisib is largely distributed in Harderian gland in pigmented and non-pigmented rats. The applicant should discussed the large distribution in ocular tissues (uveal tract and Harderian gland) in QWBA study and its potential safety consequences (**OC**). A dedicated study to determine brain penetration was performed. Parsaclisib has limited brain penetration.

Metabolism

In humans, no major plasma metabolites were identified. Parsaclisib was the major analyte present in plasma from all species examined with intact parent compound. The metabolites of parsaclisib were formed by hydroxylation, glucuronidation, or a combination of those pathways. Parsaclisib is primarily metabolized by CYP3A4. In rats and dogs, parsaclisib was also the major drug-related material found in plasma. Metabolite M3 was the most abundant metabolite observed in plasma from rats and dogs, with M4 observed to a lesser extent.

The secondary pharmacodynamics program demonstrated that parsaclisib does not possess clinically significant off-target pharmacological activity.

Excretion

In rat, dog and human ^{14}C mass balance studies, the elimination of drug-derived radioactivity after oral and IV dosing was complete. The excretion of radioactivity was the lowest in urine from rats and dogs, with most of the radioactivity excreted in bile and feces from these species. In humans, most of the radioactive dose was recovered in feces (60.6%), and most of that was intact parent compound (34.3% of total dose).

3.2.4. Toxicology

3.2.4.1. Single dose toxicity

There were no adverse effects following single oral doses of parsaclisib to SD rats (up to 300 mg/kg) or beagle dogs (up to 30 mg/kg).

3.2.4.2. Repeat dose toxicity

In rats, after repeat-dose administration of parsaclisib, lymphoid depletion was observed. Indeed, this lymphoid depletion was revealed by decreased lymphocytes, and/or decreased cellularity in multiple lymphoid organs, including lymph nodes, spleen, thymus, and GALT(B-cell regions). The dose-related findings in the lymphoid system were coherent with the pharmacodynamic properties of parsaclisib driven. Indeed, all plasma exposure were largely above IC_{50} for inhibition of PI3Kδ (IC_{50} = 1.19 nM). These effects were considered adverse based on their severity. In 28-d study, rat were dosed at 10, 30 and 100 mg/kg/d lymphoid depletion were considered adverse at 30 and 100 mg/kg/d. Lymphoid depletion was resolved by recovery necropsy. Moreover, in this study, adverse depletion of bone marrow occurred in females at 100 mg/kg per day (70-fold the intended clinical exposure), and hypospermatogenesis was noted in males at 30 (7-fold the intended clinical exposure) and 100 mg/kg per day. As a result, the NOAEL was 10 mg/kg per day. Reversibility In 3-month and 6-month study, test related lymphoid depletion were not considered adverse due to the absence of clinical and/or histological complications of immunosuppression up to the highest tested dose (15 mg/kg/d, 10-fold the intended clinical exposure). The applicant has not noticed any findings in other organs considered as adverse therefore this dose of 15 mg/kg/d was determined as the NOAEL. However, in 3-month rat study, testicular atrophy/hypoplasia was noted in 2 males in each of the treated groups and in 1 male

at recovery necropsy at the highest tested dose of 15 mg/kg/d. Given these observed findings and the potential impact on the fertility potential (see OC in fertility section), the NOAEL determined at 15 mg/kg/d need to be further discussed. To complete the toxicologic profile determined in rats, it is noticed that hepatotoxicity was observed at 100 mg/kg in non-pivotal rat studies (75-fold the intended clinical exposure), this toxicity was not observed in the pivotal 28-d study where the same dose of 100 mg/kg per day was evaluated and/or longer-term studies with lower doses and was not observed in dogs.

In dogs, after repeat-dose administration of parsaclisib, lymphoid depletion was also observed. Dog is more sensitive than rat. It is also confirmed that these observed immunosuppressive effects were pharmacologically driven given that dog plasma exposure were above the IC_{50} for inhibition of PI3Kδ (IC_{50} = 1.72 nM) determined in dogs at all dose levels in 28 days, 3 and 9 month study. This lymphoid depletion became more severe with the duration of dosing. Widespread inflammation was observed secondary to immunosuppression. No other target organ was identified by the applicant. Dogs were not sexually mature, the relevance of testicular findings could not be determined (see reproductive section below). Based on severity of the lymphoid depletion, the NOAEL was 1 mg/kg per day in the 28-day study and 1.5 mg/kg per day in the 3-month study and inflammation in the GI tract and lungs secondary to immunosuppression was observed in dogs and led to death or euthanasia in some animals administered ≥ 3 mg/kg per day for 28 days or ≥ 0.5 mg/kg per day for 9 months. After 9 months in dogs, subacute inflammation was also noted in lymphoid tissues, liver, trachea, kidney, bladder, prostate, vagina, and cervix. There were also findings of hemorrhage in colon and ileum.

Loss of fur pigmentation was noted in dogs at ≥ 0.5 mg/kg per day starting approximately 3 months after dose initiation; histologic evaluation of the skin conducted at the end of 9-month study did not reveal any remarkable changes. This loss of dark fur pigmentation was observed at relevant clinical exposure. The relationship of this finding to the pharmacologic activity of parsaclisib and relevance to patients is uncertain. The applicant should deeply discuss the potential mechanism of action of this finding, its relevance to humans. Moreover, this finding need to be mentioned in the SmPC section 5.3 with the lack of margin of exposure and its relevance to clinical situation (**OC**).

3.2.4.3. Genotoxicity

A standard test battery was performed with parsaclisib according ICH guideline S2 (option 1). Parsaclisib was not mutagenic in an Ames assay (T13-07-07). Negative results were also observed in an *in vitro* chromosome aberration assay (T13-07-06) in absence of metabolic activation; however, inconclusive results were observed with metabolic activation. Indeed, an increase of structural aberrant cells (clastogenicity) at the highest dose (469 µg/ml) but this positive result was not confirmed in the repeated assay with an adapted design (doses tested at a narrower interval). To deal with this inconclusive results, an *in vivo* micronucleus test (T13-07-05) was performed and negative results were observed. Parsaclisib were measured in blood samples and a systemic exposure were confirmed, however, no proof of the bone marrow exposure was given since no reductions in the ratio of PCEs to total erythrocytes in the test article groups compared to the respective vehicle control groups were observed at 24 and 48 hours post-dose. The applicant should discuss this point to reassure that parsaclisib reached the bone marrow and the negative results could be considered relevant (**OC**).

3.2.4.4. Carcinogenicity

Carcinogenicity studies for parsaclisib have not been conducted. Given the ICH guideline S9 is applicable for the intended indication (R/R MZL), the lack of carcinogenicity studies is acceptable.

3.2.4.5. Reproductive and developmental toxicity

A fertility and early embryonic development study was conducted rats wherein animals treated orally from either 9 weeks (males) or 2 weeks (females) before mating at doses ranging from 3 to 30 mg/kg/day were bred with untreated animals of the opposite sex. No adverse effects on male or female reproductive endpoints and early embryonic development was reported in this study up to the high dose level of 30 mg/kg/day (17-fold human exposure based on free AUC levels). However, hypospermatogenesis was observed in males at 30 mg/kg/day, in association with decreased weights of reproductive organs (testes, epididymides, cauda epididymides) at all dose levels. Testis sperm concentration and sperm production rate were also affected at ≥3 mg/kg with statistical significance reached at 10 mg/kg/day, but in the latter case all values remaining within the historical control range. It is noted that (reversible) hypospermatogenesis was also reported in the 28-day rat toxicity study, and that decreased testes weight was noted in the 28-day and 6-month rat toxicity studies. Considering rat-to-human exposure multiples based on free AUC levels, a safety margin of 5 can be derived for hypospermatogenesis based on the fertility and 6-month studies, with effects occurring from 5.7-fold the clinical exposure in the 28-day study. Decreases in testes weight were reported from the low dose levels corresponding to clinical exposure levels in the fertility, 28-day study, and 6-month studies. The absence of functional effect on rat male fertility is noted, however a risk for any effect on human male fertility cannot be fully excluded solely on this basis. It is also noted that the pharmacological target PI3K is involved in male reproduction, mostly via PI3K β isoform. Although paraclisib was reported to be selective for PI3Kδ, it was shown to affect PI3Kβ signalling at IC50 values 1.4- to 4.7-fold lower than the unbound Cmax value in patients at the MRHD (report IN VITRO-13.04.2). Therefore, potential effects on human spermatogenesis mediated by drug-related effects on PI3Kβ signalling cannot be excluded. Hence, findings on male reproductive organs (weight, histology, sperm parameters) should be reported in SPC 5.3 with a corresponding modification of SPC 4.6/ fertility reflecting e.g. that parsaclisib may impair male fertility based on studies conducted in rats (**OC**).

In embryo-fetal development toxicity studies, there was no evidence of maternal and embryo-foetal toxicity in rats and in rabbits at doses up to 50 mg/kg/day and 30 mg/kg/day, respectively. At these dose levels, the multiples of exposure based on total/free AUC levels were 17/38 in rats and 11/19 in rabbits. A pre- and post-natal development toxicity study was not conducted with parsaclisib in accordance with ICH S9 guidance.

3.2.4.6. Toxicokinetic data

Interspecies comparison

Animal-to-human exposure ratios cited within this MAA were calculated taking into consideration total AUC levels corrected for protein binding. However, the reported values appear to be over-estimated since the starting point for human exposure was a total AUC_{0-24} level at the MRHD of 13 µM.h (pharmacology/pk/toxicology written summaries) instead of 16.8 µM.h (SPC section 5.2). Likewise, a total Cmax level at the MRHD of 1.70 µM is used instead of 1.9 µM. The applicant should update the animal-to-human exposure ratios with the values mentioned in SmPC section 5.2 and updated according the related documents.

Bone marrow depletion and hepatotoxicity were observed in rats at exposure largely above the clinical exposure at the intended dose for the MAA in the MZL indication (20 mg QD), while lymphoid depletion and its secondary findings, were observed at clinical exposure or even below in dogs. Loss of dark fur pigmentation was also observed at relevant clinical exposure.

3.2.4.7. Tolerance

Local tolerance studies have not been performed with parsaclisib.

3.2.4.8. Other toxicity studies

Immunotoxicology endpoints, including comprehensive hematology and histopathology of immune tissues were included in general toxicology studies in rats and dogs. Therefore, dedicated immunotoxicity studies were not conducted. Although no immunotoxicity studies with parsaclisib were presented, however, as the oral repeat dose toxicity studies in rats and dogs (studies T13-06-03, T16-05-04, T17-09-06, T13-06-04, T16-05-05) indicated decrease lymphoid tissues. Therefore lymphoid organs may be the potential targets for parsaclisib. The applicant should present an overview of findings in toxicity studies that could relate to a potential for immunotoxicity.

In silico genotoxicity assessment of potential impurities was provided. The classification is acceptable. Indeed, six compounds, INCB071025, INCB071026, INCB056234, INCB085621, INCB078879 and hydrazine, indicated structural alerts and were classified as ICH M7 Class 3. As none of these impurities have been tested for mutagenicity, they were treated as potential genotoxic impurities. On the other hand, hydrazine, a known mutagenic carcinogen, was assigned ICH M7 Class 1. However, due to advanced cancer indication Q3A limits apply for these impurities (see Quality AR).

A neutral red uptake GLP phototoxicity assay was performed with parsaclisib. Parsaclisib did not demonstrate phototoxic potential. As recommended in the scientific advice, the applicant has provided information on phototoxic potential; however, no data was submitted considering initial considerations as described in ICH guideline S10 (photochemical properties). Therefore, the applicant should specify the wavelength at which parasaclisib absorbs and the molar extinction coefficient (MEC). Finally the applicant should confirm that the wavelengths of light applied in 3T3 NRU assay (T17-03-11) were relevant for the determination of the potential phototoxicity and to the clinical situation.

3.2.5. Ecotoxicity/environmental risk assessment

ERA of parsaclisib was performed in accordance to the current guidelines, a Phase I ERA was provided first with the dafault market penetration factor (Fpen of 0.01 (1%)); however the resulting predicted environmental concentration in surface water (PEC surface water) is above the trigger value of 0.01 µg/L. PEC surface water of parsaclisib hydrochloride was re-calculated using a refined FPEN based on the orphan designation of parsaclisib hydrochloride. The prevalence mentioned in orphan designation at COMP meeting could be used to refine FPEN as reported in Q&A of ERA guideline (EMA/CHMP/SWP/44609/2010 Rev. 1, may 2016). The updated PEC surface water is below the trigger value, therefore there is no need for phase II. There is no PBT potential and toxicity data in animals and human raised no endrocrine concern. Therefore, parsaclisib is not expected to pose a risk to the environment. The partition coefficient (POW) and the distribution coefficient (DOW) of parsaclisib in octanol/aqueous buffers was determined by the potentiometric technique (Analytical Service Report (2018). INCB050465: pKa and logP). The log DOW in octanol/ pH 5 buffer, octanol/ pH 7 buffer and octanol/ pH 9 buffer was determined to be 2.53, 2.57 and 2.57, respectively. The log POW was determined to be 2.57 ± 0.01 at 24.9°C. Consequently, parsaclisib has a low tendency to bioaccumulate in aquatic organisms (log POW<3) and consequently, no screening for persistence, bioaccumulation and toxicity is required (log POW<4.5). The applicant is asked to provide the cited reference for the determination the log Kow ("Analytical Service Report (2018). INCB050465: pKa and logP in order to assess the PBT potential of parsaclisib hydrochloride (OC).

Summary of main study results

Substance (INN/Invented Name): parsaclisib			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	(pH 5) log D_{OW} 2.53 (pH 7) log D_{OW} 2.57 (pH 9) log D_{OW} 2.57	No potential for PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	F_{PEN} default Refined F_{PEN}	0.10 µg/L 0.0015 µg/L	< 0.01 threshold No need for Phase II
Other concerns (e.g. chemical class)			No concern for endocrine potential

3.2.6. Discussion on non-clinical aspects

To support the proposed treatment of adult patients with relapsed or refractory marginal zone lymphoma, studies were conducted to characterize the *in vitro* properties of parsaclisib, a novel, potent, and selective inhibitor of PI3Kδ. Its activity against and selectivity for Class I PI3K isoforms were first assessed with biochemical enzyme assays and then further evaluated with the PI3K isoform specific signaling assays in DLBCL, MCL, ALL and AML cells. Although, parsaclisib was not tested in MZL cell lines (e.g. VL51) the results obtained with other haematological malignancies cell lines (in particular MCP cell lines, also an indolent lymphoma) could be considered relevant for the intended MZL indication. Parsaclisib was evaluated in two murin model for haematological malignancy (Rec-1 xenograft model of MCL and Pfeiffer xenograft model of DLBCL). Parsaclisib was not assessed in MZL model but MCL mice model (Rec-1 xenograft model) which will also represent an indolent lymphoma could be considered acceptable for this application. The second model, DLBCL mice model (aggressive lymphoma) could be considered as supportive data. Parsaclisib was also evaluated in a standard safety pharmacology core battery studies according the relevant recommendations (ICH guideline S7). The pharmacokinetic profile of parsaclisib was extensively studied *in vitro* as well as in non-clinical species using Sprague-Dawley rats, beagle dogs and cynomolgus monkeys. Parsaclisib has been evaluated in nonclinical toxicology studies that meet requirements as defined in ICH S9. Although long-term studies were not requested in ICH guideline S9, repeat-dose toxicity studies included up to 6 months in duration in rats and up to 9 months in dogs, probably because parsaclisib was developed in non-oncologic indications. These two long-term studies completed the non-clinical profile determined for parsaclisib. The potential genetic toxicity of parsaclisib was evaluated in a bacterial reverse mutation assay, *in vitro* chromosomal aberrations assay in human peripheral blood lymphocytes, and *in vivo* micronucleus study in rats. Potential embryofetal developmental toxicity was evaluated in rats and rabbits, and a fertility and early embryonic development study was conducted in rats. Phototoxicity was investigated in an *in vitro* neutral red uptake study in BALB/c 3T3 mouse fibroblasts. Starting materials, potential process impurities, and process

intermediates were evaluated *in silico* for potential mutagenicity using QSAR software. All pivotal nonclinical studies were conducted according the GLP requirements. Non-clinical scientific advices given in 2019 (EMA/CHMP/SAWP/493962/2019) for the non-clinical development was largely followed except for the discussion requested about the potential to induce Torsades de Pointes cardiac arrhythmias via an inhibition of cardiac potassium currents (IKr, IKs) (**OC**).

Parsaclisib was a potent inhibitor of PI3Kδ (IC_{50} = 1 nM); however, parsaclisib showed modest activity (IC50 ~30-100 nM) in a PI3Kβ-specific signaling assay, suggesting > 30-fold selectivity over PI3Kβ versus PI3Kδ. Therefore, the high selectivity of parsaclisib for PI3Kδ claimed by the applicant is questionable. The unbound Cmax value of 141 nM at the MRHD (maximum recommended human dose, 20 mg once daily) is 141-fold higher than IC_{50} values of PI3Kδ inhibition but also 1.4- to 4.7-fold higher than the IC_{50} values of PI3Kβ inhibition, thus at the MRHD, PI3Kδ and PI3Kβ-specific signalling pathways could be both inhibited (**OC**).

The minimal pharmacologic active dose was not clearly identified in the two xenografted mice models. In the Rec-1 xenograft model of MCL, 1 mg/kg/d was identified whereas in Pfeiffer xenograft model of DLBCL, the three experiment performed showed disparate results in terms of dose-dependency (tumor volume diminution) and statistically significance (pAKT levels) (**OC**).

The safety pharmacological studies on single oral dose parsaclisib administration revealed that only effect of parsaclisib was lower respiratory frequency and minute volume following single oral dose parsaclisib administration. As the respiratory changes were considered parsaclisib-related, the applicant should clarify the long-term effect of parsaclisib on the respiratory frequency and minute volume (**OC**).

The PK profile of parsaclisib was satisfactory addressed in the relevant species and did not raise particular concerns, except for the distribution observed in ocular tissues (**OC**).

The secondary pharmacodynamics program demonstrated that parsaclisib does not possess clinically significant off-target pharmacological activity. However, considering that M4 is the major metabolite of parsaclisib seen in rats, dogs, and humans, the applicant should clarify whether studies can be expected to have sufficiently also covered exposure to metabolite M4 and should justify why such specific studies with metabolite M4 are not needed (**OC**).

Lymphoid depletion was the most prominent adverse findings in rat and dog, but dog presented more severe effects at clinical relevant concentrations and secondary widespread inflammation led to poor clinical conditions or euthanasia of consistent number of animals during the 9-months study. Bone marrow depletion and testicular findings with hypospermatogenesis was also noted in rats at limited margins of exposure. The applicant indicated that there were no other target organ in dog; however loss of fur pigmentation was noted in dogs at relevant clinical exposure starting approximately 3 months after dose initiation. The mechanism and its relevance to human is not known (**OC**).

Animal-to-human exposure ratios reported within this MAA appear to be over-estimated since the starting point for human exposure was lower than those mentioned in SmPC section 5.2 (**OC**). RMP Part II Module SII and SmPC section 5.3 should be updated according the adequate animal-to-human exposure ratios (**OC**).

Inconclusive results of the *in vitro* chromosome aberration assay were observed and the proof of the bone marrow exposure submitted in the negative *in vivo* micronucleus assay, which was submitted to settle on this concern, is insufficient (**OC**).

In rats, decreased testes weight were reported from the low dose levels corresponding to clinical exposure levels in the fertility, 28-day study, and 6-month studies. Hypospermatogenesis was also noted in rats in the fertility and 28-day studies at ≥ 5.7-fold clinical exposure (based on unbound AUC levels). Moreover, some effects were also noted on sperm parameters in the fertility study and partly reported

in the current SPC 5.3 section. Moreover, potential effects on human spermatogenesis mediated by drug-related effects on PI3Kβ signalling cannot be excluded since parsaclisib was shown to affect this pathway in vitro at concentrations below those reached in patients at the MRHD. The absence of functional effect on rat male fertility is noted, however a risk for any effect on human male fertility cannot be fully excluded solely on this basis considering the abovementioned findings (**OC**).

Although no immunotoxicity studies with parsaclisib were presented, however, as the oral repeat dose toxicity studies in rats and dogs (studies T13-06-03, T16-05-04, T17-09-06, T13-06-04, T16-05-05) indicated decrease lymphoid tissues. Therefore lymphoid organs may be the potential targets for parsaclisib. The applicant should present an overview of findings in toxicity studies that could relate to a potential for immunotoxicity (**OC**).

Parsaclisib did not demonstrate phototoxic potential in standard *in vitro* phototoxicity assay (3T3 NRU); however photochemical properties need to be specified to ensure that the method used in the test were relevant to determine a phototoxic potential (**OC**).

Finally, parsaclisib is not expected to pose a risk to the environment. The applicant is asked to provide the cited reference for the determination the log Kow ("Analytical Service Report (2018). INCB050465: pKa and logP") in order to assess the PBT potential of parsaclisib hydrochloride (OC).

3.2.7. Conclusion on non-clinical aspects

The review of non-clinical data available for parsaclisib indicates no major issues for concern. There are, however, a number of other concerns and SmPC modifications that should be satisfactorily addressed.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Study Identifier (Type of Study); Location of Study Report Registry Number(s)	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, and Route of Administration	Number of Participants Enrolled	Healthy Participants or Diagnosis of Participants	Estimated Duration of Treatment	Study Status; Type of Report	Countries Involved
Pivotal Study								
INCB 50465-204 (Efficacy); 5.3.5.2 NCT03144674; EudraCT 2017-000970-12	Efficacy (ORR)	Phase 2, open-label, single-arm study with 2 cohorts and 2 treatment groups per cohort	Treatment A: Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW PO *OR* Treatment B: Parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD PO	Cohort 1 (ibrutinib experienced) Treatment A: 4 Treatment B: 6 Cohort 2 (BTKi naive) Treatment A: 28 Treatment B: 72	Participants with histologically confirmed R/R MZL, including extranodal, nodal, and splenic subtypes	As long as participant is receiving benefit	Ongoing; Interim	Belgium, France, Germany, Israel, Italy, Poland, Spain, United Kingdom, United States

INCB 50465-203 (Efficacy); 5.3.5.4 NCT03126019; EudraCT 2017-001624-22	Efficacy (ORR)	Phase 2, open-label, single-arm study	Treatment A: Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW PO *OR* Treatment B: Parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD PO	Treatment A: 23 Treatment B: 103	Participants with histologically confirmed R/R FL	As long as participant is receiving benefit	Ongoing; Interim	Canada, Czech Republic, Denmark, Germany, Hungary, Israel, Italy, Poland, Spain, Sweden, United Kingdom, United States
INCB 50465-205 (Efficacy); 5.3.5.4 NCT03235544; EudraCT 2017-003148-19	Efficacy (ORR)	Phase 2, open-label, single-arm study with 2 cohorts and 2 treatment groups per cohort	Treatment A: Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW PO *OR* Treatment B: Parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD PO	Cohort 1 (ibrutinib experienced) Treatment A: 12 Treatment B: 41 Cohort 2 (BTKi naive) Treatment A: 31 Treatment B: 77	Participants with pathologically confirmed R/R MCL, with documentation of either overexpression of cyclin D1 or t(11;14)	As long as participant is receiving benefit	Ongoing; Interim	Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, Poland, Spain, United Kingdom, United States
INCB 50465-101[a] (Safety, tolerability, efficacy, PK); 5.3.3.2 NCT03235544; EudraCT 2017-003148-19	Safety and tolerability	Phase 1, open-label, dose-escalation study	Parsaclisib 5, 10, 15, 20, 30, and 45 mg QD PO (as of Protocol Amendment 8, participants in all cohorts who had completed 9 weeks of treatment were able to transition to a maintenance dosing regimen of parsaclisib 20 mg or less QW PO)	Parsaclisib monotherapy: 72	Participants with R/R B-cell malignancies (except Burkitt's lymphoma and precursor B-lymphoblastic leukemia/ lymphoma) or R/R Hodgkin's lymphoma	As long as participant is receiving benefit	Complete; Full and Addenda	United States
INCB 50465-202 (Efficacy); 5.3.3.2 NCT02998476; EudraCT 2016-002205-19	Efficacy (ORR)	Phase 2, open-label, single-arm study with 2 cohorts	Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW PO	Group A (BTKi naive): 55 Group B (BTKi experienced): 5	Participants with histologically confirmed R/R DLBCL	As long participant is receiving benefit	Complete; Full and Addendum	Australia, Belgium, Canada, Czech Republic, France, Italy, Poland, South Korea, Spain, United Kingdom, United States

Table 1 Summary of clinical pharmacology studies

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen[a]	Number of Participants	Healthy Participants or Diagnosis of Participants	Duration of Treatment	Study Status
INCB 50465-104	Route of elimination and mass balance; metabolite profile and PK	Open-label mass balance study	Parsaclisib 20 mg tablets and oral solution of [^{14}C]parsaclisib (200 µCi/mg); Parsaclisib 20 mg followed by an oral solution of [^{14}C]parsaclisib (200 µCi ~ 2.2 mg)	7	Healthy participants	Single dose	Completed
INCB 50465-105	Effect of itraconazole (a potent CYP3A4 inhibitor) or rifampin (a potent CYP3A4 inducer) on parsaclisib PK	Open-label, fixed-sequence, single-dose parsaclisib and multiple-dose itraconazole (Cohort 1) or rifampin (Cohort 2)	Parsaclisib tablets 5 mg and 10 mg; Parsaclisib 10 mg and itraconazole 200 mg QD (Cohort 1); parsaclisib 20 mg and rifampin 600 mg QD (Cohort 2)	36	Healthy participants	Two single doses of parsaclisib separated by multiple doses of itraconazole (11 days' duration)/rifampin (12 days' duration)	Completed
INCB 50465-108	Effect of hepatic dysfunction on parsaclisib PK	Open-label, single-dose study	Parsaclisib 20 mg tablets; Parsaclisib 20 mg	24	Healthy participants and those with varying degrees of hepatic dysfunction	Single dose	Ongoing
INCB 50465-109	Effect of renal impairment and hemodialysis on parsaclisib PK	Open-label, single-dose study	Parsaclisib 20 mg tablets; Parsaclisib 20 mg	16	Healthy participants and those with varying degrees of renal impairment	Single dose	Ongoing

[a] Route of administration used in all studies was oral.

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Parsaclisib (INCB050465) is a potent, highly-selective, next generation inhibitor of PI3Kδ. Parsaclisib directly blocks PI3K signalling-mediated cell proliferation in normal and malignant B-cells and indirectly controls tumour growth by lessening immunosuppression through regulatory T-cell inhibition. Parsaclisib has been shown to inhibit PI3Kδ signalling and tumour growth in human xenograft tumour models of mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma.

The applicant seeks marketing approval for parsaclisib as monotherapy in the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL).

The drug product for registration application are immediate-release tablets for oral (PO) use with five strengths of 1, 2.5, 5, 10, and 20 mg containing parsaclisib as hydrochloride. The 10 mg strength was developed later and was therefore not included in any clinical trial.

The proposed recommended dose of 20 mg parsaclisib once daily (QD) for 8 weeks followed by 2.5 mg QD was selected based on the overall efficacy, safety pharmacodynamic (PD), and pharmacokinetic (PK) data as well as preliminary signals of clinical benefit from the clinical development program. In case of adverse events or when co-administered with strong CYP3A4 inhibitors, dose reduction for the 8 weeks starting dose down to 10 or 5 mg and for the maintenance dose down to 1 mg are proposed. The use of strong and moderate CYP3A4 inducers during treatment with parsaclisib should be avoided.

Parsaclisib has molecular weight of 469.34 g/mol as hydrochloride salt and 432.88 g/mol as free base. The molecular formula is $C_{20}H_{23}Cl_2FN_6O_2$ (as hydrochloride salt) or$C_{20}H_{22}ClFN_6O_2$ (as free base).

Overall, the current clinical pharmacological program for parsaclisib encompasses six completed clinical studies as well as nine ongoing Phase 1 and Phase 2 studies. A confirmatory Phase 3 trial (INCB 50456-302) is planned.

For this marketing application, the pivotal Phase 2 study INCB 50465-204 (MZL population), nine clinical studies evaluating safety of parsaclisib as monotherapy and in combination therapy (INCB 50465-101, 50465-102, 50465-111, 50465-112, 50465-202, 50465-203, 50465-205, 50465-801, INCB 53914-102) and two clinical pharmacology healthy volunteer studies evaluating mass-balance (INCB 50465-104) and drug-drug interactions with rifampin and itraconazole (INCB 50465-105) are included**.**

The PK of parsaclisib was investigated by non-compartmental analysis (NCA) as well as by population modelling. In total, PK data as of the cut-off dates from four completed (INCB 50465-101, INCB 50465-104, INCB 50465-105, and INCB 50465-202) and four ongoing studies (INCB 50465-111, INCB 50465-203, INCB 50465-204, and INCB 50465-205), with overall 191 and 414 participants exposed to parsaclisib, respectively, were in the analyses for this marketing application. Among these data, studies INCB 50465-101, INCB 50465-111, INCB 50465-202, INCB 50465-203, INCB 50465-204, and INCB 50465-205 were integrated in the population PK and exposure-response (E-R) modelling analyses Report: DMB-20.133.1. The target population (patients with MZL) were included in studies INCB 50465-101, INCB 50465-111 and INCB 50465-204. Overall, the population PK analysis dataset included 3376 plasma parsaclisib concentration records from 537 from lymphoma patients. Further, a PBPK model was developed to predict parsaclisib drug-drug interactions with CYP3A4 inhibitors and inducers.

To support parsaclisib PK profiling, data from 13 in vitro studies using human biomaterials were submitted to identify the enzymes involved in the parsaclisib metabolism and to investigate enzyme induction and inhibition as well as transporters inhibition potential.Parsaclisib is being investigated in ongoing hepatic impairment (INCB 50465-108) and renal impairment (INCB 50465-109) studies and PK data are not currently available.

Of note, in the phase 2 studies in patients (INCB 50465-202, INCB 50465-203, INCB 50465-204, and INCB 50465-205) presented in pop PK, parsaclisib concentrations were measured and included in population PK analysis, but concentration vs time profiles and PK data were not individually presented. Overall, this results in a fair number of PK data which were either barely presented (only in population PK), or not yet available (IR and IH); this is a definite weak point of this application (see MO for doses, and OCs for specific populations).

Methods

Three analytical methods for parsaclisib in plasma and one for parsaclisib in urine are presented and acceptable ; altogether 3 plasma methods were used throughout the clinical trials. In most studies method DMB-17.137 by Incyte was applied. However, bridging between two of the plasma analysis methods, DMB-16.104 and DMB-17.137, was not discussed and should be presented by the applicant (**OC**).

Pharmacokinetic analysis

The PK of parsaclisib was investigated by non-compartmental analysis (NCA) and population PK modelling (Report: DMB-20.133.1).

NCA analysis was performed per usual calculation standards.

The population PK model was developed using Monolix software (Version 2020 Release 1, Lixoft SAS, Antony, France). The development process was proceed stepwise following a graphical data inspection. A covariate search was performed identifying potential factors affecting the PK of parsaclisib. The final models were used to simulate exposures and evaluating the extent of patient factors on primary and secondary PK parameters. Model-based exposures were used for exposure-response analyses of efficacy and safety measures. Model evaluation and selection were based on commonly used statistical and graphical criteria.

Absorption

Absolute bioavailability

Mass balance study (INCB 50465-104) showed that 32.3% and 60.6% of the total radioactivity was excreted in urine and feces, respectively, of healthy participants., while 34.3% of the parsaclisib dose was recovered as unchanged in faeces. Therefore, approximately 65.7% of Parsaclisib was absorbed after oral administration. This confirms classification of Parsaclisib as BCS class III.

Parsaclisib is rapidly absorbed after oral administration. The median T_{max} is 1 hour under fasted state. The solubility of parsaclisib (pKa=4.06) in aqueous medium appears pH-dependent.

Since no absolute oral bioavailability study was performed, the exact oral bioavailability of parsaclisib from commercial formulation is unknown.

Tmax in generally reached within one hour.

Relative bioavailability/ Bioequivalence

PK studies with only the 5 mg and 20 mg were performed. Dose proportionately was shown from 5 mg to 20 mg, but it is unknown if the PK is also dose proportional from 1 mg to 5 mg (parsaclisib is a substrate for the intestinal transporter P-glycoprotein). Furthermore, parsaclisib is a BCS class III compound. The 1 mg and 2.5 mg strengths are qualitatively not similar to the 5 mg, 10 mg and 20 mg and also not to each other. The 5 mg, 10 mg and 20 mg strengths are qualitatively similar. Dissolution

data has been provided for the 20 mg strength only. Therefore absence of BE studies is not acceptable right now and BE should be discussed for the lowest strength tablets, see Quality + PK MO.

Influence of food

In the population PK analysis, only data obtained in the fasted state were included. A high fat meal reduces Cmax by 42%, AUC24 by 8%, and delays Tmax from 1 to 5 hours post dose. It is not considered clinically significant.

The solubility of parsaclisib (pKa=4.06) in aqueous medium was found to be pH-dependent (please refer to *in vitro* solubility data: > 3.18 mg/mL in pH 1.2 buffer, > 3.15 mg/mL in pH 2.0 buffer, and 0.24 mg/mL in pH 7.4 buffer). Thus, parsaclisib appears most soluble at low pH and considered relatively insoluble at pH 7.4.) Based on food-effect study, pH-dependent solubility do not translate into significant changes in parsaclisib absorption, hence, studies with drugs which increase gastric pH are not considered mandatory.

Distribution

Parsaclisib is 92.4% bound to human plasma proteins in vitro, with limited association to red blood cells, Vss/F in population PK was found at 69.3 L (20%), and in clinical studies Vz/F was found around 25 to 40 L.

Elimination

Mass balance

T1/2 is around 10h, and in population analysis: The estimated geometric mean (CV%) value of CL/F of parsaclisib is 2.95 L/h (33%). Faecal elimination was the main route of elimination of parsaclisib.

Metabolism

There was no major metabolite ; the observed plasma metabolites were formed by hydroxylation, glucuronidation, or a combination of those pathways, a glucuronide and hydroxylated metabolite (M7) being the main minor metabolite in plasma counting for 6% of total radioactivity after oral dosing.

No active metabolites have been identified for parsaclisib. Unchanged parent drug is the predominant component in plasma counting 78% of quantified parsaclisib related fractions up to 24h indicating slow first-pass metabolism.

Interconversion

Parsaclisib has two chiral centers, the applicant should briefly comment on risks of conversion of the chiral centers. (**OC**).

Dose proportionality and time dependencies

Dose proportionality has been assessed and proven from 5 to 45 ng/mL. The applicant still must justify their claim of dose linearity from 2.5 mg dose. And as the 1 mg dose in required in some specific case and includes a 1 mg tablet, the applicant should comment on dose linearly or absence thereof between 1 mg and 5 mg doses (oc).

The pivotal pharmacokinetic study -101 was the only study evaluating the achivment of steady state. According to study report, steady state conditions of parsaclisib were reached on or after 8 days of 20

mg once daily dosing in participants with B-cell malignancies. In clinical summary, applicant concluded that steady state is reached after 3 days (however, no justification for such claim has been provided). applicant is asked to clarify this inconsistency (**additional OC to LoQ**) as latter is more in line with terminal half-life values reported after single dose administration in healthy subjects (t1/2 approx. 12 to 14 h) or in popPK analysis for participants with lymphoma (t1/2 approx. 13 h).

Inter- and intra-individual variability

In Study INCB050465-101, the overall intersubject CV% was 24% and 17% for Cmax and AUC0-t, respectively.

The applicant should comment on intra-individual variability (**OC**).

Based on the population PK analysis, IIV were mild to moderate for V1 (19.1 %CV), CL (33.1 %CV), V2 (34.4 %CV), Tlag (37.6 %CV), and Q (56.7 %CV), but high for ka (95.7 %CV). In addition intra-individual / intra-occasion variability (IOV) on Tlag (49.1 %CV) and ka (170 %CV) were identified.

Pharmacokinetics in target population

In total, 3376 parsaclisib plasma concentration-records from 537 patients from studies INCB 50456-101 (72 of 88 patients with FL, MCL, MZL[n=9], or DLBCL), INCB 50456-111 (17 of 17 Japanese patients with lymphoma whereof n=2 with MZL), INCB 50456-202 (57 of 60 patients with DLBCL), INCB 50456-203 (124 of 126 patients with FL), INCB 50456-204 (110 of 110 patients with MZL), and INCB 50456-205 (157 of 161 patients with MCL) were included in the population PK analysis.

Overall participants received parsaclisib doses once daily (QD) of 5 mg (n=1), 10 mg (n=3), 15 (n=3), 20 mg (n=496), 30 mg (n=27) or 45 mg (n=4). PK samples after administration of a maintenance dose of 2.5 QD or 20 mg QW from week 9 onwards were drawn sparse in study INCB 50456-203 at week 12. All other PK samples were drawn within cycle 1 day 1 and week 4 and not during the administration of maintenance dose.

Among the 537 patients, 62.2 % were male and 37. 8 % female. The median body weight was 76 kg (range: 39 to 171 kg) and the BMI ranged from 15 to 51.2 kg/m^2 (median = 26.5 kg/m^2). The age ranged from 30 to 95 years (median 70 years). The median value of the calculated creatinine clearance was 75.4 mL/min/1.73 m^2 (40 to 170 mL/min/1.73 m^2). In total, 24. 8 % had normal renal function, 54.7 % were classified having mild and 19.9 % moderate renal impairment. Three participants had missing values in eGFR. Overall 88.6 % had normal hepatic function and 10.2 % were classified has mild hepatic impaired. Only one patient had moderate hepatic impairment and five participants were not classified due to missing laboratory information. Among the data used for population PK analysis, 81.4 % of the population were White, 3.7 % Black, and 4.1 % (n=22) Asian, whereof 17 were Japanese (from overall population 3.2 %). Overall, 31 (5.8 %) were Hispanic or Latino and 75 % (n=403) not Hispanic / Latino. Race and Ethnicity were unknown for 2.6 % and 19.2 %, respectively. ECOG score at baseline was 0 for 53.8 % of the overall population, 39.5 % and 6.7 % had ECOG score of 1 and 2 at baseline, respectively.

The final population PK model for parsaclisib in adult patients is a 2-compartment disposition model with a first-order absorption with lag time and a linear elimination. A combined residual error model was used. The typical population parameters were as followed: CL=2.95 L/h, V1(central)=25.1 L, V2(peripheral)=20.3 L, ka=6.96 h^{-1}, and Tlag=0.194 h. IIV were mild to moderate (V1=19.1 %CV, CL=33.1 %CV, V2=34.4 %CV, Tlag=37.6 %CV, Q=56.7 %CV), but high for ka (95.7 %CV). IOV on Tlag was 49.1 %CV and high on ka (170 %CV). RSE were < 8 % for the fixed effects, < 17 % for IIV and

IOV, and mostly < 50 % for covariates with exception for the effect of mild renal impairment on CL (RSE=53.2%). The correlation coefficient between CL and V1 was estimated to be 0.742. The standard deviation of the additive errors was estimated as 17.9 (8.36% RSE; 95% CI: 14.9 - 20.8; bootstrap: 19.1 with 95% CI 13.3 - 32.6)), and the proportional residual error was estimated at 9.85 % (RSE=3.09%). Bootstrap results were generally similar.

Special populations

The impacts of various covariates on parsaclisib PK parameters and post hoc exposure metrics ($C_{avg,ss}$, $C_{max,ss}$, and $C_{min,ss}$) at steady state were investigated. The typical participant was assumed being a White, male patient with lymphoma aged 66.3 years, with a body weight of 76.3 kg, and normal renal function.

No dose adjustments are proposed based on sex, age, body weight, race, baseline laboratory tests of albumin (range, 22-51 g/L), alkaline phosphatase (range, 33-464 U/L), ALT (range, 5-133 U/L), AST (range, 5-167 U/L), total bilirubin (range, 2-43 µM), cancer type, ECOG status (0, 1, or 2), or mild or moderate renal impairments.

Renal impairment

A dedicated renal impairment study (INCB 50465-109) with 48 planned participants is ongoing and PK data are not currently available.

Among the 573 patients included in the population PK analysis, 24.8 % (n=133) had a normal renal function, 54.7 % (n=294) had mild and 19.9 % (n=107) moderate renal impairment. Three participants had missing values in eGFR, thus unknown renal function classification. Participants with severe renal impairment were excluded from clinical studies. During population PK modelling, renal functions (mild or moderate impaired vs. normal) were statistically significant covariates on CL and volume of distribution (V1). Therefore, patients with mild and moderate renal impairments have about 6.8% and 18% lower CL values (CL=2.75 L/h and 2.42 L/h, respectively) and 6.3% and 10% lower volumes of distribution (V1=23.5 L and 22.5 L, respectively), compared to those with normal renal function.

Participants with mild or moderate renal impairments tended to have higher level of exposures than those with normal renal function. The GMRs of $C_{avg,ss}$, $C_{max,ss}$, and $C_{min,ss}$ in participants with mild renal impairment were 1.07 (90% CI: 1.01, 1.13), 1.02 (90% CI: 0.972, 1.08), and 1.14 (90% CI: 1.04, 1.25), respectively, compared to participants with normal renal function. The GMRs for moderate renal impairment were 1.21 (90% CI: 1.13, 1.29), 1.12 (90% CI: 1.05, 1.19), and 1.39 (90% CI: 1.25, 1.56), respectively, compared to participants with normal renal function.

No dose adjustments are proposed for patients with mild or moderate renal impairment. For participants with severe renal impairment or end-stage renal disease, there were no data to determine whether a dose adjustment would be needed.

Hepatic impairment

A dedicated hepatic impairment study (INCB 50465-108) with 40 planned participants is ongoing and PK data are not currently available.

Observed baseline serum albumin levels were generally within the normal range (median = 42 g/L; 22 to 51 g/L). The mean alkaline phosphatase was 98.9 U/L (median=82 U/L, 33 to 464 U/L), but Japanese participants had much higher alkaline phosphatase levels (mean=257 U/L, median=243 U/L, 194 to 391 U/L). The overall median ALT value was 17 U/L (5 to 133 U/L), while that of participants in Study INCB 50465-101 was relatively higher (median=22 U/L, 5 to 71 U/L). Median AST was 21 U/L (5 to 167 U/L). The median total bilirubin level was 8.0 µM (2.0 to 43.0 µM). Total bilirubin was higher in Japanese participants (median=10.3 µM, 5.13 to 37.6 µM).

Among the 537 patients included in the population PK analysis, 88.6 % (n=476) had a normal hepatic function, 10.2 % (n=55) mild hepatic impairment, and only one patients (0.2 %) moderate hepatic impairment. No patient had severe hepatic impairment. Five participants (0.9 %) had missing laboratory tests of total bilirubin at baseline, resulting in unknown hepatic function classification.

Hepatic function was not a statistically significant covariate on the PK of parsaclisib.

No dose adjustment proposed based on baseline laboratory tests of albumin, alkaline phosphatase, ALT, AST, and total bilirubin. No dose adjustments is proposed for patients with mild hepatic impairment. There were not sufficient data to determine whether a dose adjustment would be needed for participants with moderate or severe hepatic impairment.

Gender

No formal PK study investigating gender on the PK of parsaclisib was performed.

During population PK modelling, gender (sex) was a statistically significant covariate on volume of distribution (V1). Female participants had an 8% lower V1, at a value of 23.1 L (male: 25.1 L). The geometric mean ratios for females versus males were within 80 to 125 % (range 0.8 to 1.25) for C_{avg} and C_{min}. Compared to males, females are expected to have higher C_{max} levels compared to males (GMR 1.26 [90% CI: 1.21, 1.32]).

No dose adjustment was proposed based on gender.

Race/Ethnicity

A formal PK study investigating the PK of parsaclisib in Japanese patients was performed (INCB 50465-111).

During population PK modelling, race, tested as White versus non-White was not a statistically significant covariate on the PK of parsaclisib. Ethnicity was not tested as covariate.

Based on the final PK model, individual predicted PK parameters were generated. Results showed that CL, V1, and Q are about 22 %, 27.5 %, and 45 % lower in Japanese compared to the typical population estimate (i.e. 2.95 L/h, 25.1 L, and 3.34 L/h, respectively). Individual predicted ka values for each occasion reveal, that absorption is faster in Japanese (ka occasion 1: 6.56 h^{-1} vs. 5.06 h^{-1} for the overall population, ka occasion 2: 7.7 h^{-1} vs. 4.75 h^{-1} for the overall population).

No dose adjustment was proposed based on race or ethnicity.

Body weight

No formal PK study investigating body weight on the PK of parsaclisib was performed.

During population PK modelling, body weight was a statistically significant covariate on clearance (CL), volume of distribution (V1) and intercompartmental clearance (Q). BMI was not tested as covariate.

The population typical CL increases with increasing body weight (estimate 0.332). Participants with weighing 55.5 kg and 106 kg (the 10^{th} and 90^{th} percentiles) have typical CL values that are 10% lower and 11% higher, respectively, than that of a 76.3-kg participant.

Typical V1 values are 21 % lower and 26 % higher (estimate: 0.705) for patients weighing 55.5 kg and 106 kg, respectively, compared to the reference. The GMR range for patients weighing 55.5 kg was 0.779 to 0.825, and for the heavier patients (106 kg) 1.22 to 1.3.

Intercompartmental clearance Q increases with increasing body weight (estimate: 1.06). Participants with weighing 55.5 kg and 106 kg have typical Q values that are 30% lower and 42% higher,

respectively, than that of a 76.3-kg participant (55.5 kg: GMR 0.714 [90 % CI: 0.630, 0.798] and 106 kg: 1.42 [90 % CI: 1.26, 1.59]).

C_{max} GMR for patients weighing 39-63 kg are 1.24 (90% CI: 1.17, 1.31) and for patients weighing 92-171 kg 0.768 (90% CI: 0.725, 0.814).

No dose adjustment is proposed based on body weight.

Age

No formal PK study investigating age on the PK of parsaclisib was performed.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials			

During population PK modelling, age was a statistically significant covariate on CL. CL decreases with increasing age (estimate: -0.215). Participants with lymphoma at an age of 52 years or 81 years (the 10th and 90th percentiles) have typical CL values that are 5.2 % higher or 4.1 % lower, respectively, than those of a 66.3-year-old participant.

With increasing age $C_{avg,ss}$, $C_{max,ss}$, and $C_{min,ss}$ are expected to increase with age (here patients aged 70-95 years compared to 66.3 years). GMR are 1.06 (90% CI: 0.996, 1.14), 1.05 (90% CI: 0.977, 1.12), and 1.08 (90% CI: 0.957, 1.21) for $C_{avg,ss}$, $C_{max,ss}$, and $C_{min,ss}$, respectively.

No dose adjustment is proposed based age.

Pharmacokinetic interaction studies

In vivo drug-drug interactions assessment

Overall, the in vivo parsaclisib interaction profile was appropriately characterized with estimating the effect of strong CYP3A4 inducer and inhibitor, respectively rifampin and itraconazole, on the PK of parsaclisib in healthy participants. Rifampin coadministration decreased parsaclisib exposure and maximal concentration by 77% and 43%, respectively, in comparison to parsaclisib given alone. Itraconazole coadministration increased parsaclisib exposure and maximal concentration by 204% and 121%, respectively, in comparison to parsaclisib given alone.

Based on in vivo results, the applicant specified a contraindication for the coadministration of parsaclisib with potent CYP3A inducers but also recommends dose adjustment for parsaclisib coadministration with strong CYP3A4 inhibitors.

In silico drug-drug interactions assessment

Parsaclisib PBPK model was developed for two purposes, *i.e.* to predict the effect of other strong, moderate and weak inhibitors and inducers on parsaclisib PK. Although the PBPK modeling strategy would be convenient, the PBPK model presents serious shortcomings and is therefore not supported for those intended use:

- The final parsaclisib PBPK model is not assessable due to missing information in model structure and results.

- Since the final parsaclisib model is used as a victim in the DDI application, the metabolic clearance is a critical parameter. However, the absorbed fraction (fa) and the fraction metabolized through CYP3A4

(fmCYP3A4), which are both used in CLint, CYP3A4 computation, are empirically parameterized to 85% and 100%, respectively.

- The presented model qualification to predict parsaclisib interactions with CYP3A4 inhibitors and inducers is considered insufficient.

Overall, there are evidence that the PBPK model does not describe sufficiently parsaclisib PK and its metabolism. Consequently, the presented model should not be used to simulate parsaclisib interaction as victim drug. Reference to PBPK modeling in SmPC should thus not be made. Because sufficient clinical data was provided to document parsaclisib interactions with strong CYP3A4 perpetrators, the PBPK model issues are not further pursued.

Pharmacokinetics using human biomaterials

In vitro drug-drug interactions assessment

Parsaclisib is shown to be a substrate of CYP3A4 and -2C8 enzymes at clinical concentration levels. Parsaclisib is also transported by intestinal P-gp, but it is likely that saturation occurs in clinical situation. Hence, its intestinal absorption follows passive diffusion through enterocytes.

The in vitro DDI assessment process presents two main shortcomings:

- CYP3A induction potential of parsaclisib cannot be ruled out at this stage,
- UGT inhibition potential of parsaclisib has not been studied.

Inhibition of the transporter BSEP (ABCB11) has not been investigated. (**OC**)

In vitro studies indicated that parsaclisib is an inhibitor of P-glycoprotein with an IC_{50} value of 18.1 µM. The $IC_{50}/2$ (9.1 µM) is lower than the threshold maximal intestinal concentration of 18.5 µM (0.1 × dose/250 mL). Thus, parsaclisib may be an inhibitor of P-glycoprotein in the intestine.

In vitro studies indicated that parsaclisib is an inhibitor of OCT2 and MATE1 with an IC_{50} value of 8.7 µM and 7.0 µM, respectively. The $IC_{50}/2$ (4.4 µM and 3.5 µM, respectively) is lower than the threshold maximal systemic concentration of 4.6 µM (50 × $C_{max,unbound}$). Thus, parsaclisib may be an inhibitor of OCT2 and MATE1 at systemic concentrations.

Therefore, the applicant should be requested to investigate if parsaclisib is a clinically relevant inhibitor of P-glycoprotein in the intestine and of OCT 2 and MATE1 systemically. (**OC**)

3.3.1.2. Pharmacodynamics

Mechanism of action

Parsaclisib is a potent, next-generation PI3Kδ inhibitor (IC50 = 1.1 ± 0.5 nM), with approximately 20,000-fold selectivity over the other PI3K family members *in vitro* (PI3Kα, PI3Kβ, and PI3Kγ).

Class I PI3Ks, which include PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, catalyze the phosphorylation of phosphatidylinositol-4,5-bisphosphate, giving rise to phosphatidylinositol-3,4,5-trisphosphate, which functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion, and migration. PI3Kδ is the main isozyme responsible for the activation of the PI3K pathway in B-cell biology, functioning as a downstream mediator of the B-cell receptor (Shin et al 2020). Since aberrant signal transduction via the PI3K pathway has been observed in malignant B-lymphocytes, agents that inhibit this signaling pathway, and particularly PI3Kδ, can be of therapeutic value in B-cell malignancies.

Parsaclisib directly blocks PI3K signaling-mediated cell proliferation in B-cell lines in vitro and in vivo and indirectly controls tumor growth by lessening immunosuppression through regulatory T-cell inhibition in a syngeneic lymphoma model (Shin et al 2020).

However, the applicant should discuss the relevance of pAkt inhibition with parsaclisib specifically in the target MZL population. (**OC**)

Primary and Secondary pharmacology

Primary pharmacology

Relevant data for clinical primary pharmacology in the intended indication mainly come from INCB 50465-101 (study 101) a phase 1/2 dose escalation study and from study INCB50465-204 (Study 204), the pivotal phase II trial for this application.

Ex vivo assays for PI3K activity on whole blood shows that for all tested doses (5 to 45 mg, i.e. covering the initial intended dose of 20mg but not the maintenance dose of 2.5 mg QD), mean pAkt (a major downstream target of PI3K) inhibition are >80% at D1 and > 90% at day 15 with the exception of the 20mg dose, the intended induction dose at which 34 patients were treated (i.e. more patients than in any other dose levels), which shows a large variability. The applicant should discuss the large variability observed at C1D15 for mean pAkt inhibition at 20 mg QD (**OC**).

In addition, the applicant should justify the choice of the maintenance dose of 2.5mg QD based on pharmacological consideration (**MO**).

In studies CITADEL-101 and CITADEL-204, 30 DEA in common were found to be downregulated. Of these 30 DEA, 22 exhibited sustained decrease at week 4 and week 16 i.e. after transition to maintenance doses. Those analytes are involved in activation and proliferation of B and T cells. Results of 2 analytes in particular seem to be impacted by the maintenance schedule. Indeed, CXCL13 and TNFRSF9 are less downregulated at week 16 in the QW schedule than in the QD schedule suggesting a potential better sustained effect with the QD schedule. CXCL13 is implicated in chemotaxis of B lymphocytes and TNFRSF9 in activation of T lymphocytes.

On the other hand, as raised stated by the applicant, another set of analytes exhibited larger rebounds towards baseline expression following dose transition, indicating that further explorations are needed to better characterize a potential link with clinical outcome.

Overall, these analyses were exploratory and adequate biomarkers still needs to be characterized.

Relationship between plasma concentration and response

Exposure-response (E-R) analyses for efficacy and safety were conducted to describe the relationship between exposure of parsaclisib and (1) ORR, (2) PFS, and (3) to assess the relationship between parsaclisib exposures and selected clinical safety endpoints as deemed appropriate. The following endpoints were chosen:

Efficacy: Objective response rate (ORR), progression free survival (PFS), duration of response (DOR), and time to objective response (T2RESP).

Safety: All grade treatment-emergent adverse events (TEAEs) of diarrhoea, nausea, fatigue, rash, neutropenia, colitis, and thrombocytopenia; ≥ Grade 3 adverse events (AEs) of diarrhoea, neutropenia, and colitis; serious adverse events (SAEs) of diarrhoea and colitis; TEAEs leading to dose interruption, reduction, or discontinuation.

Different population PK model-derived exposure metrics were investigated. For the time-to-event (TTE) endpoints PFS, DOR or T2RESP Cox hazard models were developed, binary logistic regression models were developed for ORR and safety measures. As exposure metrics, maximum, minimum, and average concentration at steady state ($C_{max,ss}$, $C_{min,ss}$, and $C_{avg,ss}$) at the dose level of actual starting dose for first 8 weeks were teted, and with respect to cumulative daily average dose from Day 1 to the day of first incidence of the event of interest (C_{max_CD}, C_{min_CD}, and C_{avg_CD}).

Results were compared for the recommended doses and "other doses" or "non-recommended" doses. Recommended doses were defined as 20 mg QD for 8 weeks followed by 2.5 mg QD from week 9 onwards. All other doses were "other doses" or "non-recommended" doses. These consisted of various doses of 5, 10, 15, 20, 30, and 45 mg QD in study INCB 50465-101 with PK data obtained in Cycle 1 Days 1, 8. In study INCB 50465-111, 10 and 20 mg QD were investigated with PK data obtained in Cycle 1 Days 1, 8, 15. In study INCB 50465-202, a maintenance dose of 20 mg QW, but no PK samples were drawn during this phase. In INCB 50465-203, 20 mg QW maintenance dose was investigated compared to 2.5 mg QD (PK measures on day 1, week 4 and week 12). Recommended dose were given in studies INCB 50465-203, INCB 50465-204, and INCB 50465-205, but PK measures of the 2.5 mg maintenance dose was only done in study INCB 50465-203 (day 1, week 4 and week 12). In studies INCB 50465-204 and INCB 50465-205 only Day 1 and Week 4 PK measures were performed (i.e. under 20 mg QD dosing).

E-R analysis of efficacy endpoints was performed separately by lymphoma types for studies INCB 50465-203 (124 of 126 patients with FL), INCB 50465-204 (100 of 110 patients with MZL), and INCB 50465-205 (105 of 161 patients with MCL). Data from Studies INCB 50465-203 and INCB 50465-204 were also pooled and analysed as indolent non-Hodgkin lymphoma (iNHL; 224 of 236 patients with FL and MZL). A summary of ORR and Kaplan Meier statistics of TTE (PFS, DOR, and T2RESP) by study and treatment is provided in Table 2.

Table 2: Summary of ORR and Kaplan Meier statistics of TTE (PFS, DOR, and T2RESP) by study and treatment

Study INCB 50456	**-203**	**-204**	**-205**	**Pooled -203/-204**
Number of patients:	124 (of 126) patients with FL	100 (of 110) patients with MZL	105 (of 161) patients with MCL	224 (of 236) patients with FL/MZL as iNHL
Responders:	95 (76.6%)	58 (58%)	72 (68.6%)	53 (68.3%)
ORR (%)				
recommended dose	(n=101/124) 79.2%	(n=72/100) 58.3%	(n=75/105) 69.3%	(n=173/224) 70.5%
non-recommended dose	(n=23/124) 65.2%	(n=28/100) 57.1%	(n=30/105) 66.7%	(n=51/224) 60.8%
Kaplan Meier median PFS				
recommended dose	(n=101/124) 15.8 months	(n=72/100) 16.5 months	(n=75/105) 13.6 months	(n=173/224) 15.8 months
non-recommended dose	(n=23/124) 15.8 months	(n=28/100) 16.5 months	(n=30/105) 13.8 months	(n=51/224) 15.8 months
Kaplan Meier median DOR				

	recommended dose	(n=80/95) 14.7 months	(n=42/58) 12.2 months	(n=52/72) 13.7 months	(n=122/153) 13.6 months
dose	non-recommended	(n=15/95) 14.7 months	(n=16/58) 12.2 months	(n=20/72) 13.0 months	(n=31/153) 13.6 months
Kaplan Meier median T2RESP					
	recommended dose	(n=101/124) 1.97 months	(n=72/100) 3.84 months	(n=75/105) 1.91 months	(n=173/224) 2.17 months
dose	non-recommended	(n=23/124) 1.94 months	(n=28/100) 3.68 months	(n=30/105) 1.97 months	(n=51/224) 2.07 months

Binary logistic regression models were developed for ORR. C_{avg_CD} was identified as exposure metrics correlated with ORR in MZL (and MCL) patients, while no clear relationship with any exposure metric was found in patients with FL. Alkaline phosphatase was identified as covariate on ORR in MZL. ORR was similar in patients with non-recommended and recommended dose. Summary of odds ratios for efficacy measures in MZL patients is given below:

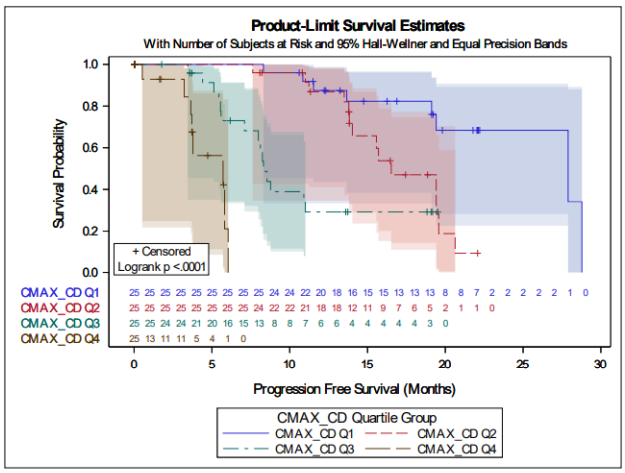
Table 3: Summary of odds ratios for efficacy measures in MZL patients

Efficacy measure, dose, and covariates		**Odds ratio (95 % CI)**
ORR (C_{avg_CD})	Recommended doses	2.12 (1.45, 3.33)
	Alkaline phosphatase	0.782 (0.651, 0.908)
	All doses	2.24 (1.62, 3.26)
	Alkaline phosphatase	0.833 (0.730, 0.937)
PFS ($C_{max,CD}$)	Recommended dose	5.33 (3.07, 10.1)
	All doses	4.98 (3.17, 8.18)
DOR ($C_{max,CD}$)	Recommended dose	6.71 (3.07, 16.5)
	Age	0.07 (0.006, 0.843)
	All doses	3.67 (2.17, 6.50)
T2RESP ($C_{max,CD}$)	Recommended dose	3.68 (2.51, 5.75)
	Body weight (male)	2.24 (1.28, 3.91)
	All doses	3.76 (2.74, 5.39)
	Sex	5.32 (1.17, 24.3)

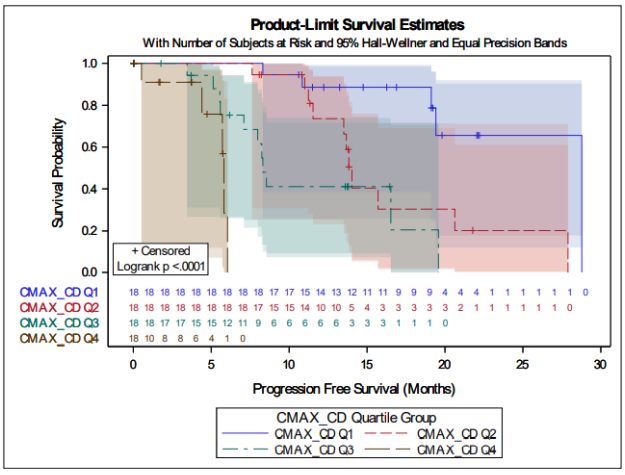
Cox hazard models were developed for PFS, DOR, and time to objective response. C_{max_CD} was identified as exposure metrics correlated with PFS, DOR and time to objective response.

PFS decreased with increasing exposure. No differences could be observed for PFS between patients with non-recommended and recommended dose and across cancer types. For PFS, no covariate was identified for MZL patients. For PFS sex and/or age were covariates in FL or MCL patients. Table 4 shows the Kaplan Meier of PFS versus parsaclisib exposure quartiles in C_{max_CD} in the whole MZL population or MZL receiving recommended dose only, respectively.

Table 4: Kaplan-Meier plot of PFS vs exposure quartiles of C_{max_CD} in patients with MZL (left) and in patients with MZL receiving in recommended dose only (right) - Study INCB 50465-204



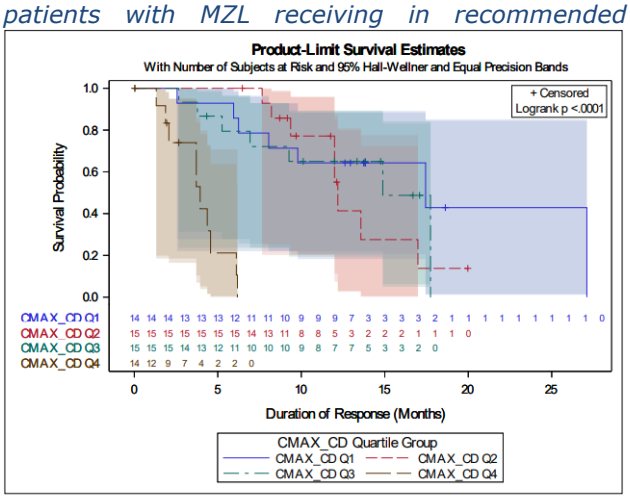
Note: The 4 quartiles in parsaclisib C_{max_CD} were demarcated by the minimum (162 nM), 25th percentile (407 nM), 50th percentile (534 nM), 75th percentile (950 nM), and the maximum (3320 nM).



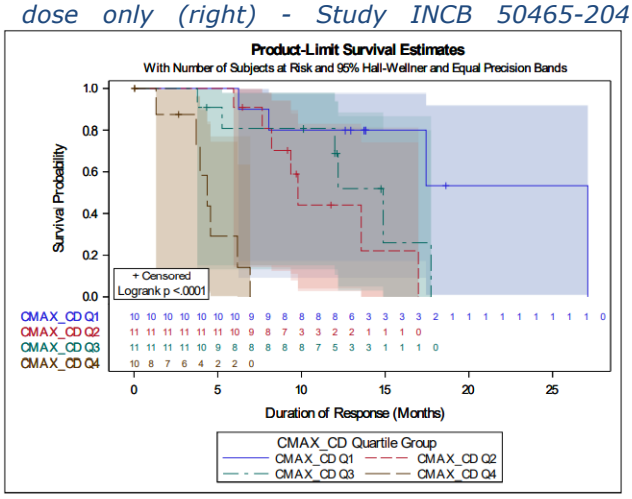
Note: The 4 quartiles in parsaclisib C_{max_CD} were demarcated by the minimum (162 nM), 25th percentile (360 nM), 50th percentile (501 nM), 75th percentile (920 nM), and the maximum (3320 nM).

DOR decreased with increasing exposure. Table 5 show Kaplan Meier plots of DOR versus parsaclisib exposure quartiles in C_{max_CD} in the whole MZL population or MZL receiving recommended dose only, respectively. Age was identified as a covariate on DOR in MZL with recommended dose. Participants with higher ages were associated with lower hazards on DOR, thus DOR was longer in older patients DOR compared to younger. Sex was identified as a predictor on DOR in the whole MCL population. Males were associated with higher hazards (shorter DOR) than females. No covariate was identified for DOR in MCL with recommended dose only. In the FL population C_{avg_CD} was identified as exposure metrics correlated with DOR. Age and ECOG status at baseline were identified as covariate in the whole FL population, whereas only age was identified for those with recommended dose only. Participants with older ages were associated with lower hazards (thus longer DOR) than younger participants, and participants with more severe disease status at baseline (ie, ECOG > 0) were associated with lower hazards in DOR, thus longer DOR.

Table 5: Kaplan Meier plot of DOR vs exposure quartiles of C_{max_CD} in patients with MZL (left) and in patients with MZL receiving in recommended dose only (right) - Study INCB 50465-204



Note: The 4 quartiles in parsaclisib C_{max_CD} were demarcated by the minimum (162 nM), 25th percentile (413 nM), 50th percentile (501 nM), 75th percentile (702 nM), and the maximum (1150 nM).

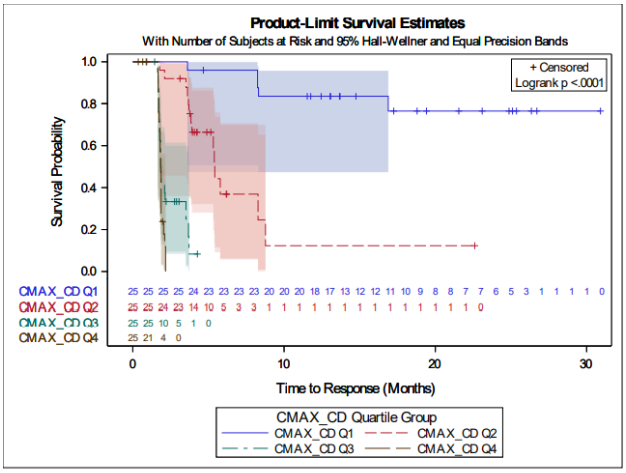


Note: The 4 quartiles in parsaclisib C_{max_CD} were demarcated by the minimum (162 nM), 25th percentile (387 nM), 50th percentile (489 nM), 75th percentile (681 nM), and the maximum (1120 nM).

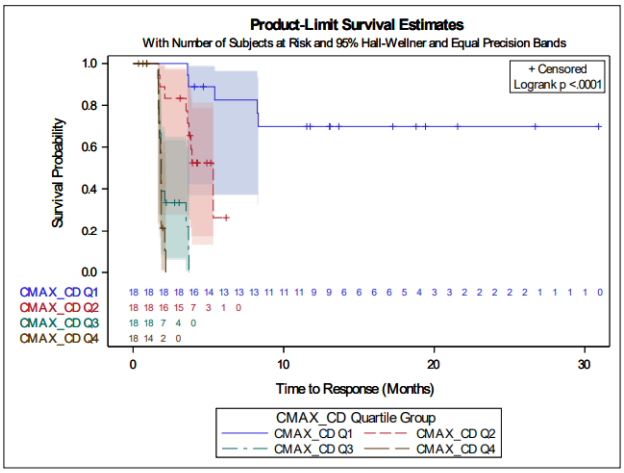
Time to objective response decreases with exposure in MZL patients. Table 6 show Kaplan Meier plots of T2RESP versus parsaclisib exposure quartiles in C_{max_CD} in the whole MZL population or MZL receiving

recommended dose only, respectively. Sex was identified as covariate. Males had higher hazards thus shorter time to response than females. Body weight was identified on time to objective response in participants with MZL treated with recommended dose only. Higher body weight was associated with higher hazards, thus shorter time to response compared to lower body weight. In the whole FL population, higher ALT was associated with higher hazards on time to objective, thus shorter tie to objective response. No covariate predictor was identified in the MCL populations.

Table 6: Kaplan-Meier plot of time to objective response vs exposure quartiles of C_{max_CD} in patients with MZL (left) and patients with MZL treated with recommended dose - Study INCB 50465-204



Note: The 4 quartiles in parsaclisib C_{max_CD} were demarcated by the minimum (218 nM), 25th percentile (603 nM), 50th percentile (1200 nM), 75th percentile (1960 nM), and the maximum (3320 nM).



Note: The 4 quartiles in parsaclisib C_{max_CD} were demarcated by the minimum (253 nM), 25th percentile (643 nM), 50th percentile (1280 nM), 75th percentile (2070 nM), and the maximum (3320 nM).

E-R analysis in safety endpoints was performed for all participants receiving parsaclisib monotherapy treatments in studies INCB 50465-101 (72 of 88 patients with FL, MCL, MZL (n=9=, or DLBCL), INCB 50465-111 (17 of 17 Japanese patients with lymphoma whereof n=2 with MZL), INCB 50465-202 (57 of 60 patients with DLBCL), INCB 50465-203 (124 of 126 patients with FL), INCB 50465-204 (110 of 110 patients with MZL), and INCB 50465-205 (157 of 161 patients with MCL), to align with the population definition of the B-Cell Malignancy Pool (Pool 1) population in the ISS. Overall, 537 participants receiving parsaclisib monotherapy treatment in the six studies were analysed. In total, 294 participants (55 %) were treated with recommended dose and 243 with other doses.

A summary of the number of participants by treatment in each E-R safety analysis population is presented in Table 7. Colitis or thrombocytopenia were excluded from logistic regression, because the incidences were < 10 % and no differences in exposure could be observed by graphical exploration.

Table 7: Summary of participants in the E-R safety analysis by treatment

Participants (n [%]) with:	Recommended Dose (N = 294)	Other Doses (N = 243)	Total (N = 537)
Picked TEAE	200 (68.0)	149 (61.3)	349 (65.0)
Diarrhoea	127 (43.2)	64 (26.3)	191 (35.6)
Nausea	46 (15.6)	55 (22.6)	101 (18.8)
Fatigue	41 (13.9)	41 (16.9)	82 (15.3)
Rash	43 (14.6)	35 (14.4)	78 (14.5)
Neutropenia	43 (14.6)	29 (11.9)	72 (13.4)
Thrombocytopenia	15 (5.1)	22 (9.1)	37 (6.9)
Colitis	27 (9.2)	6 (2.5)	33 (6.1)
Picked SAE	44 (15.0)	13 (5.3)	57 (10.6)
SAE	137 (46.6)	111 (45.7)	248 (46.2)
Picked Grade 3 or Higher TEAE	82 (27.9)	36 (14.8)	118 (22.0)
Grade 3 or Higher TEAE	183 (62.2)	142 (58.4)	325 (60.5)
TEAE Leading to Discontinuation of Drug	78 (26.5)	40 (16.5)	118 (22.0)
TEAE Leading to Dose Interruption	146 (49.7)	105 (43.2)	251 (46.7)
TEAE Leading to Dose Reduction	42 (14.3)	19 (7.8)	61 (11.4)

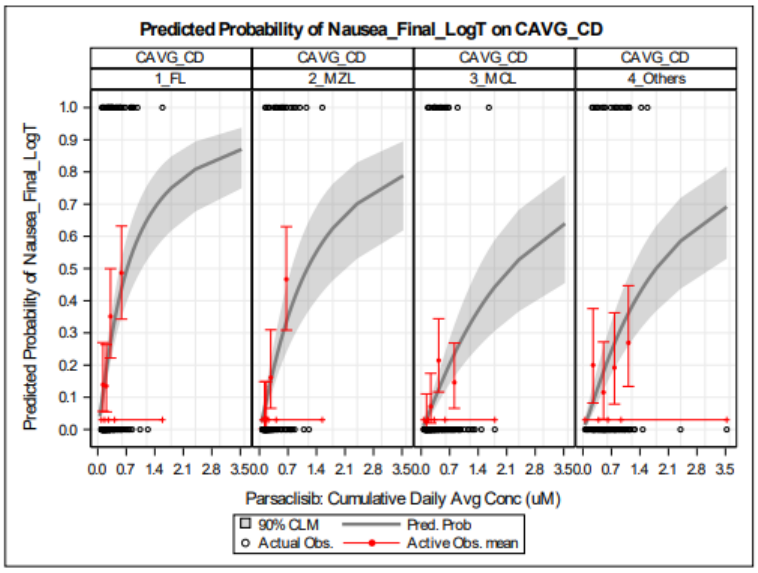
Binary logistic regression models were developed for diarrhoea, nausea, fatigue, rash, neutropenia, SAEs, SAEs picked (colitis, diarrhoea), ≥ Grade 3 AEs, ≥ Grade 3 AEs Picked (colitis, diarrhoea, neutropenia), TEAEs due to dose discontinuation and dose interruption across the six studies included. C_{avg_CD} was identified as a predictor on the incidence of diarrhoea, nausea, rash, dose discontinuation, SAE Picked. C_{avg_CD} and C_{avg_SS} were identified as a predictor on the incidence of SAE. C_{max_CD} was identified as a predictor on the incidence of fatigue, neutropenia, ≥ Grade 3 AE Picked. C_{max_CD} and C_{max_SS} were identified as a predictor on the incidence of ≥ Grade 3 AE Picked and dose interruption. None of exposure metrics evaluated was identified as significant predictors on dose reduction.

Diarrhoea: with increasing exposure incidence rates increased (iNHL), appear to plateau at/for the 3rd quartile (MCL), and decreased (other malignancies) with increasing exposure. In MCL and iNHL, higher albumin level was associated with higher incidence rates. In MCL, participants with ECOG 1 or 2 at baseline experienced lower incidence rate of diarrhoea. In iNHL, other doses was associated with lower incidence of diarrhoea.

Fatigue: higher body weight was corresponding to a higher probability of fatigue incidences.

Nausea: High level of albumin was associated with higher probability of nausea. Patients with FL and/or MZL had higher incidence rates of nausea than patients with MCL. Table 8 shows the final E-R model-predicted versus observed relationships of parsaclisib C_{avg_CD} and incidence of nausea.

Table 8: Probability of nausea by $C_{avg,CD}$ and cancer type



Note: The horizontal red line with notches shows the range of concentrations divided into quartiles of parsaclisib C_{avg_CD} (unit of nM)

Cancer Type Label	*Min*	*Q1*	*Median*	*Q3*	*Max*
1_FL	87.8	166	265	413	1590
2_MZL	67.1	152	220	410	1540
3_MCL	58.4	176	318	586	1810
4_Others	51.5	382	612	937	3530

Neutropenia: Higher neutrophil count at baseline are associated with lower incidences of neutropenia.

SAE: patients receiving other doses tended to have fewer incidences of SAE than those with recommended dose and patients with ECOG 1 or 2 are expected to have more SAEs

≥ Grade 3 AE: patients with mild impaired liver function tended to experience more ≥ Grade 3 AE. Patients receiving other doses tended to experience less ≥ Grade 3 AE than recommended dose.

≥ Grade 3 AE Picked (≥ Grade 3 AEs of colitis, diarrhoea, and/or neutropenia): Patients with higher albumin level at baseline tended to have more ≥ Grade 3 AE Picked. Participants receiving other doses tended to experience less ≥ Grade 3 AE Picked than recommended dose.

TEAEs leading to dose discontinuation: Patients receiving other doses, males, and patients with ECOG 1 or 2 at baseline tended to have fewer dose discontinuations than those receiving recommended dose.

TEAEs leading to dose interruption: Patients with MCL tended to experience more dose interruptions than those with iNHL. Other lymphoma patients (i.e. none of FL, MZL, or MCL) tended to experience lowest dose interruptions. Females and patients with larger body weight at baseline tended to experience more dose interruption.

According to ICH E14 guideline, negative ECG study results are generally defined as an upper two-sided 90% CI of ΔQTc prolongation effect <10 ms which is well retrieved in the results submitted by the applicant.

At the proposed recommended dose of 20 mg of parsaclisib which is the recommended dose, and even for the 45 mg QD dose, no large changes (greater than 20 ms) in the mean QTc interval from baseline were detected in the post dosing setting.

An OC has been raised in the clinical safety part of the report in order to discuss the clinically relevant QT prolongation cases.

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

ADME

Pharmacometrics

Overall, the results of the population PK analysis reveal that the model might be considered acceptable for the intended purpose. However, a number of points are raised as other concerns (OCs) that need to be addressed by the applicant in order to better elucidate the PK behaviour in different patient populations and for all investigated doses.

Importantly, the proposed dosing regimen is currently neither understood nor endorsed from the PK perspective. Steady state of parsaclisib after administration of 20 mg QD is achieved after 3 to 4 days. However, the starting dose of 20 mg QD is proposed to be maintained for 8 weeks. From week 9 onwards, the dose is proposed to be reduced to 2.5 mg QD, an 8-times lower daily dose. In cases of adverse events, the starting dose may be reduced to 10 or 5 mg for 8 weeks and the maintenance dose from week 9 onwards to 1 mg. It is not clear on which basis these doses were selected. Neither a discussion nor a profound justification could be found from the PK package. A general explanation on recommendations for dose adaptions (to lower or higher doses) during the treatment with parsaclisib was not provided in the PK section.

Moreover, PK data are missing; in particularly PK data of the proposed maintenance doses 2.5 mg QD and the additional 20 mg QW dose that was investigated in comparison to the 2.5 mg QD dose, were not submitted with this application. In addition, it seems that the proposed 1 mg QD dose was not investigated in humans; no PK data were submitted for this dose.

The current population PK model should be updated with healthy volunteer data (study INCB 50465-105) as well as data from the renal and hepatic impairment studies (INCB 50465-109 and INCB 50465-108) to allow a quantitative comparison between healthy and patient PK and to enrich a model and further characterise the formulation and special population effects on parsaclisib PK.

All taken together, the proposed dosing regimens are not supported from the PK perspective due to missing data and justifications. The need to submitting the missing PK data is raised as part of a multidisciplinary major objection (MO).

Special populations

A dedicated renal and hepatic impairment studies (INCB 50465-109 and INCB 50465-108) are ongoing and PK data are not currently available. It needs to be clarified when these data are awaited and information regarding the PK of parsaclisib in patients with impaired renal and hepatic functions need to be provided. The SmPC needs to be updated accordingly. Based on population PK modelling, parsaclisib exposure is expected to be higher for patients with moderate renal impairment compared to patients with normal renal function. Hepatic function was not identified as covariates, but only very limited data in patients with impaired hepatic function contributed to the analysis. The model should be updated with the data from the dedicated renal and hepatic impairment studies (see above).

Females and patients with lower body weight (55.5 kg) are expected to reach higher C_{max} levels compared to males and patients with higher body weight (76.3 kg), respectively. In contrast, patients with higher body weight (106 kg) are expected to reach lower C_{max} levels. It is currently not clear whether such differences may have an impact on safety and efficacy, respectively.

Based on the final population PK model, individual predicted PK parameters were generated for the Japanese population compared to non-Japanese. Results reveal that clearance and volume of distribution are lower and absorption seems faster in Japanese, overall resulting in higher parsaclisib exposure in this population.

Based on the presented results, age was found to statistically significant affect the clearance of parsaclisib; however, exposure seem not to be affected markedly.

A number of graphics and tables are requested to further illustrate the differences in parsaclisib's PK across patient populations (see OCs).

Relation between plasma concentration and response

Logistic regression and Cox hazard models were developed. Different exposures measures were tested. Results were compared for the recommended doses and "other doses" or "non-recommended" doses.

In total, 58 % of the MZL patients were responders. C_{avg_CD} (average concentration with respect to cumulative daily average dose from Day 1 to the day of first incidence of the event of interest) was identified as exposure metrics correlated with ORR patients. Alkaline phosphatase was identified as covariate. In MZL patients, measures of efficacy of PFS, DOR and time to objective response were associated with $C_{max,CD}$ (maximum concentration with respect to cumulative daily average dose from Day 1 to the day of first incidence of the event of interest). Overall, in patients with MZL, PFS and DOR were shorter with higher exposure, and higher exposure was associated with faster time to objective response. DOR was longer in older patients compared to younger ages. Males had a shorter time to response than females. Patients with higher body weight receiving recommended dose had a shorter time to response.

No clear association of one exposure measure with safety endpoints was found. Safety endpoints were associated with C_{avg_CD}, C_{avg_SS}, C_{max_CD}, or C_{max_SS}. However, mostly, increasing incidences were associated with increasing exposure measures across safety measures and cancer types, with exception of diarrhoea in "other malignancies", which seem to decrease with increasing exposure. "Other doses" was associated with lower incidences compared to "recommended doses".

Using cumulative daily average doses as a basis for exposure metrics is not supported, because the doses in INCB 50465-204 varied during the study (20 mg QD for 8 weeks, followed by 20 mg QW or 2.5 mg QD). Thus, the cumulative daily average dose and therewith the respective exposure metrics decrease with longer study participation. Moreover, in these analyses, duration of study participation is connected to efficacy measures (e.g. PFS), resulting in patients with early progression participating shorter, and the other way around. Overall, the exposure-response analyses are not considered informative. The applicant should discuss and explain, why the onset of safety issues was observed after > 56 weeks, although steady state of the 20 mg QD is achieved after 3-4 days and the maintenance dose from week 9 onwards is reduced to 2.5 mg QD or 20 mg QW. (OC)

Pharmacokinetic interaction studies

Parsaclisib interaction profile was properly characterized with in vitro, in vivo and in silico informations. In vitro studies showed that parsaclisib was metabolized by CYP3A4 and -2C8 enzymes at clinical concentration levels. In vivo results indicate that parsaclisib PK profile was impacted by the coadministration of strong CYP3A4 inhibitors and inducers in comparison to parsaclisib given alone. However, the developed PBPK model does not describe sufficiently parsaclisib PK and its metabolism to be used to simulate parsaclisib interaction as victim drug.

However, some points need to be further clarified by the applicant:

- Parsaclisib was an in vitro inducer of CYP3A4 at concentration above 3 µM in human hepatocytes, *i.e.* treatment of hepatocyte cultures with parsaclisib (0.3 to 30 µM) for two days resulted in a concentration dependent increase in CYP3A4 mRNA in each lot. The applicant has not further explored parsaclisib induction on CYP3A4 enzyme, notably because the CYP3A ARNm response were less than 20% of the positive control in each donor. However, this rationale is considered not applicable based on the EMA drug-drug interaction guideline (*i.e.* observed concentration-dependent increase in mRNA are above 100%). Parsaclisib induction of CYP3A4 in vivo could therefore not be ruled out. Further evidence, to exclude clinically significant induction should be provided (*e.g.* exploration of parsaclisib CYP3A4 induction potency through RIS correlation method or mechanistic static model). In absence of evidence supporting parsaclisib induction potential for CYP3A4, SmPC should be updated accordingly. (OC)

- The effect of parsaclisib as an UGT inhibitor has not been studied. According to the EMA DDI Guideline, studies on potential inhibition of UGTs are recommended if glucuronidation is one of the main elimination pathways of the drug. However, knowing that some currently marketed drugs (*e.g.* atazanavir, erlotinib, indinavir) are potent UGT inhibitors whereas they do not undergo glucuronidation, and considering the major involvement of UGT in some drugs metabolism such as paracetamol and morphine, the lack of such an investigation should be justified by the applicant. (OC)

Inhibition of the transporter BSEP (ABCB11) has not been investigated. However, considering that parsaclisib is predominantly excreted through hepatic and biliary route, it should be clarified weather parsaclisib is a substrate or inhibitor of BSEP. **(OC)**

In vitro results showed parsaclisib may be clinically relevant inhibitor of P-gp based on intestine concentrations, inhibitor of OCT2, and MATE1 based on systemic concentrations. (**OC**)

3.3.3. Conclusions on clinical pharmacology

Currently it is unclear whether the PK of parsaclisib was sufficiently investigated in humans to support the proposed dosing regimen due to missing data. Therefore, the proposed dosing regimen is not supported from the PK perspective at this stage. A multidisciplinary MO is raised and a number of OCs need to be addressed by the applicant.

3.3.4. Clinical efficacy

Table 9 Clinical studies relevant for efficacy and dosing recommendations

Study ID	**No. of study centres / locations**	**Design**	**Study Posology**	**Study Objective**	**Subjs by arm entered/ compl.**	**Duration**	**Gender M/F Median Age**	**Diagnosis Incl. criteria**	**Primary Endpoint**
INCB 5046 -204	Belgium, France, Germany, Israel, Italy, Poland, Spain, United Kingdom, United States	Phase 2, open-label, single-arm study with 2 cohorts and 2 treatment groups per cohort	Treatment A: Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW PO *OR* Treatment B: Parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD PO	Efficacy	Cohort 1 (ibrutinib experienced) Treatment A: 4 Treatment B: 6 Cohort 2 (BTKi naive) Treatment A: 28 Treatment B: 72	As long as participant is receiving benefit	Ttmt B M: 41 (56.9%) F: 31 (43.1%) Median age: 72 years	Participants with histologically confirmed R/R MZL, including extranodal, nodal, and splenic subtypes	ORR

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
INCB 5046 -203	Canada, Czech Republic, Denmark, Germany, Hungary, Israel, Italy, Poland, Spain, Sweden, United Kingdom, United States	Phase 2, open-label, single-arm study	Treatment A: Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW PO *OR* Treatment B: Parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD PO	Efficacy	Treatment A: 23 Treatment B: 103	As long as participant is receiving benefit	Ttmt B M: 58 (56.3%) F: 45 (43.7%) Median age: 69.0	Participants with histologically confirmed R/R FL	ORR
INCB 5046 -101	United States	Phase 1, open-label, dose escalation study	Parsaclisib 5, 10, 15, 20, 30, and 45 mg QD PO (as of Protocol Amendment 8, participants in all cohorts who had completed 9 weeks of treatment were able to transition to a maintenance dosing regimen of parsaclisib 20 mg or less QW PO)	Safety and tolerability	Parsaclisib monotherapy: 72	As long as participant is receiving benefit	at 20 mg QD: M: 22 (67.4%) F: 12 (35.3%) Median age: 64 years	Participants with R/R B-cell malignancies (except Burkitt's lymphoma and precursor B-lymphoblastic leukemia/ lymphoma) or R/R Hodgkin's lymphoma	clinical laboratory evaluations, physical examination results, and 12-lead ECGs.

3.3.4.1. Dose-response study

Study INCB 50465-101 (CITADEL-101) was a Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB050465 (parsaclisib) and INCB039110 (itacitinib) in Subjects with Previously Treated B-Cell Malignancies. Part 1 of this study was a dose escalation part (3+3 design), performed to determine the MTD (maximum tolerated dose) and recommended dose(s) of parsaclisib to be evaluated further. Part 3 which is relevant for this Application was a dose expansion part of parsaclisib in monotherapy in B-cell malignancies (cohort A), HL (cohort B), DLBCL (cohort C) and in indolent lymphoma (e.g. FL and MZL, cohort D).

On the 72 enrolled patients, 9 had MZL of which 4 with Nodal marginal zone B-cell lymphoma, 2 with Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphatic tissue, 2 with Splenic marginal zone lymphoma, and 1 patient with Marginal zone lymphoma.

Doses from 5 mg up to 45 mg QD were tested. Reponses were observed in all dose levels from 10 mg QD to 45 mg QD and were observed for 7/9 patients with MZL at 20 or 30 mg QD (of which 3 CR). Overall, while both doses of 20 mg and 30 mg QD showed activity and comparable safety profile, the lower dose of 20 mg was chosen to manage the safety profile.

Doses from 5 mg up to 45 mg QD were tested. Reponses were observed in all dose levels from 10 mg QD to 45 mg QD and were observed for 7/9 patients with MZL at 20 or 30 mg QD (of which 3 CR). Overall, while both doses of 20 mg and 30 mg QD showed activity and comparable safety profile, the lower dose of 20 mg was chosen to manage the safety profile. The initial switching from QD to QW schedule was set after 9 weeks as most responses occurred at the first post treatment assessment. The applicant should therefore discuss the decision to set the switch after 8 weeks of treatment in the subsequent pivotal study. (**MO**)

Although no DLT were observed up to 45 mg, discontinuation were frequent leading to adaptation of the scheme of administration. Based on clinical and preclinical data, QW administration was introduced to manage toxicities. Thus, the intended induction dose of 20 mg QD was proposed to be followed by a

maintenance dose of 20 QW. . It should be clarified if the 7 MZL patients who experience a response were treated only at the QD regimen or if they switched to QW regimen. (**OC**)

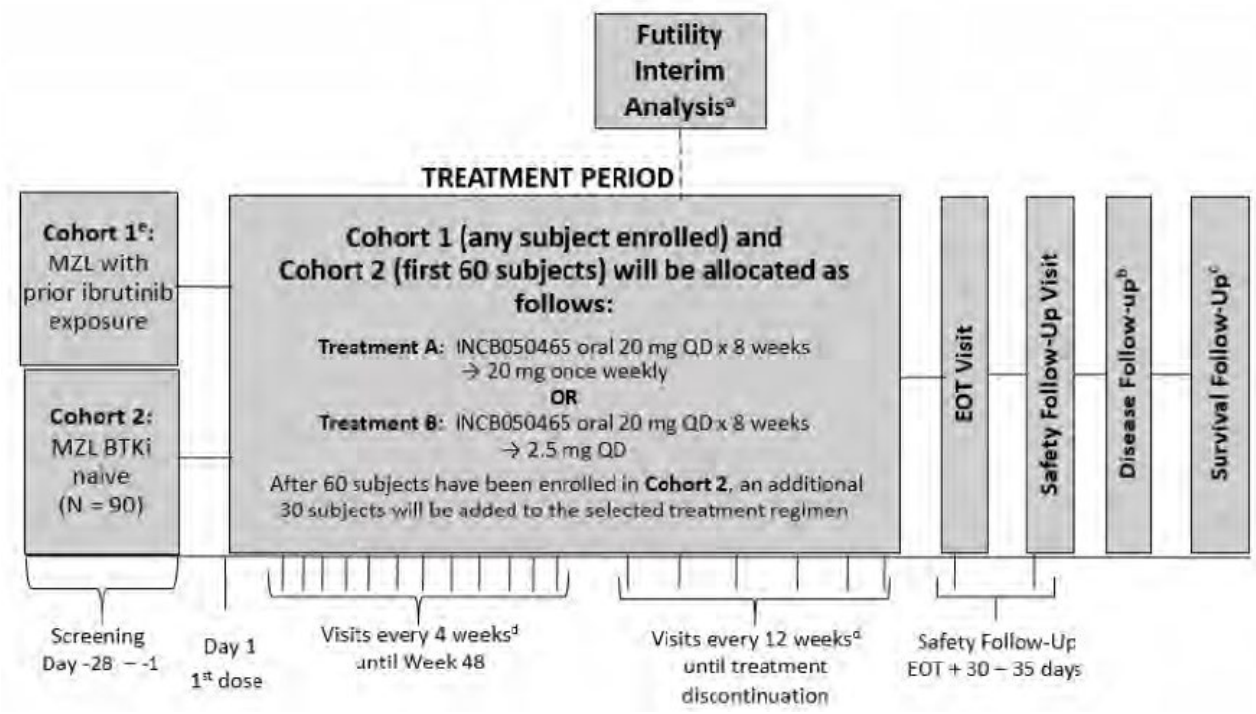
The alternative maintenance regimen of 2.5 mg QD, chosen for this application was evaluated in subsequent studies, the pivotal study 204 and the supportive study 203

3.3.4.2. Main study

INCB 50465-204-A Phase 2, Open-Label, 2-Cohort Study of parsaclisib, a PI3Kδ Inhibitor, in Subjects with Relapsed or Refractory Marginal Zone Lymphoma With or Without Prior Exposure to a BTK Inhibitor (**CITADEL-204**).

Study CITADEL -204 is an ongoing, Phase 2, open-label study of approximately 120 participants originally planned to enroll in 2 cohorts: participants who received prior ibrutinib (Cohort 1) and participants who had not received a prior BTK inhibitor (Cohort 2).

Figure 1 Design of study CITADEL-204



a. A futility analysis was performed for Cohort 2 when the first 30 participants were treated and evaluated for response.
b. Participants who discontinued study drug for a reason other than disease progression continued with disease assessments by radiologic imaging every 8, 12, or 24 weeks as appropriate until disease progression.
c. Every 12 weeks by clinical visit, telephone, or e-mail.
d. Urine pregnancy test and dispensing of study drug occurred every 4 weeks.
e. Per Protocol Amendment 3, Cohort 1 was closed to further enrollment

Methods

Study Participants

Patients were included if they had histologically confirmed MZL and received 1 line or more of systemic therapy including at least 1 anti-CD20 antibody. Patients with extranodal, nodal and splenic subtypes were eligible. Patients were required to have a radiographically measurable disease, ECOG 0-2, adequate hematologic, hepatic and renal function.

Patients were excluded if they had evidence of DLBCL transformation, history of CNS lymphoma, prior treatment with a PI3K inhibitor, ASCT within the previous 6 months, active GVHD, use or expected use of potent CYP3A4 inhibitors/inducers and uncontrolled medical conditions (including renal, hepatic, hematological, GI, endocrine, pulmonary, neurological, cerebral, or psychiatric disease).

Overall, the population included in the study is consistent with the intended indication, including the 3 MZL subtypes. However, in order to clarify the indication, the wording should specified that patients must have received at least 1 prior treatment with one anti-CD20-base therapy. The indication is proposed to be reworded as follow:

"*TRADENAME as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have previously received at least one prior anti-CD20-based therapy"*. (**MO**)

The washout period of "< 2 weeks for any investigational agent or other anticancer medications" from prior therapy, seems short to rule out any carry over effect. An analysis of the time from last dose of prior therapy to D1 should be provided (**OC**).

Treatments

Patients were allocated in one of the two following dosing regimens : parsaclisib 20 mg QD PO for 8 weeks followed by 20 mg once weekly PO (treatment A) or parsaclisib 20 mg QD PO for 8 weeks followed by 2.5 mg QD PO (treatment B) until disease progression, death, unacceptable toxicity, or consent withdrawal. Treatment B correspond to the intended dosing regimen. It is however, not fully understood how was selected the dose of 2.5 mg (see section 3.3.4.1).

Objectives and endpoints

Table 10 Objectives and endpoints of study INCB 50465-204

Objectives	Endpoints
Primary	
To assess the efficacy of parsaclisib in terms of ORR in participants with MZL that is relapsed or refractory after at least 1 systemic treatment regimen	ORR defined as the percentage of participants with CR or PR as determined by an IRC assessment of response according to CT-based response criteria for lymphomas (Cheson et al 2014)
Secondary	
To assess DOR	DOR defined as the time from the first documented CR or PR until disease progression or death from any cause among participants who achieve an objective response, as determined by radiographic disease assessment provided by an IRC
To assess CRR	CRR defined as the percentage of participants with a CR as defined by response criteria for lymphomas (Cheson et al 2014), as determined by an IRC
To assess PFS	PFS defined as the time from the date of the first dose of study drug until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause
To assess OS	OS defined as the time from the first dose of study drug until death from any cause
To assess best percentage change in target lesion size	Best percentage change in target lesion size from baseline, where target lesion size is measured by the sum of the product of the diameters of all target lesion sizes
To characterize the safety and tolerability of parsaclisib	Safety measured by AEs, 12-lead ECGs, chemistry and hematology laboratory values, vital signs, and physical examinations

Objectives	Endpoints
Exploratory	
To characterize the population PK and exposure-response of parsaclisib	CL/F and V_z/F, exposure-response with tumor size, and other clinical/safety measures, as warranted
To explore potential predictive markers associated with safety, response, or resistance to treatment and identify subgroups that would benefit from study treatment	Profile skin, stool, and blood samples for baseline, and on-treatment characteristics associated with response, resistance, and safety, including examinations of plasma markers, microbiome and blood cell characteristics, and summary of baseline tumor-specific gene expression profiles and correlation to response or resistance to study drug
To evaluate changes in HRQoL	Changes in HRQoL as reported by participants using the FACT-Lym
To evaluate MRD after response	Evaluation of MRD after response by polymerase chain reaction or next-generation sequencing

Sample size

The study originally planned to enrol in 2 cohorts: participants who received prior ibrutinib (Cohort 1) and participants who had not received a prior BTK inhibitor (Cohort 2). Given the limited availability of ibrutinib, enrolment into Cohort 1 was closed with Protocol Amendment 3 (07 DEC 2018) for feasibility reasons, after 10 participants had been enrolled.

The study was to enrol up to 90 participants into Cohort 2. If the true ORR was 60%, then there was approximately 90% or 96% probability of observing the lower bound of the 95% CI of ORR ≥ 40% with 60 or 90 participants, respectively.

Randomisation and blinding (masking)

According to the protocol and SAP, randomisation is not applicable for this study. In Appendix 16.1.7, it is stated that a randomization scheme was not used in this study.

However, the first 60 participants in Cohort 2 were allocated to either Treatment A (INCB050465 20 mg QD PO for 8 weeks followed by 20 mg QW PO) or Treatment B (INCB050465 20 mg QD PO for 8 weeks followed by 2.5 mg QD PO). The study reports describes that the allocation to either Treatment A or Treatment B was done at 1:1 ratio and the remaining participants enrolled in Cohort 2 were assigned to the selected dosing regimen Treatment Group B, through the interactive web response system. The applicant is requested to clarify this discrepancy between the SAP and the study report.

This is an open-label study, blinding is not applicable.

Statistical methods

Analysis populations

The **FAS** included all participants enrolled in the study who received at least 1 dose of parsaclisib. The FAS was used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.

The **safety** population included all participants enrolled in the study who received at least 1 dose of parsaclisib. The safety population was used for all safety analyses.

The **PK and PD evaluable populations** included all participants who received at least 1 dose of parsaclisib and provided at least 1 postdose sample for evaluation.

Adjustment for multiplicity

There was no statistical comparison between Cohort 1 and Cohort 2. Within each of the 2 cohorts, there was no statistical comparison between the 2 treatment regimens, and 2-sided 95% CIs were reported for all analyses.

Within each cohort, no adjustment for alpha-spending was considered. An IDMC was assembled to monitor safety data and study conduct on a regular and ongoing basis during the study. The futility interim analysis is described in the sample size section.

There was no formal hypothesis test.

Primary endpoint analysis

The primary efficacy analyses was to be conducted when all participants in the FAS who had achieved a response (ie, CR or PR) as determined by IRC had been followed approximately 12 months from the onset of first response.

For responses as determined by IRC, the best overall response for each participant was provided by the clinical reviewer. The ORR is defined as the proportion of participants who achieved a CR or PR as defined by the Lugano criteria (Cheson et al 2014). Participants who did not have sufficient baseline or on-study data to be assessed for tumor response were considered as non-responders and included in the denominator for the calculation of ORR.

Best overall response as determined by IRC was summarized descriptively. The ORR as determined by IRC with 95% CIs was calculated. Confidence intervals were calculated based on the exact method for binomial distributions.

Secondary endpoint analysis

Duration of response

The Kaplan-Meier estimate of median DOR as determined by IRC and its 95% CIs were provided, with the CIs calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997). Censoring of DOR will follow the same algorithm as the censoring of PFS.

Complete response rate

The CRR as determined by IRC was estimated with 95% CIs for all participants and participants who had at least 2 prior therapies in the FAS. Confidence intervals were calculated based on the exact method for binomial distributions.

Progression free survival

The total number of participants whose disease progressed as determined by IRC or who died and the number of participants censored were summarized. The Kaplan-Meier estimate of median PFS as determined by IRC and its 95% CIs was provided, with the CIs calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997). Progression-free survival rates at Month 6, 12, 18, 24, and 36 were also provided with 95% CIs calculated using Greenwood's formula to estimate the standard error.

Censoring for PFS will follow the algorithm outlined in Table 2, which is based on FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (2015) and Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1
No valid postbaseline response assessments	Censored	Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing) before the missed assessments

NE = not evaluable.

Overall survival

The number of participants who died and the number of participants censored were summarized. The Kaplan-Meier estimate of median OS and its 95% CIs were presented, with the CIs calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997). Survival rates at Month 6, 12, 18, 24, and 36 were also provided with 95% CIs calculated using Greenwood's formula to estimate the standard error. For participants who were still alive at the time of the analysis, OS was censored on the date the participant was last known to be alive.

Best Percentage Change in Disease Burden

The best percentage change from baseline, defined as the largest decrease in target lesion sizes during the study, was summarized, and a waterfall plot produced.

Interim analysis

An interim futility analysis was planned for Cohort 2 when the first 30 participants (Treatment A and Treatment B combined) had been treated and evaluated for response or had permanently discontinued study drug because of disease progression, withdrawal of consent, or death.

Cohort 2 would have been terminated for futility if ≤ 10 of the 30 participants responded (ie, CR or PR) based on assessments provided by the IRC. The probability of stopping at interim for futility was 0.29 with a true response rate of 40%, 0.05 with a true response rate of 50%, or 0.003 with a true response rate of 60%.

An IDMC was charged with evaluating interim futility results. The IDMC consisted of clinicians and an independent statistician. The IDMC was to make recommendations to the sponsor at the planned interim

futility analysis for Cohort 2. The process by which the IDMC would make recommendations and decisions was documented in the IDMC Charter. Additional operational details of the interim analyses, including tables, figures, and listings provided to the IDMC, were provided in the IDMC Charter.

Changes to planned analyses

With protocol amendment 3 (7 December 2018), the enrolment in Cohort 1 was closed and the decision was made to include an additional 30 subjects into Cohort 2, who were to receive the selected treatment regimen. In addition, subjects may switch over to the selected treatment regimen.

There were 3 version of the statistical analysis plan (SAP). Some of the main changes are summarised below.

SAP version	Main changes from previous version
Original (21 February 2019)	N/A
Amendment 1 (27 August 2020)	Efficacy evaluable analysis set removed and full analysis set (FAS) to be used instead for all efficacy analyses (at FDA request) PFS censoring updated Details added on how crossover participants are to be summarised
Amendment 2 (28 January 2021)	Primary analysis timing clarified Sensitivity analyses added to assess the potential impact of crossover participants

Further changes made outside of the protocol or SAP (and made either before or after database lock) are described in the study report, and notably include ORR subgroup analyses per investigator-assessment, BOR/ORR sensitivity analyses excluding assessments after crossover, time-to-response analysis and DOR sensitivity analysis.

Results

Participant flow

Table 11 Analysis populations All screened population

PROTOCOL: INCB 50465-204 (Page 1 of 1)
DRUG/INDICATION: INCB050465/Relapsed or Refractory Marginal Zone Lymphoma DATABASE VERSION: 27 JUL 2021
TLF Version: CSR (Data Cutoff: 14 MAY 2021) TASK: Database Lock

Table 1.1.1

Analysis Populations
(Population: All-screened Population)

	Cohort 1			Cohort 2			
Number of Participants in Analysis Population (n [%])	Treatment A (N=4)	Treatment B (N=6)	Total (N=10)	Treatment A (N=28)	Treatment B (N=72)	Total (N=100)	Total (N=159)
Participants screened	N/A	N/A	N/A	N/A	N/A	N/A	159 (100.0)
Screen failures	N/A	N/A	N/A	N/A	N/A	N/A	47 (29.6)
Screened, not enrolled	N/A	N/A	N/A	N/A	N/A	N/A	2 (1.3)
Withdrawal by Participant	N/A	N/A	N/A	N/A	N/A	N/A	1 (0.6)
Other	N/A	N/A	N/A	N/A	N/A	N/A	1 (0.6)
Participants enrolled	4 (100.0)	6 (100.0)	10 (100.0)	28 (100.0)	72 (100.0)	100 (100.0)	110 (69.2)
Full analysis set [1]	4 (100.0)	6 (100.0)	10 (100.0)	28 (100.0)	72 (100.0)	100 (100.0)	110 (69.2)
Safety population [2]	4 (100.0)	6 (100.0)	10 (100.0)	28 (100.0)	72 (100.0)	100 (100.0)	110 (69.2)

Table 12 Summary of Participant Disposition in Cohort 2-Naïve to BTK inhibitor (Full Analysis Set)

Variable, n (%)	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Participants treated	28 (100.0)	72 (100.0)	100 (100.0)
Participants with ongoing treatment	11 (39.3)	20 (27.8)	31 (31.0)
Participants discontinued from treatment	17 (60.7)	52 (72.2)	69 (69.0)
Primary reason for treatment discontinuation			
Adverse event	3 (10.7)	27 (37.5)	30 (30.0)
Progressive disease	11 (39.3)	20 (27.8)	31 (31.0)
Withdrawal by participant	1 (3.6)	2 (2.8)	3 (3.0)
Physician decision	1 (3.6)	1 (1.4)	2 (2.0)
Protocol deviation	1 (3.6)	1 (1.4)	2 (2.0)
Death	0 (0.0)	1 (1.4)	1 (1.0)
Participants withdrawn from study	5 (17.9)	21 (29.2)	26 (26.0)
Primary reason for study withdrawal			
Death	3 (10.7)	11 (15.3)	14 (14.0)
Other	2 (7.1)	4 (5.6)	6 (6.0)
Withdrawal by participant	0 (0.0)	4 (5.6)	4 (4.0)
Lost to follow-up	0 (0.0)	2 (2.8)	2 (2.0)

Protocol deviations

Table 13 Summary of Protocol Deviations Cohort 2: Bruton's Tyrosine Kinase Naïve (Full Analysis Set)

Deviation Categories	Treatment Group: Treatment A (N=28)	Treatment B (N=72)	Total (N=100)
Number (%) of participants who had any protocol deviations	27 (96.4)	65 (90.3)	92 (92.0)
Adverse Event	1 (3.6)	2 (2.8)	3 (3.0)
Concomitant Medications	0 (0.0)	4 (5.6)	4 (4.0)
Entry Criteria	2 (7.1)	3 (4.2)	5 (5.0)
Informed Consent	6 (21.4)	14 (19.4)	20 (20.0)
Non Compliance With Study Procedure - Missed Assessment	24 (85.7)	59 (81.9)	83 (83.0)
Non Compliance With Study Procedure - Out Of Window Assessment	24 (85.7)	53 (73.6)	77 (77.0)
Non Compliance With Study Treatment	5 (17.9)	7 (9.7)	12 (12.0)
Other	8 (28.6)	13 (18.1)	21 (21.0)

Protocol deviations were numerous (92%) and mainly related to non-compliance with study procedure-missed assessment for 83% of patients or out of window assessment for 77% of patients for both treatment groups. No information is provided as to which are considered major deviations. Covid-19 related protocol deviations were provided as justification by the applicant. However, COVID-19 related protocol deviations account only for 22 to 35% of these deviations. In addition, an average of 20% of patients in both categories "informed consent" and "other" are described but not detailed. Therefore, the applicant should detail and discuss the impact on data integrity of the protocol deviations of each of the following categories "non-compliance with study procedure-missed assessment and out of window assessment" not related to COVID-19, "informed consent" and "other". (**OC**)

Additionally more details are requested on the inclusion/exclusion criteria violations. These included violations for inclusion criteria 2 (Histologically confirmed MZL, including extranodal, nodal, and splenic subtypes) and 5 (Subjects must be willing to undergo an incisional or excisional lymph node or tissue biopsy or provide a lymph node or tissue biopsy from the most recent available archival tissue).

applicant should provide additional information on these subjects to confirm that they indeed had the diagnosis of r/r MZL and would support the use of their data in the efficacy analysis (**OC**).

Recruitment

As of the data cut-off date (14 May 2021), enrollment was complete in all countries. A total of 100 participants were enrolled in Cohort 2 (ibrutinib naïve) at 44 study sites: 15 in the US, 8 in Italy, 4 in Israel, 5 in France, 5 in Spain, 2 in Poland, 2 in Great Britain, 2 in Belgium, and 1 in Germany..

With the first participant was dosed on 18 December 2017, the median follow-up time from the first dose date to the data cutoff date was 26.68 months (range: 15.8-40.9 months) for Cohort 2 and 24.94 months (range: 15.8-40.9) for Treatment B (i.e. intended dosing regimen).

Conduct of the study

A total of 4 global amendments were noted. They were related to improvement of safety of the clinical trial (additional guidance on doses modifications and dose reduction schedules) or modification of the design for closure of cohort 1 and increased of the number of subject in cohort 2.

Baseline data

Table 14 Summary of Demographics and Baseline Characteristics in Cohort 2 (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Age (years)			
Mean (STD)	68.1 (9.22)	69.8 (13.30)	69.3 (12.27)
Median	67.0	72.0	71.0
Min, max	52, 86	35, 95	35, 95
Age group, n (%)			
< 65 years	8 (28.6)	20 (27.8)	28 (28.0)
≥ 65 years	20 (71.4)	52 (72.2)	72 (72.0)
Sex, n (%)			
Male	12 (42.9)	41 (56.9)	53 (53.0)
Female	16 (57.1)	31 (43.1)	47 (47.0)
Race, n (%)			
White/Caucasian	23 (82.1)	60 (83.3)	83 (83.0)
Black/African American	0 (0.0)	1 (1.4)	1 (1.0)
Asian	0 (0.0)	1 (1.4)	1 (1.0)
Other	5 (17.9)	10 (13.9)	15 (15.0)
Ethnicity, n (%)			
Not Hispanic or Latino	19 (67.9)	57 (79.2)	76 (76.0)
Hispanic or Latino	3 (10.7)	4 (5.6)	7 (7.0)
Not reported	2 (7.1)	2 (2.8)	4 (4.0)
Unknown	1 (3.6)	4 (5.6)	5 (5.0)
Other	3 (10.7)	5 (6.9)	8 (8.0)
Geographic region, n (%)			
Rest of world	21 (75.0)	45 (62.5)	66 (66.0)
North America	7 (25.0)	27 (37.5)	34 (34.0)
Body mass index (kg/m^2)			
Mean (STD)	25.66 (4.91)	26.76 (5.20)	26.46 (5.12)
Median	25.13	25.90	25.77
Min, max	16.9, 34.5	17.4, 48.9	16.9, 48.9
ECOG performance status, n (%)			
0	15 (53.6)	46 (63.9)	61 (61.0)
1	11 (39.3)	23 (31.9)	34 (34.0)
2	2 (7.1)	3 (4.2)	5 (5.0)

Baseline Disease Characteristics

Table 15 Summary of Baseline Disease Characteristics in Cohort 2 (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Time since initial diagnosis (years)[a]			
Mean (STD)	6.44 (5.547)	5.26 (4.453)	5.59 (4.785)
Median	4.74	4.37	4.60
Min, max	0.3, 20.1	0.1, 19.8	0.1, 20.1
Subtypes, n (%)			
Nodal MZL	6 (21.4)	25 (34.7)	31 (31.0)
Extranodal MZL - MALT	11 (39.3)	23 (31.9)	34 (34.0)
Splenic MZL	11 (39.3)	24 (33.3)	35 (35.0)
MZL related to infection, n (%)			
Yes	1 (3.6)	2 (2.8)	3 (3.0)
No	27 (96.4)	69 (95.8)	96 (96.0)
Missing	0 (0.0)	1 (1.4)	1 (1.0)
MZL related to *H. Pylori*-induced infection, n (%)			
Yes	0 (0.0)	1 (1.4)	1 (1.0)
No	28 (100.0)	70 (97.2)	98 (98.0)
Missing	0 (0.0)	1 (1.4)	1 (1.0)
Ann Arbor staging, n (%)			
Stage I	1 (3.6)	6 (8.3)	7 (7.0)
Stage II	3 (10.7)	4 (5.6)	7 (7.0)
Stage III	1 (3.6)	7 (9.7)	8 (8.0)
Stage IV	22 (78.6)	52 (72.2)	74 (74.0)
Missing	1 (3.6)	3 (4.2)	4 (4.0)
Presence of B-symptoms, n (%)			
No	22 (78.6)	56 (77.8)	78 (78.0)
Yes	6 (21.4)	15 (20.8)	21 (21.0)
Fever	0 (0.0)	2 (2.8)	2 (2.0)
Night sweats	5 (17.9)	12 (16.7)	17 (17.0)
Weight loss	1 (3.6)	5 (6.9)	6 (6.0)
Other	2 (7.1)	2 (2.8)	4 (4.0)
Missing	0 (0.0)	1 (1.4)	1 (1.0)
Bone marrow involvement, n (%)			
No	9 (32.1)	33 (45.8)	42 (42.0)
Yes	18 (64.3)	30 (41.7)	48 (48.0)
Unknown	1 (3.6)	8 (11.1)	9 (9.0)
Missing	0 (0.0)	1 (1.4)	1 (1.0)
Relapsed/refractory status to the most recent prior therapy, n (%)			
Relapsed	13 (46.4)	33 (45.8)	46 (46.0)
Refractory	14 (50.0)	35 (48.6)	49 (49.0)
Unknown	1 (3.6)	4 (5.6)	5 (5.0)

The equal repartition of the 3 subtypes is unexpected. Indeed, NMZL subtype which represents less than 10% of MZL appear overrepresented whereas the subtype ENMZL (70% of MZL) appears underrepresented. The applicant should explain this discrepancy compared to epidemiological data. (**OC**)

The study included subjects who were diagnosed 0.1 years before the study. The fact that there might have been patients whose condition progressed rapidly is acknowledged and could thus benefit from the inclusion into the current study. Nevertheless, additional supportive information regarding previous treatment regimens, reasons for treatment discontinuation, r/r status and inclusion into the study should be provided for the subjects who have been included into the study less than 3 months since the start of the study **(OC).**

Additional information on the study subjects who are questionable in terms of their fulfilment of the enrolment criteria should also be provided. There are 4 subjects with unknown relapse/refractory status, thus it should be clarified how they represent the population under investigation or which information confirmed their refractory/recurrence status (e.g. how they are considered eligible for the study). **(OC).**

Prior and concomitant medication

Table 16 Summary of Prior Systemic Cancer Therapy in Cohort 2 (Full Analysis Set)

Variable, n (%)	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Participants with prior systemic therapy	28 (100.0)	72 (100.0)	100 (100.0)
Number of prior systemic therapy regimens			
1	16 (57.1)	33 (45.8)	49 (49.0)
2	6 (21.4)	25 (34.7)	31 (31.0)
3	3 (10.7)	10 (13.9)	13 (13.0)
4	1 (3.6)	3 (4.2)	4 (4.0)
≥ 5	2 (7.1)	1 (1.4)	3 (3.0)
Min	1	1	1
Median	1.0	2.0	2.0
Max	8	5	8
Participants with prior radiation	4 (14.3)	7 (9.7)	11 (11.0)
Participants with surgery or surgical procedure	8 (28.6)	11 (15.3)	19 (19.0)
Participants with prior hematopoietic stem cell transplant	1 (3.6)	3 (4.2)	4 (4.0)

All participants received at least 1 anti-CD20 antibody as monotherapy or in a combination regimen. The other most common prior systemic therapies by WHO drug term were cyclophosphamide (47.0%), bendamustine (44.0%), vincristine (35.0%), prednisone (28.0%), and doxorubicin (26.0). However, it is not clear from the provided tables how many patients had rituximab alone or in association, and what those associations were. The applicant should provide a summary of prvious treatment lines received. (**OC**)

In Cohort 2, all 100 participants were on at least one concomitant medication. The most commonly used concomitant medications in Cohort 2 were Bactrim (93.0%), and anilides, paracetamol, and acyclovir (33.0% each).

All participants received a standard PJP prophylaxis regimen as determined by the investigator.

Numbers analysed

The FAS for cohort 2 comprised a total of 100 subjects in which 28 patients received treatment A (20 mg QD followed by 20 mg QW) and 72 received treatment B (20 mg QD followed by 2.5 mg QD). The safety population also included all participants enrolled in the study who received at least 1 dose of parsaclisib. The safety population was used for all safety analyses.

Outcomes and estimation

Unless otherwise specified, Treatment A comprises participants who received parsaclisib 20 mg QD for 8 weeks and switched to the 20 mg QW maintenance dose, including participants who later crossed over to the 2.5 mg QD maintenance dose (3 patients).

The results of the interim analysis (data cutoff 08 JAN 2019) showed that the futility boundary was not crossed and the enrollment continued until 100 participants were treated.

Primary endpoint

Table 17 Summary of Best Overall Response and Objective and Complete Response Rates Based on IRC Assessment in Cohort 2 (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Objective response[a], n (%)	16 (57.1)	43 (59.7)	59 (59.0)
95% CI[b]	37.2, 75.5	47.5, 71.1	48.7, 68.7
CR, n (%)	3 (10.7)	4 (5.6)	7 (7.0)
95% CI[b]	2.3, 28.2	1.5, 13.6	2.9, 13.9
BOR[c], n (%)			
CR	3 (10.7)	4 (5.6)	7 (7.0)
PR	13 (46.4)	39 (54.2)	52 (52.0)
Stable disease	7 (25.0)	21 (29.2)	28 (28.0)
Progressive disease	2 (7.1)	0 (0.0)	2 (2.0)
Not evaluable	2 (7.1)	2 (2.8)	4 (4.0)
Not assessed[d]	1 (3.6)	6 (8.3)	7 (7.0)

Note: Cohort 2 comprised participants who were naive to prior BTK inhibitor.
[a] Participants who had best overall response of CR or PR.
[b] The CI was calculated based on the exact method for binomial distribution.
[c] BOR was the best response recorded prior to and including the first PD, in the order of CR, PR, SD, PD, and NE. Any assessments after new anti-lymphoma therapy were excluded from the best overall response determination.
[d] No post-baseline response data available.

Among the 43 participants who had CR or PR in cohort 2B, median time to response was 8.14 weeks (range: 5.0-36.1 weeks); response was observed by the time of first planned assessment (Week 8) in 67.4% of responders.

Considering that both dosing regimens showed similar efficacy data according to above data (section 3.3.2.1) that less patients discontinued treatment due to an adverse event in cohort 2A than in cohort 2B, the choice of the maintenance dose at 2.5 mg QD over 20 mg QW with is not fully understood and should be better explained with regards to efficacy and safety data, especially since dose escalation study did not assess this dose level and since it not supported by pharmacological studies (**MO**).

The applicant provided a sensitivity analysis for ORR and BOR by censoring the 3 crossover patients who switch from treatment A to treatment B during the maintenance period. 2/3 crossover participants achieved PR as BOR before switching and 1/3 participant achieved CR as BOR after switching to treatment B. It is agreed that sensitivity analysis showed similar results to primary analysis.

The SmPC of parsaclisib recommends a dose decrease to 10 mg QD then 5 md QD if adverse reactions occurs during weeks 1 to 8 and to 1 mg QD if adverse reactions occurs from week 9. An analysis and a discussion of efficacy data for patients who experienced a dose decrease is requested (**OC**).

In the SmPC section 5.1, The applicant included information about patients who previously received ibrutinib at the intended dosing regimen. It is considered that these information should not be included in the SmpC considering the low sample size (n=6), and the lack of authorized PI3K in EU.

In addition, while the rate of each type of MZL included in CITADEL-204 study may be informative, the ORR for subgroup of MZL type, refractory and relapse patient are not considered statistically compelling and should be deleted as well.

The applicant is requested to delete any information in section 5.1 related to the cohort 1 and any information on efficacy for subgroups. (**OC**)

Secondary endpoints

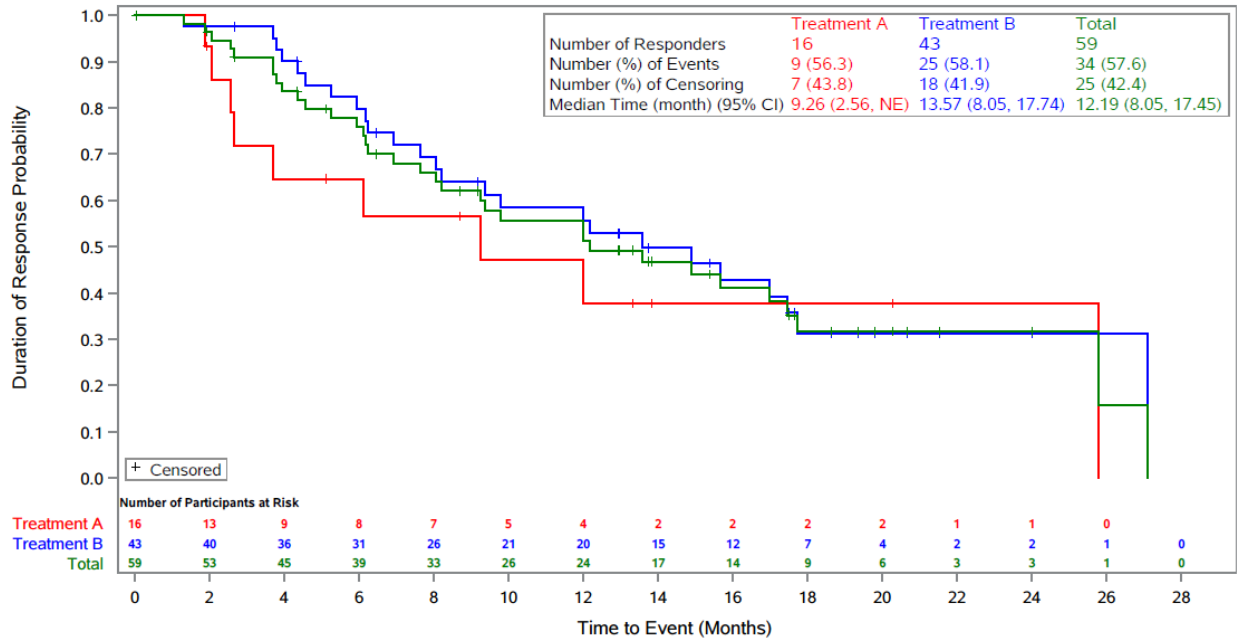
Duration of Response Based on IRC Assessment

Table 18 Summary of Duration of Response Based on IRC Assessment in Cohort 2 (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Number of objective responders[a], n (%)	16 (57.1)	43 (59.7)	59 (59.0)
Number of participants with events[b]	9 (56.3)	25 (58.1)	34 (57.6)
Disease progression	9 (56.3)	22 (51.2)	31 (52.5)
Death	0 (0.0)	3 (7.0)	3 (5.1)
Number of participants censored[b]	7 (43.8)	18 (41.9)	25 (42.4)
Ongoing with study	6 (37.5)	14 (32.6)	20 (33.9)
New anticancer treatment started	1 (6.3)	0 (0.0)	1 (1.7)
Study discontinuation	0 (0.0)	3 (7.0)	3 (5.1)
Death or progression after ≥ 2 missed assessments	0 (0.0)	1 (2.3)	1 (1.7)
Median DOR (months) (95% CI)[c]	9.26 (2.56, NE)	13.57 (8.05, 17.74)	12.19 (8.05, 17.45)

Note: Cohort 2 comprises participants who are naive to prior BTK inhibitor.
[a] Participants who have BOR of complete or PR.
[b] Percentages were calculated based on the number of objective responders as denominator.
[c] The 95% CI was calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).
Source: Table 2.2.1.2.

Table 19 KM Estimates of DOR Based on IRC Assessment in Cohort 2 (Full Analysis Set)



Progression-Free Survival Based on IRC Assessment

Table 20 Summary of Progression-Free Survival Based on IRC Assessment in Cohort 2 (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Number of participants with events, n (%)	14 (50.0)	33 (45.8)	47 (47.0)
Disease progression	13 (46.4)	28 (38.9)	41 (41.0)
Death	1 (3.6)	5 (6.9)	6 (6.0)
Number of participants censored	14 (50.0)	39 (54.2)	53 (53.0)
No baseline or no valid postbaseline assessment	3 (10.7)	5 (6.9)	8 (8.0)
Study discontinuation	0 (0.0)	6 (8.3)	6 (6.0)
Ongoing with study	9 (32.1)	22 (30.6)	31 (31.0)
Death or progression after ≥ 2 missed assessments	1 (3.6)	3 (4.2)	4 (4.0)
New anticancer treatment started	1 (3.6)	3 (4.2)	4 (4.0)
Median PFS (months) (95% CI)[a]	19.42 (8.77, NE)	16.53 (11.53, 20.63)	17.74 (13.50, 20.63)
PFS rate (95% CI)[b]			
Month 6	0.784 (0.556, 0.904)	0.865 (0.747, 0.930)	0.843 (0.745, 0.906)
Month 12	0.610 (0.384, 0.775)	0.637 (0.494, 0.750)	0.630 (0.512, 0.727)

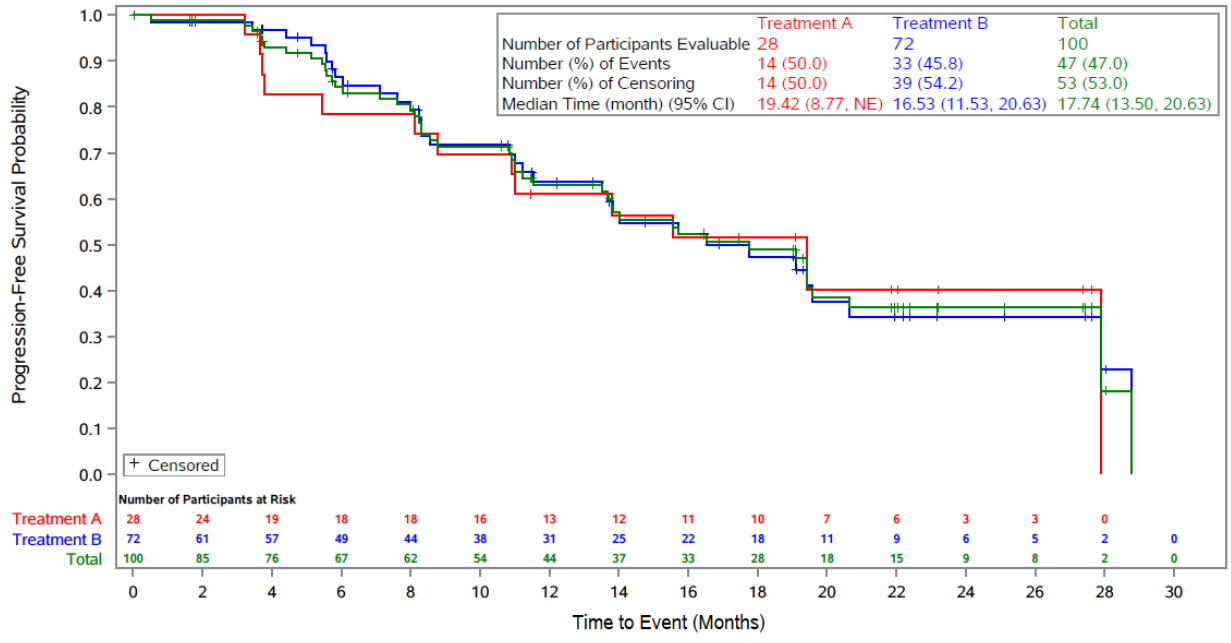
Note: Cohort 2 comprises participants who are naive to prior BTK inhibitor.

[a] The 95% CI was calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

[b] The 95% CI was calculated using Greenwood's formula to estimate the standard error.

Source: Table 2.2.3.2.

Table 21 Kaplan-Meier Estimates of Progression-Free Survival Based on IRC Assessment in Cohort 2 (Full Analysis Set)



Median DOR (95% CI) at the intended dosing regimen was 13.57 months (8.05, 17.74), superior to the median DOR in treatment arm A (9.26 months, 95% CI: 2.56, NE). This duration should be put into perspective with the indolent nature of MZL and the absence of control arm. To be noted, in the AUGMENT trial assessing RTX + lenalidomide vs RTX + placebo which is chosen in the below MAIC, median DOR (95% CI) was 17.4 months in R² arm and Not Evaluable for comparator arm with a median follow-up of 28.30 months. However, no comparison of PFS between both trials in th MAIC was performed.

Median PFS (95% CI) at the intended dosing regimen was 16.53 months (11.53, 20.63), numerically lower than PFS in treatment group A (19.42 months). Similarly to DOR, these results are to be analysed with regards to the lack of control arm and the indolent nature of MZL.

It is agreed that sensitivity analysis for DOR and PFS were consistent with the primary analysis. The data cut-off date is 14 may 2021, considering the low maturity of data at this date, the applicant is requested to provide for an update of efficacy results (**OC**).

Section 5.1 of the SmPC describes PFS for cohort 2, ibrutinib naïve patients at the intended posology which is not endorsed. Indeed, PFS is a secondary endpoint of a SAT which is difficult to interpret. According to the guideline on SmPC, it does not meet the conditions of being statistically compelling and clinically relevant to be included in 5.1. In addition, a low maturity of PFS data can be observe with <50% of events.

The applicant is requested to delete from section 5.1 of the SmPC any information regarding PFS which is not considered statistically compelling nor clinically relevant due to the nature of the single arm pivotal study. (**OC**)

Overall Survival

Table 22 Summary of Overall Survival Cohort 2: Bruton's Tyrosine Kinase Naïve (Population: Full Analysis Set)

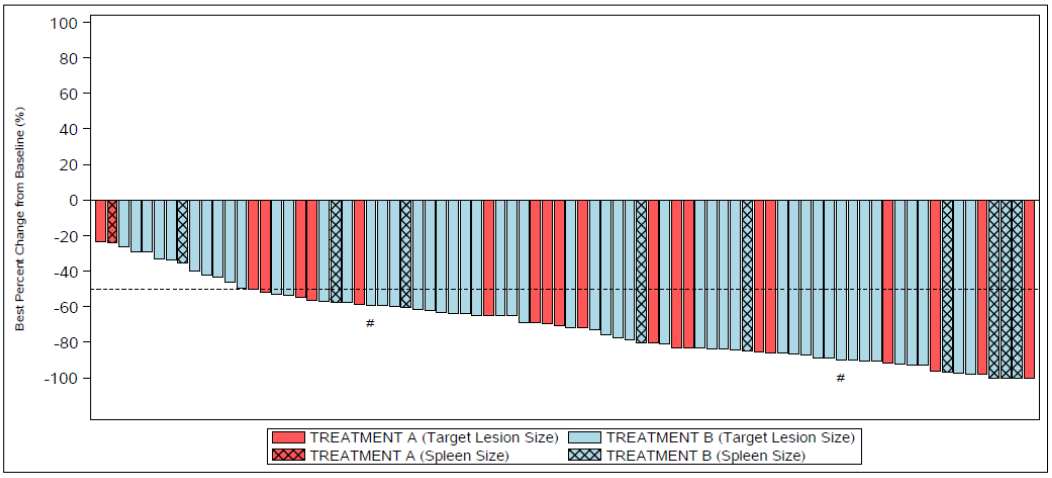
	Treatment Group		
Variable	Treatment A (N=28)	Treatment B (N=72)	Total (N=100)
Number (%) of Participants Who Died	3 (10.7)	12 (16.7)	15 (15.0)
Number (%) of Participants Censored	25 (89.3)	60 (83.3)	85 (85.0)
Median Overall Survival (months) (95% CI) [a]	36.70 (NE - NE)	NR (NE - NE)	36.70 (36.70 - NE)
Survival Rate (95% CI) [b]			
Month 6	1.000 (1.000 - 1.000)	0.972 (0.892 - 0.993)	0.980 (0.921 - 0.995)
Month 12	1.000 (1.000 - 1.000)	0.897 (0.797 - 0.950)	0.927 (0.852 - 0.964)

Median OS at the intended posology was not reached as 60 patients (83%) were still alive at the data cut-off.

Best Percentage Change From Baseline in Disease Burden Size Based on IRC Assessment

Table 23 Best Percentage Change From Baseline in Disease Burden Size Based on IRC Assessment

Figure 4.2.6.2
Waterfall Plot of Best Percent Change in Disease Burden as Determined by Independent Review Committee
Cohort 2: Bruton's Tyrosine Kinase Naïve
(Population: Full Analysis Set)



PROGRAM/OUTPUT:F_WF_SPD_IRC2/F_4_2_6_2_WF_SPD_IRC2 **DATE(TIME): 23AUG21(11:36)**

Treatment A: INCB050465 20 MG QD FOR 8 WKS + 20 MG QW; Treatment B: INCB050465 20 MG QD FOR 8 WKS + 2.5 MG QD
Note 1: For each participant with measurable lesions at baseline, target lesion size as measured by sum of product of diameters of all target lesions will be used as the measure for disease burden. For splenic marginal zone lymphoma participants who have splenomegaly only at baseline, the spleen size as measured by the enlarged portion of the splenic length (ie, splenic length in excess of the 13 cm normal threshold) will be used as the measure for disease burden.
Note 2: This plot includes participants who had baseline and at least one postbaseline valid measurements for disease burden. No participant in this plot had best overall response of NE.
Note 3: A number sign (#) indicates participants who had clinical PD observed on/before the date of radiological PD and new anti-lymphoma therapy.
Reference: Listing 2.6.4.1.2, 2.6.4.2.2

All 70 participants who had a baseline and at least a post baseline measurement of target lesion, had a reduction in the sum of product lesion diameter, of which 59 participant had best reduction > 50% from baseline.

Ancillary analyses

Endpoints Based on Investigator Assessment

- *Primary endpoint*

Table 24 Summary of Best Overall Response and Objective and Complete Response Rates Based on Investigator Assessment in Cohort 2 (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks Then 20 mg QW (N = 28)	Treatment B 20 mg QD for 8 Weeks Then 2.5 mg QD (N = 72)	Total (N = 100)
Objective response[a], n (%)	23 (82.1)	50 (69.4)	73 (73.0)
95% CI[b]	63.1, 93.9	57.5, 79.8	63.2, 81.4
CR, n (%)	5 (17.9)	6 (8.3)	11 (11.0)
95% CI[b]	6.1, 36.9	3.1, 17.3	5.6, 18.8
BOR[c], n (%)			
CR	5 (17.9)	6 (8.3)	11 (11.0)
PR	18 (64.3)	44 (61.1)	62 (62.0)
Stable disease	4 (14.3)	15 (20.8)	19 (19.0)
Progressive disease	0 (0.0)	1 (1.4)	1 (1.0)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)
Not assessed[d]	1 (3.6)	6 (8.3)	7 (7.0)

[a] Participants who had BOR of CR or PR.
[b] The CI was calculated based on the exact method for binomial distribution.
[c] Best overall response was the best response recorded prior to and including the first PD, in the order of CR, PR, SD, PD and NE. Any assessments after new anti-lymphoma therapy were excluded from the best overall response determination.
[d] No post-baseline response data available.
Note: Cohort 2 comprises participants who are naive to prior BTK inhibitor.
Source: Table 2.1.2.2

- *Secondary endpoints*

Table 25 Summary of Duration of Response as Reported by Investigator Cohort 2: Bruton's Tyrosine Kinase Naïve (Population: Full Analysis Set)

Variable	Treatment Group: Treatment A (N=28)	Treatment Group: Treatment B (N=72)	Total (N=100)
Number (%) of Objective Responders [a]	23 (82.1)	50 (69.4)	73 (73.0)
Number (%) of Participants with Events [b]	11 (47.8)	23 (46.0)	34 (46.6)
Disease Progression	11 (47.8)	20 (40.0)	31 (42.5)
Death	0 (0.0)	3 (6.0)	3 (4.1)
Number (%) of Participants Censored [b]	12 (52.2)	27 (54.0)	39 (53.4)
Study Discontinuation	1 (4.3)	6 (12.0)	7 (9.6)
Ongoing With Study	10 (43.5)	19 (38.0)	29 (39.7)
Death or Progression after >=2 Missed Assessments	1 (4.3)	0 (0.0)	1 (1.4)
New Anticancer Treatment Started	0 (0.0)	2 (4.0)	2 (2.7)
Median Duration of Response (months) (95% CI) [c]	17.51 (7.43 - NE)	14.88 (10.58 - NE)	17.51 (12.02 - NE)

Table 26 Summary of Progression-Free Survival as Reported by Investigator Cohort 2: Bruton's Tyrosine Kinase Naïve (Population: Full Analysis Set)

Variable	Treatment Group: Treatment A (N=28)	Treatment B (N=72)	Total (N=100)
Number (%) of Participants with Events	11 (39.3)	29 (40.3)	40 (40.0)
Disease Progression	11 (39.3)	25 (34.7)	36 (36.0)
Death	0 (0.0)	4 (5.6)	4 (4.0)
Number (%) of Participants Censored	17 (60.7)	43 (59.7)	60 (60.0)
No Baseline or No Valid Postbaseline Assessment	1 (3.6)	3 (4.2)	4 (4.0)
Study Discontinuation	1 (3.6)	7 (9.7)	8 (8.0)
Ongoing With Study	12 (42.9)	27 (37.5)	39 (39.0)
Death or Progression after >=2 Missed Assessments	2 (7.1)	3 (4.2)	5 (5.0)
New Anticancer Treatment Started	1 (3.6)	3 (4.2)	4 (4.0)
Median Progression-Free Survival (months) (95% CI) [a]	NR (13.80 - NE)	19.81 (14.75 - NE)	23.59 (16.56 - NE)
Progression-Free Survival Rate (95% CI) [b]			
Month 6	0.849 (0.645 - 0.940)	0.869 (0.754 - 0.932)	0.863 (0.771 - 0.920)
Month 12	0.770 (0.557 - 0.889)	0.746 (0.614 - 0.839)	0.753 (0.646 - 0.832)

Higher ORR and CR were observed when assessed by investigator compared to IRC. An OC is raised in section 3.3.1.8 statistical methods regarding comparison of both assessment. Median DOR in treatment A group was 17.51 months according to investigator's while it was 9.26 months according to IRC. In addition, differences are also observed for PFS in both treatment groups. The applicant should discuss the main discrepancies between IRC and investigator assessment (**OC**).

Efficacy Assessment of Participants Who Had 2 or More Prior Therapies

ORR and BOR for patients who had 2 or more prior systemic therapies in cohort 2 according to IRC are overall consistent with the primary analysis. ORR (95% CI) at the intended posology is 53.8% (37.2, 69.9) with CR accounting for 5.1% (2 patients) and PR for 48.7% (19 patients). ORR (95% CI) according to investigators assessment was higher than IRC 69.2 % (52.4, 83.0) but CR was consistent (5.1%).

Subgroup analyses

No difference are highlighted by the subgroups analysis. However, in the absence of a control arm, assessment of subgroup analysis is challenging.

Nevertheless, based on pharmacokinetic assessment, the exposure range is expected to be lower than that usually accepted for heavier patients (section 2.1.9.5). Therefore, a subgroup analysis of efficacy results by body weight is requested. (**OC**)

3.3.4.3. Summary of main efficacy results

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

Table 27 Summary of efficacy for trial CITADEL-204 (INCB 5064-204)

Title: A Phase 2, Open-Label, 2-Cohort Study of INCB050465, a PI3Kδ Inhibitor, in Subjects With Relapsed or Refractory Marginal Zone Lymphoma With or Without Prior Exposure to a BTK Inhibitor (CITADEL-204)		
Study identifier	Protocol number INCB 50465-204; EudraCT 2017-000970-12; NCT03144674	
Design	This is an ongoing, Phase 2, multicenter, open-label study of parsaclisib in participants with relapsed or refractory marginal zone lymphoma (MZL) who previously received 1 or more lines of systemic therapy, including at least 1 anti-CD20 antibody. The study was originally planned to enroll participants into 1 of 2 cohorts as follows: Cohort 1 for participants previously treated with ibrutinib and Cohort 2 for participants who were Bruton's tyrosine kinase inhibitor (BTKi) naive. Data from Cohort 1 and Cohort 2 were analyzed separately. Given the limited availability of ibrutinib, enrollment into Cohort 1 was closed for feasibility reasons (N = 10). All participants in Cohort 1 and the first 60 participants enrolled in Cohort 2 were allocated to 1 of 2 treatment groups as follows: Treatment A: parsaclisib 20 mg once daily (QD) for 8 weeks followed by 20 mg once weekly Treatment B: parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD After the first 60 participants were enrolled in Cohort 2, an additional 30 participants were to be allocated to 1 of the 2 treatment groups to better understand the safety and efficacy of that selected treatment regimen. After a preliminary evaluation of efficacy and safety data, Treatment B was selected and Treatment A closed to further enrollment. Participants previously allocated to Treatment A were allowed to switch to Treatment B. Thereafter, treatment B was selected as the recommended dose regimen for the clinical development program of parsaclisib in non-Hodgkin lymphoma, including MZL (Study INCB 50465-204). The main efficacy results for all participants who received Treatment B are provided in this table.	
	Duration of treatment phase:	Participants received treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.
Hypothesis	There was no formal hypothesis testing.	
Cohorts	BTKi naive	Treatment A: Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW. Treatment B: Parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD. Number treated: 72 participants.
	Prior BTKi	Parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD. Number treated: 6 participants.

Endpoints and definitions	Primary endpoint	Objective response rate (ORR)	The proportion of participants who achieved a complete response (CR) or partial response (PR) as determined by an Independent Review Committee (IRC) based on the Lugano Classification.
	Secondary endpoints	Complete response rate (CRR)	The proportion of participants who achieved a CR as determined by an IRC based on the Lugano Classification.
		Duration of response (DOR)	The time from the first documented CR or PR until disease progression or death from any cause among participants who achieve an objective response, as determined by radiographic disease assessment by an IRC.
		Progression-free survival (PFS)	The time from the date of the first dose of study drug until the earliest date of disease progression, as determined by radiographic disease assessment by an IRC, or death from any cause.
		Overall survival (OS)	The time from the first dose of study drug until death from any cause.
		Best percentage change from baseline in disease burden	Best percentage change in disease burden from baseline, measured in terms of target lesion size as the sum of the product of the diameters of all target lesions for participants with measurable disease at baseline and measured in terms of spleen size as the enlarged portion of the splenic length for participants who had only splenomegaly at baseline.
Database lock	14 MAY 2021 (data cutoff date) Enrollment completed.		
Results and Analysis			
Analysis Description	**Primary Analysis**		
Analysis population and timepoint description	The full analysis set included all participants enrolled in the study who received at least 1 dose of parsaclisib. The primary efficacy results were analyzed after all participants who received Treatment B and achieved a response (ie, CR or PR), as determined by IRC review, had been followed for at least 12 months from the onset of first response.		
Descriptive statistics and estimate variability	Cohort 2 treatment B		BTKi naïve treatment B 20 mg QD for 8 weeks then 2.5 mg QD
	Number of participants		72
	ORR (95% confidence interval [CI])		59.7% (47.5, 71.1)

	CRR (95% CI)	5.6% (1.5, 13.6)
	DOR, median (95% CI)	13.57 months (8.05, 17.74)
	PFS, median (95% CI)	16.53 months (11.53, 20.63)
	OS, median (95% CI)	Not reached.
	Best percentage change from baseline in disease burden	All 50 participants who had a valid baseline and at least 1 valid postbaseline target lesion measurement had a reduction from baseline in the sum of the product of target lesion diameters, including 40 participants with best reductions of > 50% from baseline. An additional 9 participants with splenomegaly only at baseline and valid postbaseline spleen measurements had a reduction from baseline in the enlarged portion of the splenic length, including 8 participants with best reductions of > 50% from baseline.
Effect estimate per comparison	Not applicable.	
Notes	As of the data cutoff, the most common reasons for parsaclisib discontinuation among participants who were BTKi naive and who received the recommended dose of parsaclisib (Treatment B) were adverse events (37.5%) and progressive disease (27.8%). The most common reason for study withdrawal was death (15.3%). The most common reason for parsaclisib discontinuation among participants who had received prior ibrutinib and who received Treatment B was progressive disease (50.0%); the most common reason for study withdrawal was death (33.3%).	

3.3.4.4. Clinical studies in special populations

The applicant should provide the following table as part of the answers to the day 120 LoQ (**OC**)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials			
Non Controlled trials			

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Not Applicable

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

Matching adjust indirect comparison

In the absence of head-to-head trials comparing parsaclisib with the existing treatments for r/r MZL, the estimates of the comparative efficacy were derived by means of meta-analyses of the aggregate level data in the studies of relevant comparators identified by the systematic literature review (SLR), followed by the matching-adjusted indirect comparison of the pooled evidence for each comparator group with parsaclisib, using individual patient data (IPD) from the CITADEL-204 trial. . This was performed in an effort to address the CHMP request for contextualization of the parsaclisib clinical data, and to supplement evidence from the single-arm Phase 2 pivotal Study INCB 50465-204, a MAIC analysis was conducted.

Analysis steps

The indirect comparison of parsaclisib to existing treatments was achieved by:

1. Identification of the studies describing clinical efficacy of existing treatments by means of a systematic literature review (SLR)
2. Grouping of the identified studies according to the treatment under investigation considering its mechanism of action and pharmacological class (e.g. chemoimmunotherapy, PI3K, hematopoietic SCT, etc.)
3. To determine whether the studies identified within each treatment class are sufficiently homogeneous to allow meta-analyses and the derivation of class-specific effects.
4. Where feasible, conducting a series of Matching-Adjusted Indirect Comparisons (MAICs) of parsaclisib using data from CITADEL-204 study against each treatment class for the relevant efficacy outcomes.
5. Deriving the relative effects of parsaclisib vs existing treatments in r/r MZL.

Overall, it is agreed that the applicant conducted the SLR in accordance with published guidelines.

Feasibility

The feasibility assessment revealed considerable differences across studies within treatment classes in several aspects, including but not limited to study designs, populations enrolled, interventions assessed, and outcomes measured. Given the potential to introduce excessive unexplained heterogeneity, it was deemed that comparator studies should not be combined and hence no meta-analyses were feasible. Therefore, MAICs were conducted against single studies and the effect of parsaclisib against pooled treatment classes was not estimated.

Statistical methods

MAIC is a non-parametric likelihood reweighting method of comparing treatment effects while minimizing bias that results from prognostic or effect-modifying (EM) baseline characteristics that are imbalanced across trial populations. This is achieved by applying weights to individual patients in a trial, for which IPD are available, and matching their weighted summary statistics to those of a comparator trial population, where only aggregate data are reported.

Quantitative analyses

Analyses were performed with the CITADEL-204 patient-level data for a wide set of variables identified through the literature as potential prognostic variables and/or effect modifiers in r/r MZL. For each endpoint of interest (i.e., ORR, PFS), the following variables were assessed: age, gender, race, ECOG

PS, disease stage and subtype, bone marrow involvement, LDH concentration larger than upper limit of normal (ULN), number of prior systemic regimens, relapsed/refractory to the most recent prior therapy, prior stem cell transplantation. Multivariable regression models were fitted for each endpoint including all potential effect modifiers as covariates. Variable selection was then performed based on Akaike Information Criterion (AIC) using bidirectional elimination, which can be described as a combination of forward selection and backward elimination.

KOL feedback

Clinical input was sought to understand which population characteristics are potential prognostic variables and/or effect modifiers for r/r MZL patients. Three experts in haematological oncology were presented with a list of potential effect modifiers/prognostic variables in separate interviews and asked to comment on the influence of each covariate on the outcomes of interest and on whether the variable selection was supported by their clinical experience and expertise. The clinicians were also requested to prioritise the variables according to their prognostic value. In addition, KOLs were asked to comment on the clinical heterogeneity across studies within each treatment class. Specifically, they were asked to comment on the following:

- Patient populations (study inclusion and exclusion criteria, and baseline characteristics)
- Treatment characteristics (dose and dosing schedule, administration route, duration of treatment)
- Outcome (definitions, outcome ascertainment, timing of outcome measurement, duration of follow-up)
- Study design (type of study, geographical setting).

Estimation of MAIC weights

To enable an adjusted comparison between parsaclisib and the available comparative evidence sources, individual patients in CITADEL-204 were assigned statistical weights that adjust for their over- or underrepresentation relative to the average treatment effect modifiers and prognostic variables observed in the comparative evidence source. As a result, after weighting, the average baseline characteristics (mean and variance or proportion of patients within a category) were balanced for the patients in CITADEL-204 and the comparator populations. Weights were derived using a form of propensity score weighting. Following the estimation of the weights, the distribution of the re-scaled weights was visually examined to determine whether specific patient(s) or groups of patients (based on covariate values) are over- or under-represented in the analysis.

The robustness of the analyses was also evaluated by approximating the effective sample size (ESS). For a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate.

Missing data

During the matching process, the estimation of patient-specific weights requires that the matching covariates are available for all patients enrolled in CITADEL-204. However, this was not always be the case. As a result, when such variables were included in the matching process, a weight could not be estimated for the patients for which the relevant data was missing and hence these patients were removed from the dataset.

Statistical analyses incorporating MAIC weights

After the matching procedure was conducted and the weights were derived, efficacy outcomes were compared between balanced treatment groups using analyses that incorporate the derived weights. For

both endpoints, a reweighted relative treatment effect (and standard error) for parsaclisib versus the relevant comparator treatment or class was estimated using the reweighted absolute effect of parsaclisib and the reported absolute effect of the relevant comparator treatment or class.

Model fitting and model selection

For PFS, the assumption of proportional hazards (PH) was assessed by visual inspection of the log cumulative hazard plots for non-linearities and by inspecting the Schoenfeld residuals. Hazard ratios were obtained by fitting a weighted Cox-proportional hazards model using the survey package whenever the PH assumption was met. When PH was not met, survival models were fit to the original and weighted CITADEL-204 data as well as the digitized comparator data. Alternative survival parametric models including exponential, Weibull, log-logistic, log-normal, gompertz and generalized gamma distributions were fitted to the weighted CITADEL-204 and the digitized comparator data. Model selection included visual comparison as well as calculation of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), where lower values indicate better fit to the data. When different parametric models fitted the best for weighted CITADEL-204 and the comparator data, an overall best-fitting model was chosen based on visual assessment and an aggregated ranking score. For instance, if a model fitted the best according to AIC (i.e., first in ranking), but it did not fit as well based on BIC (say third in ranking), its aggregated ranking score would be 4 (i.e., 1 + 3).

Results

The applicant identified a number of effector modifiers and prognostic variables to ensure adequate population matching. However some clinical factors that may affect the response were not taken into account as they were not available in CITADEL-204 such as bulky disease, double refractoriness, and POD24.

Following the matching process sample size were drastically lowered to achieve 14 patients for the control arm of study AUGMENT.

- *Objective response rate*

Table 28 Summary of relative ORR estimates of parsaclisib versus comparators. Results for the main analysis (Full analysis set, N = 100) and for subgroup analysis (Treatment group B, N = 72)

ORR - MAIC against trial (treatment)	Naïve comparison				Matching-adjusted comparison			
	Parsaclisib		Comparator	Parsaclisib vs comparator	Parsaclisib		Comparator	Parsaclisib vs comparator
	N	ORR (95% CI)	ORR (95% CI)	Odds ratio (95% CI)	ESS	ORR (95% CI)	ORR (95% CI)	Odds ratio (95% CI)
Primary analysis (Full analysis set, N = 100)								
AUGMENT (LEN + RTX) – Tx class 1	80	63.7 (53.2, 74.2)	64.5 (45.4, 80.8)	0.97 (0.41, 2.29)	33	68.4 (58.2, 78.6)	64.5 (45.4, 80.8)	1.2 (0.42, 3.35)
PCYC (Ibrutinib) – Tx class 4	84	63.1 (52.8, 73.4)	48.0 (35.0, 62.0)	1.82 (0.93, 3.6)	44	67.6 (57.6, 77.6)	48.0 (35.0, 62.0)	2.23 (0.97, 5.1)
AUGMENT (PBO + RTX) – Tx class 6	80	63.7 (53.2, 74.2)	43.8 (26.4, 62.3)	2.27 (0.98, 5.21)	14	75.7 (66.3, 85.1)	43.8 (26.4, 62.3)	4.01 (1.16, 13.74)
Sensitivity analysis: using the longest available follow up from PCYC-1121 (33.1 months) [59]	84	63.1 (52.8, 73.4)	58.0 (NA, NA)	1.22 (0.62, 2.41)	44	67.6 (57.6, 77.6)	58.0 (NA, NA)	1.49 (0.65, 3.42)
Subgroup analyses (Treatment group B, N = 72)								
AUGMENT (LEN + RTX) –Tx class 1	55	67.3 (54.9, 79.7)	64.5 (45.4, 80.8)	1.13 (0.45, 2.86)	13	75.4 (64.0, 86.8)	64.5 (45.4, 80.8)	1.68 (0.41, 6.89)
PCYC-1121 (Ibrutinib) – Tx class 4	58	65.5 (53.3, 77.7)	48.0 (35.0, 62.0)	2.03 (0.97, 4.26)	25	70.4 (58.7, 82.1)	48.0 (35.0, 62.0)	2.53 (0.89, 7.24)
AUGMENT (PBO + RTX) – Tx class 6	55	67.3 (54.9, 79.7)	43.8 (26.4, 62.3)	2.64 (1.07, 6.49)	6	89.8 (81.8, 97.8)	43.8 (26.4, 62.3)	11.36 (1.84, 69.41)

Abbreviations: CI, confidence interval; ESS, effective sample size; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; NA, not available; ORR, Objective response rate; PBO, placebo; RTX, rituximab; Tx, treatment.

Note: As discussed in Section 5.1.4, the starting sample size in CITADEL-204 was reduced from the initial N = 100 because some of the covariates that were included in the matching process had missing values in CITADEL-204 and were therefore excluded from the analyses.

Odds ratio of ORR following MAIC numerically favors parsaclisib compared to LEN + RITUX, ibrutinib and RTX alone with estimated odds ratio between 1.2 and 4.01. However, except for RTX, 95% CI were large, thereby highlighting the uncertainty around point estimate, and overlap the null value

- *Progression-free survival*

Table 29 Median PFS and comparative progression-free survival estimate of parsaclisib (Full analysis set, N = 100) versus ibrutinib (PCYC-1121 study)

Analysis	Treatment	N / ESS	Median PFS, months (95% CI)	PFS HR (95% CI)
Primary analysis (Full analysis set, N = 100)				
Naïve (unweighted) comparison	Parsaclisib	84	16.53 (13.5, 27.8)	0.88 (0.54, 1.45)
	PCYC (Ibrutinib) - 19.4 months follow up	-	14.4 (8.6, NR)	
Matching-adjusted comparison	Parsaclisib	44	19.12 (8.31, 27.9)	0.8 (0.45, 1.42)
	PCYC (Ibrutinib) - 19.4 months follow up	-	14.4 (8.6, NR)	
Sensitivity analysis (PCYC -1121, 33.1 months follow-up)				
Naïve (unweighted) comparison	Parsaclisib	84	16.53 (13.5, 27.8)	1.17 (0.72, 1.92)
	PCYC (Ibrutinib) – 33.1 months follow up	-	15.48 (12.22, 30)	
Matching-adjusted comparison	Parsaclisib	44	19.12 (11.53-27.9)	1.02 (0.58, 1.82)
	PCYC (Ibrutinib) – 33.1 months follow up	-	15.48 (12.22, 30)	
Subgroup analyses (Treatment group B, N = 72)				
Naïve (unweighted) comparison	Parsaclisib	58	16.53 (11.53, 27.9)	0.86 (0.5, 1.5)
	PCYC (Ibrutinib)	-	14.4 (8.6, NR)	
Matching-adjusted comparison	Parsaclisib	25	19.12 (8.31, 27.9)	0.81 (0.43, 1.52)
	PCYC (Ibrutinib) - 19.4 months follow up	-	14.4 (8.6, NR)	

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; NR, not reached; PFS, Progression-free survival
Note: As discussed in Section 5.1.4, the starting sample size in CITADEL-204 was reduced from the initial N = 100 because some of the covariates that were included in the matching process had missing values in CITADEL-204 and were therefore excluded from the analyses.

No interpretation on PFS results can be drawn considering the very large 95% CI providing a low level of information.

3.3.4.7. Supportive study

INCB 50465-203-A Phase 2, Multicenter, Open-Label Study of parsaclisib, a PI3Kδ Inhibitor, in Relapsed or Refractory Follicular Lymphoma (CITADEL-203)

Objectives and endpoints

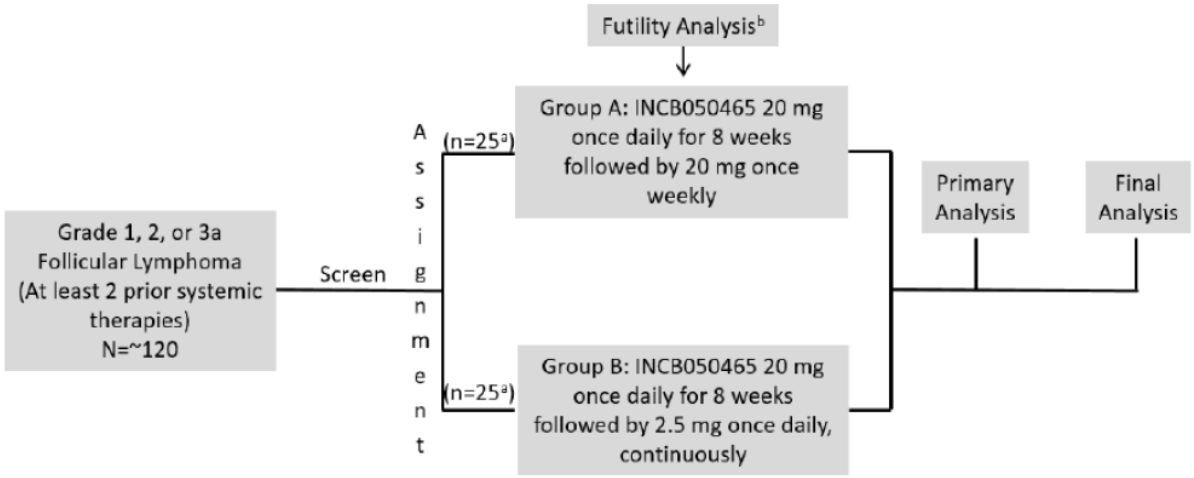
The primary objective was to assess efficacy in term of ORR (defined as the percentage of patient with CR and PR). Secondary objectives are also the same than CITADEL-204 (CRR, DOR, PFS, OS, best percentage change in target lesion and safety and tolerability of parsaclisib). Selection criteria were similar to CITADEL-204 except for the diagnosis. Patients must had a confirmed diagnosis of FL, must have received at least 2 prior systemic therapies and ineligible to HSCT.

Design

CITADEL-203 is an ongoing Phase 2, multicenter, open-label study of approximately 120 participants in which the first 50 participants were planned to be assigned in a 1:1 ratio to 1 of 2 treatment groups:

Treatment A or Treatment B (Table 31). The remaining 70 participants were planned to be allocated to 1 of the 2 treatment groups to better understand the safety and efficacy of that treatment regimen.

Table 30 Study Design of CITADEL-203



[a] The first 50 participants were planned to be assigned in a 1:1 ratio to Treatments A and B. The remaining 70 participants were planned to be enrolled in the selected treatment group (Treatment B).
[b] A futility analysis was performed when the first 50 participants were evaluated for response.

Selection criteria

Participants must have been at least 18 years of age with a histologically confirmed diagnosis of FL (Grade 1, 2, or 3a) who had received at least 2 prior systemic therapies and considered ineligible for HSCT. Participants must have had radiographically measurable lymphadenopathy or extranodal lymphoid malignancy at baseline, been willing to provide a biopsy, and have ECOG performance status of 0 to 2.

Participants must not have had transformation of disease to diffuse large B-cell lymphoma, must not have had a history of central nervous system lymphoma, must not have received prior treatment with other PI3Kδ inhibitors or a Bruton's tyrosine kinase inhibitor, and must not have received allogeneic stem cell transplant within the previous 6 months or autologous stem cell transplant within the previous 3 months before the first dose of study treatment.

Study treatment

Participants in Treatment A received parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW; participants in Treatment B received parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD

RESULTS

Studied Period: 14 MAR 2018 to 14 MAY 2021 (data cutoff date)

Primary Endpoint

Objective and Complete Response Rates Based on Independent Review Committee Assessment

Table 31 Summary of Best Overall Response and Objective and Complete ResponseRates Based on Independent Review Committee Assessment (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks then 20 mg QW (N = 23)	Treatment B 20 mg QD for 8 Weeks then 2.5 mg QD (N = 103)	Total (N = 126)
Objective response[a], n (%)	15 (65.2)	81 (78.6)	96 (76.2)
95% CI[b]	42.7, 83.6	69.5, 86.1	67.8, 83.3
Complete response, n (%)	4 (17.4)	20 (19.4)	24 (19.0)
95% CI[b]	5.0, 38.8	12.3, 28.4	12.6, 27.0
BOR[c], n (%)			
Complete response	4 (17.4)	20 (19.4)	24 (19.0)
Partial response	11 (47.8)	61 (59.2)	72 (57.1)
Stable disease	6 (26.1)	12 (11.7)	18 (14.3)
Progressive disease	0	6 (5.8)	6 (4.8)
Not evaluable	0	2 (1.9)	2 (1.6)
Not assessed[d]	2 (8.7)	2 (1.9)	4 (3.2)

[a] Participants who have BOR of CR or PR.
[b] The CI was calculated based on the exact method for binomial distribution.
[c] Best overall response is the best response recorded prior to and including the first progressive disease, in the order of CR, PR, stable disease, progressive disease, and not evaluable. Any assessments after new antilymphoma therapy are excluded from the BOR determination.
[d] No postbaseline response data available.

Secondary endpoints

Duration of Response Based on Independent Review Committee Assessment

Table 32 Summary of Duration of Response Based on Independent Review Committee Assessment (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks then 20 mg QW (N = 23)	Treatment B 20 mg QD for 8 Weeks then 2.5 mg QD (N = 103)	Total (N = 126)
Number of objective responders[a], n (%)	15 (65.2)	81 (78.6)	96 (76.2)
Number of participants with events[b]	9 (60.0)	30 (37.0)	39 (40.6)
Disease progression	9 (60.0)	28 (34.6)	37 (38.5)
Death	0	2 (2.5)	2 (2.1)
Number of participants censored[b]	6 (40.0)	51 (63.0)	57 (59.4)
Study discontinuation	1 (6.7)	7 (8.6)	8 (8.3)
Ongoing with study	4 (26.7)	36 (44.4)	40 (41.7)
Death or progression after ≥ 2 missed assessments	0	1 (1.2)	1 (1.0)
New anticancer treatment started	1 (6.7)	7 (8.6)	8 (8.3)
Median DOR (months) (95% CI)[c]	14.06 (3.19, 17.74)	17.48 (10.38, NE)	15.87 (11.99, 20.34)

Note: Results are based on the data cutoff date of 14 MAY 2021.

[a] Participants who have BOR of CR or PR.

[b] Percentages were calculated based on the number of objective responders.

[c] The 95% CI was calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

Progression-Free Survival Based on Independent Review Committee Assessment

Table 33 Summary of Progression-Free Survival Based on Independent Review Committee Assessment (Full Analysis Set)

Variable	Treatment A 20 mg QD for 8 Weeks then 20 mg QW (N = 23)	Treatment B 20 mg QD for 8 Weeks then 2.5 mg QD (N = 103)	Total (N = 126)
Number of participants with events, n (%)	11 (47.8)	45 (43.7)	56 (44.4)
Disease progression	11 (47.8)	40 (38.8)	51 (40.5)
Death	0	5 (4.9)	5 (4.0)
Number of participants censored, n (%)	12 (52.2)	58 (56.3)	70 (55.6)
Median PFS (months) (95% CI)[a]	13.90 (8.31,19.88)	15.80 (11.07, 22.14)	14.03 (11.30, 19.55)
PFS rate (%) (95% CI)[b]			
Month 6	79.8 (54.4, 91.9)	77.3 (67.2, 84.6)	77.6 (68.6, 84.3)
Month 12	65.3 (37.3, 83.1)	59.3 (47.7, 69.2)	60.2 (49.6, 69.2)

[a] The 95% CI was calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

[b] The 95% CI was calculated using Greenwood's formula to estimate the standard error.

ORR (95% CI) at the intended dosing regimen in FL was 78.6% (69.5, 86.1) with 19.4% (12.3, 28.4) of CR and 59.2% of PR. Therefore ORR and CR in FL was higher than in MZL (59.7% and 5.6 % respectively).

Median DOR (95% CI) was 17,48 months (10.38, NE) and median PFS was 15.80 (11.07, 22.14). All cited endpoints support an activity of parsaclisib which appear to be more beneficial for patient with FL than MZL with regards to the higher rate of OR and CR.

However, as discussed already in this AR, the result of this study should be interpreted very cautiously as even though both disease have a lot of features in common, it doesn't preclude of different responses to a specific treatment.

3.3.5. Discussion on clinical efficacy

The applicant has requested a conditional marketing authorization for parsaclisib (Tradename to be determined at the time of the review) in the following indication:

"TRADENAME in monotherapy is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL)."

The main source of data for this application is provided by the results of the pivotal phase II clinical trial INCB 50465-204 (CITADEL-204). This is an ongoing, open-label study in subjects with relapse or refractory MZL. Supportive data are provided by a phase 1/2 dose escalation study in subjects with previously treated B-cell malignancies (CITADEL-101), a systematic literature review (SLR) followed by a matching-adjusted indirect comparison (MAIC) and an ongoing phase 2 open label study in patients with relapse or refractory follicular lymphoma (CITADEL-203).

Design and conduct of clinical studies

INCB 50465-204 (*CITADEL-204*) is an ongoing, Phase 2, open-label study of parsaclisib in Subjects with Relapsed or Refractory Marginal Zone Lymphoma.

Patients were included if they had histologically confirmed MZL and received 1 line or more of systemic therapy including at least 1 anti-CD20 antibody. Patients with extranodal, nodal and splenic subtypes were eligible. Patients must had a radiographically measurable disease, ECOG 0-2, adequate hematologic, hepatic and renal function.

Patients were excluded if they had evidence of DLBCL transformation, history of CNS lymphoma, prior treatment with a PI3K inhibitor, ASCT within the previous 6 months, active GVHD, use or expected use of potent CYP3A4 inhibitors/inducers and uncontrolled medical conditions.

Overall, the population included in the study is consistent with the intended indication, including the 3 MZL subtypes. However, in order to clarify the indication, the wording should specified that patients must have received at least 1 prior treatment with one anti-CD20-based therapy. The indication is proposed to be reworded as follow:

"*TRADENAME as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have previously received at least one prior anti-CD20-based therapy"*. (**MO**)

Patients were then allocated in one of the two following dosing regimens: parsaclisib 20 mg QD PO for 8 weeks followed by 20 mg once weekly PO (treatment A) or parsaclisib 20 mg QD PO for 8 weeks followed by 2.5 mg QD PO (treatment B) until disease progression, death, unacceptable toxicity, or consent withdrawal, the latter being the intended posology.

The primary objective of study CITADEL-204 was efficacy in term of ORR defined as the percentage of participants with CR or PR determined by an IRC according to CT-based response criteria for lymphoma. Secondary objectives were to assess DOR, CRR, PFS, OS, percentage change in target lesion and characterize safety and tolerability of parsaclisib.

ORR is acceptable as primary endpoint in view of the design of this pivotal study INCB 50465-204 (single arm trial) and considering the review of response by an IRC, which is endorsed.

There are obvious uncertainties related to the design of the pivotal study, which is a phase 2 single-arm, 2-cohort open-label study. Establishing efficacy in single-arm studies can be challenging due to the lack of comparator and the potential selection bias.

While the protocol and statistical analysis plan (SAP) both state that enrolment could continue up to 90 patients, it is noted that 100 patients were enrolled in the end (i.e. 10 more patients were included, representing an 11% increase to the original sample size). This change has been clarified in the Protocol Amendment 3 with rationale being that Cohort 1 was closed and additional subjects were allowed to be enrolled in order to better understand the safety and efficacy parameters. This rationale is considered limited and thus the applicant should provide additional justification for the sample size increase. An additional analysis should also be performed where the primary endpoint analysis (overall and by treatment arm) is repeated based on the first 90 enrolled participants only (**OC**)

Some clarifications from the applicant are expected regarding the initial sample size for Cohort 1 (participants who received prior ibrutinib), and regarding the procedure for treatment allocation of the first 60 patients of Cohort between Treatment A and B (**OC**).

The study has no formal hypothesis test and no multiplicity adjustment was planned, whether between cohorts, or primary / secondary endpoints in any cohort. It should be further noted that no comparisons were intended between the two treatment regimens within Cohort 2.

The first SAP was finalised >1 year after first participant dosed and some important changes were made to the design and statistical methods as part of protocol amendments and SAP revisions, while the study was ongoing. These included the closing of Cohort 1, a sample size increase for Cohort 2, and several updates of analysis specifications. Overall, these concerns highlight the exploratory nature of the study, and cannot be addressed retrospectively.

It is noted that the PFS censoring rules are not in line with the Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/27994/2008/Rev.1), which recommends that the principles of intent-to-treat should be followed as far as possible. As a consequence, the applicant is requested to perform a PFS sensitivity analysis in accordance with the guideline and comment on its consistency (**OC**).

The statistical methods are otherwise generally standard and appropriate for the corresponding primary and secondary endpoints of an exploratory single arm study.

Responses as determined by IRC were used for the primary analysis, with investigator assessment used as exploratory analysis. However, an assessment of the concordance between IRC and investigator could not be found. The applicant is requested to provide summaries of concordance in BOR, ORR as well as in disease progression between IRC and investigator assessment (**OC**).

The protocol states that there were 2 radiologists assessing the CT images and their opinion was used by IRC to assess the outcome measures. There are cases where one radiologist provided results of complete response while the other reported stable disease or even progression. The fact that the assessments might have differed from one radiologist to the other are acknowledged, but would request further details on how these divergent situations were managed and what was the procedure for choosing the radiology assessor whose report was used by the IRC members should be provided. **(OC)**

The effort to contextualize the results from the phase 2 single-arm open-label study using a MAIC analysis, providing some external comparative evidence, is acknowledged. The analysis process and the statistical methods themselves are not objected to. Nevertheless, and as appropriately described in the MAIC summary report provided by the applicant, there are several important limitations that prevent any meaningful conclusions from being drawn.

The feasibility assessment highlighted the heterogeneity of the studies identified, thereby limiting the MAIC analyses to comparisons versus single studies. In addition, the sparse reporting of baseline characteristics for the MZL population in the published evidence limited not only the assessment of between-study heterogeneity, but also prevented an adequate matching adjustment for the MAIC analysis.

As acknowledged by the applicant's report, an unanchored MAIC relies on the constancy of the absolute effects, which is a strong and unrealistic assumption. Indeed, all prognostic and predictive variables are assumed to be observed and adjusted for. As a consequence, treatment effect estimates resulting from the MAIC analyses are likely biased, with a bias that is not quantifiable.

The initial low sample size of the pivotal study, and the even lower effective sample size (ESS) resulting from the MAIC analysis were also unlikely to provide sufficient precision for the planned comparisons.

In conclusion, the MAIC analyses may provide some contextualisation of the pivotal study results, however its interpretation is limited by several deficiencies, some related to the data available from the pivotal study and the published evidence, some more generally associated with the use of external controls. Therefore, it does not adequately address the main methodological concern of the phase 2 pivotal trial, i.e. the lack of a randomised comparator.

Efficacy data and additional analyses

On the 159 patients screened, 100 patients were enrolled in cohort 2 with 28 patients in cohort 2A (cohort 2, treatment A 20mg QD/20 mg QW) and 72 patients in cohort 2B (cohort 2, treatment B 20mg QD/2.5 mg QD).

Main reasons for discontinuation were adverse events and progressive disease. Whereas less patients discontinued treatment due to an adverse event in cohort 2A than in cohort 2B (3/28 patients, 10% vs 27/72 patients, 37.5% respectively), more patients discontinued treatment for progressive disease in cohort 2A than in cohort 2B (11/28 patients, 39% vs 20/72 patients, 27.8% respectively). However, to balance these results, it is to be noted that median duration of treatment in cohort 2A was longer than in cohort 2B (616.5 days vs 354.5 days respectively). Considering that both dosing regimens showed similar efficacy data, the choice of the maintenance dose at 2.5 mg is not fully understood and should be better explained, especially since dose escalation study did not assess this dose level and since it not supported by pharmacological studies (**OC**).

Protocol deviations

Protocol deviations were numerous (92%) and mainly related to non-compliance with study procedure-missed assessment for 83% of patients or out of window assessment for 77% of patients for both treatment groups. No information is provided as to which are considered major deviations. COVID-19 related protocol deviations were provided as justification by the applicant. However, covid-19 related protocol deviations account only for 22 to 35% of these deviations. In addition, an average of 20% of patients in both categories "informed consent" and "other" are described but not detailed. No specification on which deviations were considered major deviations were provided. Therefore, the applicant should detail and discuss the impact on data integrity of the protocol deviations of each of the

following categories "non-compliance with study procedure-missed assessment and out of window assessment" not related to COVID-19, "informed consent" and "other". (**OC**)

A total of 4 global amendments were noted. They were related to improvement of safety of the clinical trial (additional guidance on doses modifications and dose reduction schedules) or modification of the design for closure of cohort 1 and increased of the number of subject in cohort 2.

Baseline Demographic characteristics

At the intended posology, median age (range) was 72.0 years (35-95 years) with 72.2% ≥65 years and median BMI was 25.90 (17.4, 48.9). ECOG performance status was mainly 0 or 1 (63.9% and 31.9% respectively). 56.9% of patients were male, 83.3% were Caucasian and 13.9 % were "other" (neither Asian nor black/African American) which is consistent with the intended population (Cerhan and Habermann, 2021; Rossi, 2022). 37.5% were recruited in North America and 62.5% in the rest of the world.

Baseline disease characteristics

Median (range) time since initial diagnostic was 4.37 years (0.1, 19.8 years), the three subtypes each represented a third of the trial population. On the 100 patients study CITADEL-204, only one patient had a MZL related to H. Pylori infection (and 1 patient with MZL related to other infection), the majority of patients (72.2%) had a stage IV disease at baseline with an absence of B-symptoms (77.8%) but 17% had nights sweats. 41.7% of patients had bone marrow involvement, 45.8% had relapse disease and 48.6% had refractory disease.

The equal repartition of the 3 subtypes is unexpected with regards to epidemiologic data on the rate of each subtype. Indeed, NMZL subtype which represent less than 10% of MZL appear overrepresented whereas the subtype ENMZL appear underrepresented. The applicant should explain this discrepancy with epidemiological data. (**OC**)

Prior and concomitant medication

Most of the patients had received 1 or 2 prior lines of systemic therapy at the intended posology (45.8% and 34.7% respectively) and median (range) number of prior systemic therapy was 2 (1-5). 7 patients (9.7%) had prior radiation, 15.3 % (11 patients) had prior surgery and 4.2 % (3 patients) had prior hematopoietic stem cell transplant. All patients received at least a prior systemic therapy with rituximab. However, it is not clear from the provided tables how many patients had previous rituximab alone or in association, and what those associations were. (**OC**)

Outcomes and estimations

ORR and other efficacy data were based on the FAS which comprises all 100 included participants in cohort 2 and corresponds therefore to the ITT analysis.

- Primary endpoint

At the intended posology, ORR (95% CI) was 59.7% (47.5, 71.1) with BOR of CR in 5.6 % (4 patients) and PR in 54.2 % (39 patients), SD was observed in 29.2 % (21 patients). The CRR is considered low and the relevance of this result in the context of an indolent disease with guidelines providing several recommended treatment in 2L+ MZL is questioned and should be addressed by the applicant. (**MO**)

Among patients who responded, median time to response was 8.14 weeks (range: 5.0-36.1 weeks), corresponding to the first planned assessment of response. An attempt to compare ORR with recommended alternative treatments is provided through the below detailed MAIC.

Considering that both dosing regimens showed similar efficacy data according to above data (section 3.3.2.1) and that less patients discontinued treatment due to an adverse event in cohort 2A than in

cohort 2B, the choice of the maintenance dose at 2.5 mg QD over 20 mg QW is not fully understood and should be better explained with regards to efficacy and safety data, especially since dose escalation study did not assess this dose level, is not supported by pharmacological studies and considering the low CRR (**MO**).

Higher ORR and CRR were observed when assessed by investigator compared to IRC. An OC is raised in section 3.3.1.8 statistical methods regarding comparison of both assessment. Sensitivity analysis showed similar results to primary analysis.

In patients who had 2 or more prior systemic therapies in cohort 2 ORR (95% CI) was 53.8% (37.2, 69.9) with CR accounting for 5.1% and PR for 48.7% which is consistent with the primary analysis.

Secondary endpoints

Median DOR (95% CI) at the intended dosing regimen was 13.57 months (8.05, 17.74), superior to the median DOR in treatment arm A (9.26 months, 95% CI: 2.56, NE). This duration should be put into perspective with the indolent nature of MZL and the absence of control arm. To be noted, in the AUGMENT trial assessing RTX + lenalidomide vs RTX + placebo which is chosen in the MAIC, median DOR (95% CI) was 17.4 months in R² arm and Not Evaluable for comparator arm with a median follow-up of 28.30 months.

Median PFS (95% CI) was 16.53 months (11.53, 20.63), numerically lower than PFS in treatment group A (19.42 months). Similarly to DOR, these results are to be analysed with regards to the lack of control arm and the indolent nature of MZL. Differences are observed for PFS when assessed by IRC or investigator. The applicant should discuss the main discrepancies between IRC and investigator assessment. (**OC**)

Median OS at the intended posology was not reached as 60 patients (83%) were still alive at the data cut-off.

Finally, All 70 participants who had a baseline and at least a post baseline measurement of target lesion, had a reduction in the sum of product lesion diameter, of which 59 participant had best reduction > 50% from baseline.

Conditional marketing authorization

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation.

However, issues can be raised in particular about the ability to provide comprehensive data. Indeed, provided a favourable outcome of the CHMP, patients could receive parsaclisib under the authorized indication and would be less likely to enter the proposed phase III study. In addition, the clinical trial application is currently under review in Spain, Italy, Poland, and Hungary, and has been withdrawn at least in Czech Republic, Spain and France and rejected in Hungary at the time of this assessment. This may raise doubts about the ability to conduct this trial. Moreover, the relevance of the control arm (RTX + placebo) is questioned as according to current guidelines (NCCN, ESMO) in the intended indication, the preferred regimens are an anti-CD20 mAb + bendamustine, RCHOP, RCVP, R² or ibrutinib. Therefore, recruitment in of patient with MZL could be challenging.

Overall, the applicant is requested to further justify the unmet medical need and the major therapeutic advantage. (**MO**)

3.3.6. Conclusions on clinical efficacy

An application for a CMA has been submitted for parsaclisib in monotherapy is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma. The main source of data for this application are the results of the pivotal phase II clinical trial INCB 50465-204 (CITADEL-204) which is an ongoing, open-label study in subjects with relapse or refractory MZL who previously received an anti-CD20 mAb.

At the intended posology, ORR (95% CI) was 59.7% (47.5, 71.1) with BOR of CR in 5.6 % (4 patients) and PR in 54.2 % (39 patients), SD was observed in 29.2 % (21 patients). Among patients who responded, median time to response was 8.14 weeks (range: 5.0-36.1 weeks), corresponding to the first planned assessment of response.

Several major objection were raised during the assessment:

The relevance of the low CRR in the context of an indolent disease with guidelines providing several recommended treatment in 2L+ MZL is questioned and should be addressed by the applicant. Further to this observation, the maintenance dose is also questioned with respect to pharmacokinetics, efficacy and safety assessment.

To further provide comprehensive data, the applicant proposes to conduct a confirmatory phase 3, double blind, randomized, placebo controlled multicentre study in patients with R/R MZL in the same clinical setting than the pivotal phase 2 study for this application. Uncertainties of the feasibility of this confirmatory trial are raised in a major objection.

An additional major objection is raised on the wording of the indication, asking to introduce the notion of previous treatment with an anti-CD20 mAb and several other concerns need to be addressed.

3.3.7. Clinical safety

The characterization of the safety profile of parsaclisib as monotherapy in NHL has been provided by the applicant through one pivotal study, one supportive study (INCB 50465-203) and 5 other studies within the parsaclisib monotherapy setting in addition to 2 completed clinical pharmacology studies in 43 healthy participants. A description of safety data in MZL (CSR) along with a wider description of the safety profile within a iNHL pool and a B-cell malignancies pool, have been provided.

3.3.7.1. Patient exposure

Data derived from the clinical studies in participants with B-cell malignancies were presented for 3 pooled populations all receiving parsaclisib monotherapy:

•The iNHL Pool (N = 270, R/R FL or MZL)

•The MCL Pool (N = 170)

•The B-Cell Malignancy Pool (N = 546)

From the patients cited above, only 299 received the recommended dose regimen of 20mg QD for 8 weeks followed by 2.5 mg QD:

• 72 patients with R/R MZL from the Pivotal Study INCB 50465-204,

• 103 patients with R/R FL from the supportive Study INCB 50465-203,

• 118 patients with R/R MCL from study INCB 50465-205.

The size of the safety database is considered quite limited but could be acceptable considering the requested CMA in the MZL population. The applicant focused the safety review on subjects who received the chosen dose regimen, which is supported. Safety data collected in FL patients are of interest to support the review in MZL patients as recommended within the scientific advice. A special focus will thus be made on the iNHL pool of patients who received the recommended dose (20mg QD for 8 weeks followed by 2.5 mg QD, n=181).

The MAH opted for a 12 months review (reflecting the minimum follow-up duration for the last patient enrolled).

More widely, from the 299 patients who received the recommended dose, only 66 (22.1%) remained on treatment at data cut-off date while the median duration of treatment was of 248.0 days (range: 4-1060 days) with 34.8% of participants having received parsaclisib for at least 12 months. Dose interruptions and reductions occurred in 44.8% and 17.7% of participants who received the recommended dose, respectively. For the iNHL Pool counting 181 patients treated at the recommended dose, the above mentioned variables were similar across the two pools with a median treatment compliance of 100% (range: 76.4%-131.3%), the median duration of exposure was 9.7 (0.36, 35.3) months with 73 participants (40.3%) having accomplished at least 12 months of parsaclisib treatment. Also, dose interruptions and reductions occurred in 52.5% and 22.7% of patients, respectively.

In both iNHL and B-cell malignancies pool, demographics and baseline characteristics were generally comparable, also between doses subgroups. Approximately 50% of the participants had a baseline ECOG performance status of 0. A total of 31.1%, 27.3%, 22.2%, and 19.4% of participants had MCL, FL, MZL, and other B-cell malignancies, respectively.

The use of prior systemic anti-cancer therapies was quite different between the patients pooled within the different studies since patients enrolled within the pivotal study INCB 50465-204 (CITADEL-204) with R/R MZL had received at least 1 prior anti-CD20-based regimen when patients included within the supportive study INCB 50465-203 (CITADEL-203) with R/R FL had received at least 2 prior lines of therapy. The proportion of each treatment line, disease burden and baseline characteristics are not detailed by histology group for all patients enrolled within the iNHL pool. (OC)

In the iNHL Pool, 97.8% of participants reported general medical history, mostly vascular disorders (>40%), gastrointestinal disorders (42.2%), and metabolism and nutrition disorders (41.9%). The most frequently reported PT was hypertension (40.0%) as medical history.

Antibacterial and antiviral therapies where the most frequently reported concomitant treatments, often permitted within protocols' recommendations.

3.3.7.2. Adverse events

3.3.7.2.1. iNHL pool

General safety considerations:

Limited discussions were provided by the applicant regarding safatey data, mainly safety reviews of TEAEs of interest.

The applicant states that parsaclisib is a next generation highly potent PI3Kσ inhibitor which is assumed to improve the safety profile of these therapeutic class' isoform.

This affirmation does not seem to be strongly supported by the safety data provided from the different parsaclisib studies. In the pooled iNHL group, at the recommended dose, almost all patients (96.7%) had at least 1 AE, and about 78% of participants, which is a non-negligible rate, had at least 1 AE considered related to parsaclisib at the recommended dose.

Moreover, grade 3 and higher AEs occurred in 65.2% of patients and serious AEs occurred in 50.3% of them including 9 cases with a fatal outcome. Besides, 29.8% of the participants discontinued parsaclisib due to AEs and more than a half (53.6%) experienced drug interruption also due to AEs.

Data from the B-cell malignancies pool are comparable to those reported in the iNHL pool and data reported within arm B (recommended dose) of cohort 2 (BTKi naïve) of the pivotal study are also comparable to those reported in the iNHL pool.

AEs' incidence:

The most common AEs in the iNHL pool were reported for the gastrointestinal disorders SOC with a cumulative incidence of 71.3%. The most commonly reported PTs were diarrhoea (47%), nausea (21%) and Constipation (9.9%). The second most reported SOC was infections and infestations with a cumulative incidence of 58.6% with Pyrexia and Neutropenia presented as most reported PTs for this SOC with 18.8% and 14.9% of incidence overall. Other SOCs are also largely represented within the safety reviews submitted as follows: General disorders and administration site conditions SOC (50.8%); Skin and subcutaneous tissue disorders SOC (43.1%); Respiratory, thoracic, and mediastinal disorders SOC (41.4%) and metabolism and nutrition disorders SOC (40.3%).

It is not clear if the AEs observed with parsaclisib occurred with the same trends and frequencies throughout the different treatment periods (induction period vs maintenance dose regimens, first 3 months vs end of treatment …). Data after 12 months of treatment should also be discussed. The applicant should discuss the incidence and trends in AEs taking into considerations these variables. **(OC)**

The most common AEs at the recommended dose with a worst grade of 3 with parsaclisib in the iNHL pool are as follows: diarrhea (14.4%), neutropenia (10.5%), colitis (8.3%), and pneumonia (5.5%) corresponding to the associated SOCs: gastrointestinal disorders (26%), infections and infestations (19.9%), and blood and lymphatic system disorders (17.7%).

At the recommended dose, more than 77% of iNHL patients had at least 1 AE related to parsaclisib as per investigator assessment. The most frequently reported SOCs were gastrointestinal disorders (50.3%), skin and subcutaneous tissue disorders (25.4%), blood and lymphatic system disorders (21.0%), infections and infestations (18.8%) and general disorders and administration site conditions (17.7%). The corresponding PTs were mostly diarrhea (39.2%) and neutropenia (11.0%) and these most common AEs considered as parsaclisib-related were generally in line with the all grade AEs as well as those reported in other histological pools.

Adverse events of special interest included the following PTs: febrile neutropenia, pneumonitis, pneumonia, PJP, diarrhea, colitis, rash, exfoliative dermatitis, CMV infection, herpes simplex, varicella zoster virus infection, and intestinal perforation.

Treatment-emergent AEs of clinical interest were summarized as MedDRA SOC (SOC of infections and infestations only), grouped terms (SMQs or customized aggregates of PTs), and AESIs (based on PTs).

Time to first occurrence of diarrhea was analysed using the life-table method which was not the case for the remaining AESIs which, according to the applicant, occurred at a low frequency prohibiting observation of any statistical pattern. While it is acknowledged that only grade 3 and higher febrile neutropenia cases were selected, no information regarding selection parameters of other AESIs such as intestinal perforation, PJP, varicella zoster virus infection, CMV infection, pneumonitis and herpes simplex was provided. The applicant should clarify and provide the methodological details regarding selection of other AESIs cases for the life-table method analysis. **(OC)**

Dose-related toxicities still require deeper assessment. The applicant should discuss if some adverse events of special interest can be considered related to cumulative dose or considered dose-related. If so it should be specified accordingly under AEs in the SmPC. (**OC**)

A relevant number of patients had treatment related TEAE of anaemia and haemoglobin decreased events were observed in 183 patients (33.5%) in the B-Cell Malignancy total pool. Hence the applicant should present the assessment of these AEs. (**OC**) The exact same assessment should be submitted for pruritus AEs. (**OC**)

Infections and infestations (SOC)

Over 58% of patients treated within the iNHL pool at the recommended dose had an infection and infestations event. The most represented PTs are the following: upper respiratory tract infection (10.5%), urinary tract infection (7.7%), pneumonia (7.2%) and Herpes zoster (5%). Grade 3 or higher infection AEs were reported in 20% of the iNHL pool population at the recommended dose while serious events occurred in over 19% of them.

Dose interruption occurred in almost 15% of cases after infections events while parsaclisib discontinuation occurred in 2.2% of the cases followed by 1.7% of the cases leading to dose reduction.

Five infection cases were reported with a fatal outcome as follows: 2 sepsis cases in 2 different patients and one pneumonia all three assessed as related to the study drug and one Enterobacter sepsis along with one COVID-19 pneumonia case assessed as not related to parsaclisib (please also see section 4.4). The SmPC has been implemented with toxicity management recommendations, however, these latter need to be detailed and clarified. The applicant should update the PI with the whole topic of infection cases – including disruptions, adverse reaction percentages, Grade 3 or higher AE percentages, the median time to onset of the first occurrence of a Grade 3 or higher infection events. (OC) In addition, urinary tract infections are one of the most common infections to occur. The applicant did not submit an assessment of this risk and is expected to provide a detailed analysis of all linked cases by grade and amend the SmPC accordingly if applicable. (OC)

Diarrhea and colitis grouped terms

The review was based on grouped terms for Diarrhea and colitis including "non-infectious diarrhea" SMQ and other related PTs. Meanwhile, diarrhea widely occurred among patients treated with parsaclisib at the recommended dose (51.4%) as expected with PI3K therapies. Grade 3 or higher diarrhea occurred in 23.2% (from which 19.9% were treatment related) of exposed patients while 16.6% (14.4% treatment related) had serious diarrhea events which is quite a high frequency of SAEs. No fatal diarrhea was reported, however, two grade 4 diarrhea cases are retrieved in the summary tabulations (please also see section 4.4).

Overall, diarrhea was the most commonly reported ADR, the most commonly reported serious ADR, the most commonly reported ADR resulting in permanent discontinuation of parsaclisib (14.9%), the most commonly reported ADR leading to dose reductions (12.7%) and he most commonly reported ADR that resulted in dose interruption (18.8%).

Colitis of any grade occurred in 10.5% of patients treated within the iNHL pool at the recommended dose while Grade 3 or higher colitis was reported in 8.3% of participants. Overall, approximately 1% of patients experienced dose interruption, 2.2% had a dose reduction, and 5.5% had colitis resulting in parsaclisib discontinuation.

It is duly noted that most first occurrences of diarrhea and colitis of any grade were before Week 48, however, a delay for time to first occurrence is also noted and it seems that the incidence is higher over time. The applicant should discuss these points as for a potential increase in the seriousness of these cases over treatment periods. **(OC)** The SmPC should also include median time-to-resolution of diarrhoea and/or colitis events upon review conclusions. **(OC)** Moreover, significant clinical consequences of diarrhea were not discussed as part of the submitted analysis (ie, secondary

dehydration and other consequences), the applicant should complete the review in order to detail the frequency and severity of other relevant cases reported as related to diarrhea. **(OC)**

Sixty-four participants (21.4%) had a Grade 3 or higher diarrhoea event, and 50 participants (16.7%) had a serious diarrhoea event. Diarrhoea events led to parsaclisib interruption in 52 participants (17.4%), discontinuation in 46 participants (15.4%), and dose reduction in 24 participants (8.0%). Four participants (1.3%) had colitis leading to parsaclisib dose interruption, 4 participants (1.3%) had colitis leading to parsaclisib dose reduction, and 16 participants (5.4%) had colitis leading to parsaclisib dose discontinuation. The applicant is asked to evaluate if diarrheal/colitis events and serious diahhroea/colitis events are more common for parsaclisib than other pi3k-inhibitors, and if dose interruptions, discontinuations and reductions occur more commonly than for other pi3k-inhibitors. The applicant is asked to discuss the intolerance signals for parsaclisib. (OC)

The applicant states that 'Guidance was provided in the individual study protocols regarding supportive care for diarrhoea and colitis.' The applicant is asked to specify what type of guidance was given, and if this guidance can be further described in the SmPC, including any antidiahhroeal agents given or steroids used. (OC)

'Colitis' should be separately listed in the PI, with the appropriate footnotes. The applicant is asked to revise the currently proposed footnotes under 'diarrhoea' and rearrange, if necessary. (OC)

Rash

Rash events, based on grouped term occurred in approximately 34% of patients. The PT "rash" was the most commonly reported one (16.6%) followed by Rash maculo-papular (5.6%) and erythema (4.4%). These are known and expected AEs with PI3K inhibitors.

Grade 3 or higher rash event were reported in 6.6% of patients with a rate of 4.4% of SAEs. Parsaclisib interruption rate due to this AE was of 12.7%, 6.1% for discontinuations, and 3.9% for dose reductions. None of the rash events were fatal and most cases were confounded by the concomitant use of Bactrim

Exfoliative Dermatitis occurred in 2 participants (1.1%) of any grade. One of them had Grade 3 exfoliative dermatitis on Day 295, leading to dose discontinuation. All events resolved within few weeks.

Severe Cutaneous Adverse Reaction

Severe Cutaneous Adverse Reactions occurred in 13.8% (9.4% related to study drug) within the iNHL group (recommended dose). Stomatitis was the most reported PT (3.3%) followed by skin exfoliation (2.8%). Five participants (2.8%) had a Grade 3 or higher severe cutaneous adverse reaction event from which one fatal case of SJS (related to parsaclisib even though confounded by the co-administration of Bactrim) and two serious cases of toxic skin eruption and generalized exfoliative dermatitis. In addition one case of DRESS has occurred within the MCL pool. Despite the fact that these are known risks with PI3K inhibitors, there are scarce information within the SmPC, sections 4.2, 4.4 and 4.8 of should thus be amended in order to clarify the nature and severity of Severe Cutaneous Adverse Reactions reported within the different studies. An exhaustive description of data should be included and a firm recommendation for permanent discontinuation of parsaclisib after confirmation of the aetiology of SJS, TEN, or DRESS. (**OC**) The applicant is also asked to specify in 4.2 the management of rashes of grade 1-2, grade 3. (OC)

Neutropenia

Neutropenia events occurred in 14.9% of iNHL patients with 14.9% of Grade 3 or higher neutropenia events and approximately 4% of serious cases. Treatment discontinuation was reported for 3 patients with an estimated rate of 1.7% while no patient had dose reduction. One fatal case of febrile neutropenia should be noted. Overall, febrile neutropenia was reported in 3.9% of cases. This risk is well known with

PI3K inhibitors, directly linked to infections and well described in the SmPC. However, the applicant is asked to analyse, if there have been cases of neutropenia not resolving after treatment discontinuation and if this effect can be related to parsaclisib. (OC) Neutropenia should be included in the ADR table in section 4.8 under the SOC 'Blood and lymphatic system disorders' and if required to delete neutropenia from SOC 'investigations' (OC).

The warnings section in the SmPC is proposed to be updated with a notion that febrile neutropenia has occurred with the use of parsaclisib. The severity of febrile neutropenia should also be stated in the SmPC. (OC)

Abdominal pain

Abdominal pain was reported for 15.5% of patients and was linked to other GI disorders such as colitis which are listed in the SmPC. Abdominal pain should be separately listed in SmPC section 4.8 of the PI. (OC)

Thrombocytopenia

Overall frequency of thrombocytopenia (including platelet count decreased) was 6.6% for parsaclisib monotherapy. Patients most commonly had events with a worst Grade of ≤2, but two patients reported grade 3 and higher events although non-serious or leading to dose adjustment/discontinuation. The applicant should discuss all cases reporting significant clinical consequences of thrombocytopenia by severity (bleeding/haemorrhages). **(OC)**

Among the 299 participants at the recommended dose in the B-cell pool, nine participants (3.0%) had a Grade 3 or higher thrombocytopenia event, and 7 participants (2.3%) had a thrombocytopenia event that led to parsaclisib interruption. Therefore a relevant number of subjects had either serious thrombocytopenia and/or the need to interrupt treatment. The applicant should answer if there are specific recommendations for the interruption of treatment when thrombocytopenia occurs, and if in some cases where permanent discontinuation is needed. The applicant is to add this information in SmPC section 4.2 'Dose modifications for adverse reactions', where other similar scenarios with other ADRs are described. The applicant should consider adding a warning statement in SmPC section 4.4 and if the ADR should be further described in SmPC section 4.8. (OC)

The applicant is also asked to include thrombocytopenia in the ADR table in SmPC section 4.8 under the SOC 'Blood and lymphatic system disorders' and if required to delete thrombocytopenia from the SOC 'investigations'. (OC)

Hepatotoxicity

The grouped term "Hepatotoxicity" included the following PTs: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Blood bilirubin increased, Drug-induced liver injury, Hepatic enzyme increased, Hepatic failure, Hepatocelluar injury, Hepatotoxicity, Hyperbilirubinaemia, Hypertransaminasaemia, Liver disorder, Liver function test increased, Liver injury, Transaminases abnormal and Transaminases increased. Among iNHL patients treated with parsaclisib at the recommended dose, 9.4% had hepatotoxicity within increased ALT reported as the most common PT (7.7%) followed by increased AST (7.2%). Grade 3 or higher hepatotoxicities were reported at 2.8% rate with one patient experiencing serious hepatotoxicity (0.6%). Dose modifications due to these AEs were quite low according to the review submitted by the applicant. This being said, the PTs selected for the analysis are not endorsed and the applicant is asked to perform a wider review using the SMQ "drug related hepatic disorders" in order to have a more comprehensive view of the hepatic function safety profile of parsaclisib. A discussion of the added value of parsaclisib compared to other PI3Kd compounds should be provided for this risk

as per the conclusions of the requested review. **(OC)** Justification for absence of dose interruption or adjustment in case of hepatotoxicity should be provided. **(OC)**

Pneumonia

Seventeen patients (9.4%) experienced pneumonia events (the grouped terms selection is endorsed). The most commonly reported PT was pneumonia (7.2%) followed by Covid 19 pneumonia (1.1%) with 7.7% of patients having of Grade 3 or higher pneumonia events and the same rate for serious pneumonia events. It should be noted that two patients had fatal events of pneumonia and COVID-19 pneumonia and one case of Pneumocystis Jiirovecii Pneumonia (PJP) reported (related and resolved). Among the 546 participants in the B-Cell Malignancy Pool, 4 participants (0.7%) had PJP of any grade and 2 had grade 3 and grade 4 PJP (all resolving after PJP corrective treatment).

This is a known risk within the therapeutic class, however, guidance should be added in the SmPC section 4.2 for parsaclisib interruption in case of grade 3 and higher pneumonia as it is the case for PJP. Permanent discontinuation of parsaclisib in case PJP is confirmed should be considered while interruption should be recommended until pneumonia is resolved. The SmPC should be modified accordingly, otherwise, please justify. **(OC)**

CMV infection

In the iNHL group, 12 patients had CMV infections from which 5 were of grade 3 and higher. This is as well a known risk with PI3Kd. Guidance regarding CMV reactivation and monitoring should be added in section 4.2 of the SmPC (PCR/Ag test). **(OC)** Please also consider including prophylactic antivirals guidance for CMV infection and management of CMV reactivation in the SmPC. (**OC**)

Varicella zoster virus infections (grouped term)

Varicella zoster virus infections occurred in 12 patients from the iNHL pool, all reported as herpes zoster. Frequency and severity reported for this risk are comparable to other PI3Kd compounds. As recommended for CMV infections, more guidance should be proposed for dose adjustment if any viremia occur. (OC)

No herpes simplex virus infections were reported with a Grade 3 or higher, as serious, fatal, or led to parsaclisib dose modification.

Pneumonitis:

Among patients treated for iNHL, 4 had pneumonitis from which 3 had a Grade 3 or higher and serious pneumonitis and lead to parsaclisib discontinuation within 3 patients. Guidance should thus be included in the SmPC in view of the submitted data and the severity of the risk. (**OC**) The applicant should also consider if any of the serious or fatal events, where patients were diagnosed with noninfectious pneumonia, can be considered as pneumonitis events. (OC) SmPC section 4.4 should be updated with more information on pneumonitis event, including that serious cases have occurred without an apparent infectious cause, to provide median time to onset and time to resolution of these events, and if possible to describe, that appropriate treatment should to be initiated promptly and if parsaclisib should be permanently discontinued. SmPC section 4.8 should be updated with a detailed description of pneumonitis events. (OC)

Intestinal perforation

Only one patient in the MCL Pool had a Grade 3 worsening to a grade 4 intestinal perforation, however, given the severity of the event and knowing that this risk is identified for other marketed PI3Kd, the potential mechanism of toxicity and the possibility to consider intestinal perforation as a class effect if any plausible mechanism is identified should be discussed and the adequate SmPC amendments

implemented, otherwise, the applicant should closely monitor this risk within the PSURs if any MA is granted. **(OC)**

As a general request and since no comparison is possible, the applicant should provide a historical control analysis and discuss the claimed improvement of the safety profile of PI3Ki with parsaclisib**. (OC)**

3.3.7.2.2. Pivotal study – MZL pool

The safety results from Cohort 2 (BTKi naïve) from the pivotal study are coherent with the safety findings from iNHL and B-cell malignancies pools. Over 96% of the patients enrolled in arm B had at least 1 AE with 83 % of them having at least 1 AE considered related to parsaclisib. Diarrhea, cough, and rash were the most commonly reported AEs while Grade 3 or higher AEs occurred in 64 % of patients and serious AEs in 47% of them. These results are also consistent with those observed within the iNHL pool with very similar frequencies reported.

Six participants had a fatal outcome from which 2 were considered related to parsaclisib (one febrile neutropenia and one case of sepsis).

Among the 31 participants in Cohort 2 who discontinued study drug due to TEAEs, diarrhea and colitis were the most frequent AEs observed which is consistent with the iNHL pool findings.

AE and dose-response assessment

The applicant states that the assessment of safety and efficacy data from Study INCB 50465-101 (A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB050465 and INCB039110 in Subjects With Previously Treated B-Cell Malignancies) has highlighted a marked late-onset of some AEs, especially colitis and diarrhea in few patients and that most of the responses occurred approximately at week 9. An induction-maintenance regimen was introduced (20 mg QD for 8 weeks followed by a reduced dose-intensity maintenance dose of 2.5 mg QD in order to find a balance between efficacy and safety (preserve rapid onset of response and reduce the incidence of late-onset AEs).

It is understood that the low daily parsaclisib dose in the maintenance phase could be superior in maintaining the clinical response achieved during the induction phase, however, no submitted safety data could support the superiority of this dose regimen from a global BR perspective. As a matter of fact, 37.5% of the patients who received the recommended dose experienced serious related AEs vs 10.7% of the patients in the 20mg QW arm. Grade 3 and higher treatment related AEs also occurred more frequently in the recommended dose arm with 55.6% of the patients experiencing such events vs 28.6% of them in the 20mg QW arm. No information or comparison regarding AEs onset delays have been provided by the applicant. Since the majority of toxicities are reported more frequently within the recommended dose regimen arm with more toxicities (about 4 times higher: 10.7% in the 20mg QW arm vs 38.9% in the recommended dose arm) leading to parsaclisib discontinuation, please justify within a comprehensive and detailed analysis the assertion regarding the improvement of late-onset AEs by comparing the above cited variables between the two dose regimens. **(MO)**

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

Fatal AEs

Overall, at the recommended dose and considering all patients enrolled at this dose regimen (B-cell malignancies pool), 19 patients had fatal AEs from which 9 died within the iNHL pool (including 6 subjects included in the pivotal study).

Pivotal study:

From the 6 fatal AEs, 2 were considered by the investigator to be related to study drug (febrile neutropenia and sepsis in 1 patient each) but considered unrelated by the sponsor. This discrepancy in relationship assessment should be further justified for these fatal cases**.** The severity of Febrile

neutropenia should be stated in the SmPC. **(OC)** Other fatal AEs were confounded by general health deterioration, COVID-19 infections, Enterobacter sepsis, and mental status changes considered not related to parsaclisib by the investigator.

iNHL pool:

Nine participants (5.0%) had at least 1 fatal AE including sepsis and acute kidney injury (1 participant), fatigue and mental status changes (1 participant), and febrile neutropenia, COVID-19 pneumonia, Enterobacter sepsis, hypoglycemia, pneumonia, sepsis, and Stevens-Johnson syndrome (1 participant each). None of these events were assessed by the sponsor as related to parsaclisib despite the fact that the investigator related patients' deaths to the administration of parsaclisib. The applicant should justify such a decision by providing an aggregated analysis as part of the responses to the LoQ with summarised comprehensive narratives for each iNHL patient who experienced a fatal AE and the detailed reasons for ruling out the causal relationship of parsaclisib in the occurrence of such events. For DLBCL patients, the applicant should as well discuss in the same manner the Jaundice cholestatic fatal case along with the acute respiratory failure and the pleural effusion fatal cases. **(OC)**

Serious AEs:

At the recommended dose, over 50.3% of the iNHL pool patients had at least 1 serious AE; the most frequently occurring were associated with the SOCs "infections and infestations" (19.3%) and "GI disorders" (18.8%). Colitis was the most frequently occurring AE (7.7%) followed by diarrhea (7.2%), and pneumonia (5.5%).

At the recommended dose in the B-Cell Malignancy pool, 146 participants (48.8%) had at least 1 serious AE with the same trends, SOCs and PTs represented. Nine cases of serious adverse events of acute kidney injury in the total doses B-Cell Malignancy pool were reported. The applicant is asked to present a detailed assessment of acute kidney injury (all seriousness) with case narratives. (OC)

3.3.7.4. Laboratory findings

The majority of laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 were reported in 10% and 4% of the cases, respectively.

Laboratory parameters of special interest included decreased neutrophils, increased ALT, and increased AST.

Overall, within the iNHL population and at the recommended dose, treatment-emergent worsening of hematology parameters was observed most frequently for decreased neutrophils (48.6%). Worsening of hematological parameters to Grade 3 was observed for decreased neutrophils in 11% of the cases followed by the PT decreased lymphocytes in 7.2% of the cases while worsening to Grade 4 was observed for decreased neutrophils (3.9%) and decreased leukocytes and decreased lymphocytes in 1.7% each.

Events of chemistry laboratory abnormalities were observed most frequently for increased ALT (29.8%) and increased AST (26%). Events of worsening to Grade 3 were reported most frequently for increased ALT and decreased potassium (2.8% each) while events of worsening to Grade 4 laboratory abnormalities were observed most frequently for hyperglycaemia (3.9% with only one case not confounded by diabetes history and not considered related to parsaclisib by the investigator).

Neutropenia management in PI refers that neutrophil counts should be monitored at least every 2 weeks for the first 2 months of treatment with parsaclisib and at least weekly in patients with neutrophil counts $< 1 \times 10^9$ /L (Grade 3-4 neutropenia). Supportive care should be considered as appropriate. However, the conditional probability of the first occurrence of worsening Grade 3 or 4 decreased neutrophils using the life-table method was 6.88% before Week 8 and 6.55% from Weeks ≥

8 to < 24. The applicant is asked to discuss if monitoring of neutrophils should be advised to be longer in relation to the first occurrence of observed worsening Grade 3 or 4 decreased neutrophil counts. (**OC**)

There were 88 patients (16.1%) in the B-Cell Malignancy pool who experienced creatinine increased. The applicant is asked to assess the causality of this event in relation with parsaclisib. (**OC**)

No patients with moderate/severe hepatic or renal impairment were included in the parsaclisib submitted studies. The applicant is requested to include this information in the SPC, section 4.2 and 5.1. (OC)

Two participants in the B-Cell Malignancy Pool met the lab criteria for DILI (ALT or AST > 3 × ULN, ALP < 2 × ULN, and total bilirubin > 2 × ULN at the same visit without meeting the Hy's Law criteria:

- The first patient meeting the lab DILI criteria at day 338 but had a confounding medical history of ongoing alcoholic liver disease and hepatitis B and a negative rechallenge for parsaclisib can help to rule out a possible causality relationship between the event and parsaclisib

- The second patient also meeting the lab criteria for DILI at day 72 had multiple concurrent diseases and events (from which DRESS and septic shock) and discontinued parsaclisib 17 days before the occurrence of the first manifestation of hepatic disorders.

The applicant states that at the recommended dose, 12 patients (4.8%) had a QTcF value >480 milliseconds, from which 4 (1.6%) had a QTcF value > 500 milliseconds. The applicant is asked to provide a detailed and comprehensive analysis of all cases reporting a clinically significant ECG abnormalities in the B-cell malignancies pool. (**OC**) The applicant is asked to provide a detailed and comprehensive analysis of all cases reporting a clinically significant ECG abnormalities in the B-cell malignancies pool. The applicant should clarify if any of the patients had the criteria fulfilled for clinical QTc prolongation (long QT syndrome, LQTS) considering those subjects whose baseline measurements where in the normal range. (OC)

3.3.7.5. In vitro biomarker test for patient selection for safety

NA

3.3.7.6. Safety in special populations

No clinically significant trends were observed in the incidence or severity of AEs based on disease subtype, age, sex, race or geographic regions

The applicant is requested to fill in the table regarding incidences of various adverse event subgroups according to age **(OC)**

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs				
Serious AEs – Total				
- Fatal				
- Hospitalization/prolong existing hospitalization				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

No data are available on the use of parsaclisib in pregnant women nor on the presence of parsaclisib on breastfeeding. (OC)

Two participants had AEs of accidental overdose (one case of ingestion of 40 mg instead of 20 mg and one case of ingestion of 80 mg instead of 20 mg). No associated toxicities were reported.

3.3.7.7. Immunological events

There is no section specifically addressing immunological events. (OC)

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

Please see section 3.2.2 pharmacology

3.3.7.9. Discontinuation due to adverse events

AEs resulting in parsaclisib discontinuation occurred in 54 participants (29.8%) with diarrhea (9.4%), colitis (5.5%), and rash (2.2%) as the most frequently reported PTs. Comparable rates are reported for the B-cell malignancies pool.

The applicant is asked to specify if dose interruptions, dose reductions and dose discontinuations were counted once per participant or if there is overlap in these terms. The applicant is asked to specify what is exactly included under these terms. (OC)

Safety data shows high number of TEAEs leading to dose interruption at the recommended dose (50.5%). The applicant is asked to discuss this finding in context with other PI3K inhibitors, and analyse if there is a concern of tolerability. (OC)

The applicant is asked to analyse the time to resolution of all diarrhoea and colitis events, e.g. to present this in a table format and a figure of the KM. More specifically, the applicant is also asked to provide a separate analysis of diarrhoea and colitis events that lead to discontinuation, disruption or interruption of treatment and the mean time-to-resolution of these events (terms together and separately). (OC)

The applicant is asked to specify if there were cases, in which an AE due to parsaclisib prevented the start of another anticancer treatment. The applicant should thoroughly investigate such cases and present these. (OC)

3.3.7.10. Post marketing experience

Parsaclisib is an investigational drug and is not approved or marketed in any country. Therefore, no post-marketing data are available.

3.3.8. Discussion on clinical safety

The characterization of the safety profile of parsaclisib as monotherapy in NHL has been provided by the applicant through one pivotal study, one supportive study (INCB 50465-203) and 5 other studies within the parsaclisib monotherapy setting in addition to 2 completed clinical pharmacology studies in 43 healthy participants. A description of safety data in MZL (CSR) along with a wider description of the safety profile within a iNHL pool and a B-cell malignancies pool, have been provided. 299 subjects received the recommended dose regimen of 20mg QD for 8 weeks followed by 2.5 mg QD, including 72 patients with R/R MZL from the Pivotal Study INCB 50465-204.

The median duration of exposure for patients with iNHL (MZL and FL) treated with parsaclisib monotherapy (N = 181) at the recommended dose was 9.7 (0.36, 35.3) months which is quite limited making it difficult to draw clear conclusions regarding the long-term safety profile in this treatment setting. Moreover, the number of patients enrolled is also limited with only 72 patients with R/R MZL and an overall 181 iNHL patients treated at the chosen dose of 20 mg QD for 8 weeks followed by a reduced dose-intensity maintenance dose of 2.5 mg QD but this could be acceptable with regards to the CMA requested by the applicant.

In both iNHL and B-cell malignancies pool, demographics and baseline characteristics were generally comparable, also between doses subgroups. The use of prior systemic anti-cancer therapies was quite different between the patients pooled within the different studies since patients enrolled within the pivotal study INCB 50465-204 (CITADEL-204) with R/R MZL had received at least 1 prior anti-CD20-based

regimen when patients included within the supportive study INCB 50465-203 (CITADEL-203) with R/R FL had received at least 2 prior lines of therapy. The proportion of each treatment line, disease burden and baseline characteristics are not detailed by histology group for all patients enrolled within the iNHL pool. The applicant should clarify (OC).

In the iNHL Pool, 97.8% of participants reported general medical history, mostly vascular disorders, GI disorders and metabolism and nutrition disorders confounding numerous cases reporting similar clinical manifestations. The most frequently reported PT was hypertension (over 40%) as medical history. Antibacterial and antiviral therapies where the most frequently reported concomitant treatments, often permitted within protocols' recommendations. The applicant should discuss the possibility of mirroring the antibacterial/antiviral prophylaxis proposed within the studies protocols in the SmPC (OC).

The most common AEs in the iNHL pool were reported for the gastrointestinal disorders SOC with a cumulative incidence of 71.3%. The most commonly reported PTs were diarrhoea (47%), nausea (21%) and Constipation (9.9%). The second most reported SOC was infections and infestations with a cumulative incidence of 58.6% with Pyrexia and Neutropenia presented as most reported PTs for this SOC with 18.8% and 14.9% of incidence overall. Other SOCs are also largely represented within the safety reviews submitted as follows: General disorders and administration site conditions SOC (50.8%); Skin and subcutaneous tissue disorders SOC (43.1%); Respiratory, thoracic, and mediastinal disorders SOC (41.4%) and metabolism and nutrition disorders SOC (40.3%). Adverse events of special interest included the following PTs: febrile neutropenia, pneumonitis, pneumonia, PJP, diarrhea, colitis, rash, exfoliative dermatitis, CMV infection, herpes simplex, varicella zoster virus infection, and intestinal perforation.

The AEs trends are driven by diarrhoea/colitis, infections mostly pneumonia, neutropenia and skin reactions. Uncertainties are raised regarding safety queries for hepatotoxicity events, making it impossible to adjudicate on the assertion as parsaclisib could have an improved hepatic safety profile compared to other PI3K inhibitors (OC). More than 50% of the enrolled iNHL patients treated with parsaclisib at the recommended dose had at least 1 SAE, which is a high frequency and of big concern taking into consideration the indolent disease course (OC). Furthermore, pneumonia is one of the most frequently reported SAE also reported as one of the frequent causes of death in this treatment setting. This is a known risk within the therapeutic class, however, guidance should be added in the SmPC section 4.2 for parsaclisib interruption in case of grade 3 and higher pneumonia as it is the case for PJP. Permanent discontinuation of parsaclisib in case PJP is confirmed should be considered while interruption should be recommended until pneumonia is resolved (OC). In addition, a relevant number of patients had treatment related TEAE of anaemia and haemoglobin decreased was observed for 183 patients (33.5%) in the B-Cell Malignancy total pool. Substantial number of subjects had treatment related TEAEs of pruritus, urinary tract infections, abdominal pain cases and acute kidney injury cases. The assessment of these AEs should be provided (OC) and the management of "rash" Grade 1-2, Grade 3, thrombocytopenia and pneumonitis should also be specified within the SmPC. More broadly, the applicant should provide life-table method analysis for all identified AESIs (excluding the few ones already provided). (OC) Discontinuations of parsaclisib treatment should also be further investigated as it is the case for AEs reported with a fatal outcome. (OC)

A further point is that it is, at this stage, unclear if the AEs observed with parsaclisib occurred with the same trends and frequencies throughout the different treatment periods (induction period vs maintenance dose regimens, first 3 months vs end of treatment (one year cut-off could be chosen)…). A discussion of the incidence and trends in AEs taking into considerations these variables is expected (OC). Moreover, The applicant states that the assessment of safety and efficacy data from Study INCB 50465-101 (A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB050465 and INCB039110 in Subjects With Previously Treated B-Cell Malignancies) has highlighted a marked late-onset of some AEs, especially colitis and diarrhea in few patients and that most of the responses occurred

approximately at week 9. An induction-maintenance regimen was then introduced (20 mg QD for 8 weeks followed by a reduced dose-intensity maintenance dose of 2.5 mg QD) in order to find a balance between efficacy and safety, preserve rapid onset of response and reduce the incidence of late-onset AEs. In order to substantiate this hypothesis, the applicant submitted no safety analysis that could possibly support the better tolerance of the chosen dose regimen from a global BR perspective. In the contrary, it seems that the majority of toxicities are reported more frequently within the recommended dose regimen arm with more toxicities (about 4 times higher) leading to parsaclisib discontinuation (**MO**).

Regarding the haematological parameters, the applicant reports a significant rate (approximately between 5 and 50%) of the iNHL patients experiencing an AE related to a haematological parameter of any grade with neutropenia being the dominant AE (48.6%). Unsurprisingly, events of chemistry laboratory abnormalities were dominated by increased ALT (29.8%) and increased AST (26%) events. These results are of most importance since parsaclisib is deemed to be a lifelong treatment in contrast to the very limited exposures in the clinical development settings.

Parsaclisib is assumed to be a next generation, highly potent PI3Kσ inhibitor which is assumed to improve the safety profile of PI3K inhibitors. This affirmation does not seem to be justified by the safety data provided from the different parsaclisib studies even though it is very difficult to draw clear conclusions in the absence of comparison to SoC or another PI3K inhibitor considering the open label design of the studies.

Overall, data reported within arm B (recommended dose) of cohort 2 (BTKi naïve R/R MZL) of the pivotal study and within the B-cell malignancies pool are comparable to those reported in the iNHL pool.

Considering that the studies that are part of this CMA are ongoing, long-term safety is at this stage not known. These types of results will hopefully be provided by the planned randomised, controlled phase III study, if uncertainties regarding its conduct are dispelled.

3.3.9. Conclusions on clinical safety

The safety profile of Parsaclisib is coherent with the expected tolerance for a PI3K inhibitor. Severe diarrhoea/colitis, infections, neutropenia and severe skin reactions were the most important AEs reported. Uncertainties regarding the long term safety profile, the recommended dose regimen choice and hepatotoxicity queries are raised. No major safety issues were identified even though no comparison is possible at this time being given the uncontrolled nature of the submitted studies and the absence of historical data.

<The following measures are necessary to address the missing safety data in the context of a <conditional> MA <under exceptional circumstances>:

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns

Important identified risks	Serious Infections
Important potential risks	None
Missing information	None

Summary of safety concerns (proposed by Rapporteur)	
Important identified risks	- Serious Infections - Severe diarrhea and colitis - Severe toxic skin reactions
Important potential risks	- Safety in patients with moderate/severe hepatic impairment
Missing information	- Safety in patients with moderate/severe renal impairment - Safety in patients with clinically significant cardiac disease (including unstable angina, acute myocardial infarction, and/or cardiac conduction issues) - Use during pregnancy and in childbearing patients - Safety with long term use

3.4.1.1. Discussion on safety specification

The presentation in the RMP is deemed acceptable, however, the list of safety concerns should be revised as follows:

Patients with clinically significant cardiac disease (including unstable angina, acute myocardial infarction, and/or cardiac conduction issues) have not been exposed to parsaclisib, this information should therefore be added to the summary of safety concerns as Missing information. Studies INCB 50465-109 and INCB 50465-108 could be listed as a category 3 post authorisation studies. **(OC)**

Patients with moderate/severe renal impairment have not been exposed to parsaclisib, the applicant is requested to discuss if the safety profile of parsaclisib is expected to be different in patients with moderate/severe renal impairment and discuss the need to include this information in the RMP as a missing information.

Pending the responses to the OCs on hepatoxicity, the applicant should discuss whether hepatotoxicity should be included as an important identified or important potential risk.

Use in pregnant and childbearing patients should also be considered as missing information since no data are available. Please consider adding adequate safety endpoints to ongoing studies or propose other additional PV activities to help characterize this risk. **(OC)**

Long term safety has not been studied within the development program of parsaclisib. The applicant should include it as a safety concern and propose an additional PV activity in order to help characterize the risk within acceptable timelines. **(OC)**

It is agreed that treatment in paediatric patients should not been included in the RMP as per RMP guidance and since the indication does not include children at this stage.

The presented data are generally acceptable.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification

It is considered that the following risks should also be safety concerns:

- Severe diarrhea and colitis
- Severe toxic skin reactions
- Safety in patients with moderate/severe renal impairment
- Safety in patients with moderate/severe hepatic impairment
- Safety in patients with clinically significant cardiac disease
- Use during pregnancy and in childbearing patients
- Safety with long term use

3.4.2. Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are currently no other forms of routine pharmacovigilance activities for parsaclisib beyond adverse reactions reporting and signal detection.

Additional Pharmacovigilance Activities
There are no planned or ongoing additional pharmacovigilance activities.

3.1. Summary of planned additional PhV activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PRAC Rapporteur Assessment Comment

*The applicant proposes no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Class products Copiktra (duvelisib) and Zydelig (idelalisib), both PI3K-delta inhibitors, have a follow up questionnaire in place for de important identified risk "serious infections". The applicant is requested to include a follow up questionnaire for serious infections as routine pharmacovigilance activity in the RMP. The questionnaire should include risk factors for serious infections and specific information about the infection itself, including CMV and PJP. This information goes beyond routinely acquired follow up.(**OC**)*

No post authorisation safety studies (PASS) were proposed, which is not acceptable. There are studies ongoing outside the context of the RMP, i.e. INCB 50465-111 (phase 1b), -203 (phase 2), -204 (phase 2), -205 (phase 2), and -801 (phase 2). Furthermore the applicant proposes a confirmatory study, i.e. INCB 50465-302 (phase 3, compared to placebo). All abovementioned studies will evaluate both efficacy and safety of parsaclisib.

*The safety specification is still under evaluation. Pending the CHMP comments on the safety concerns – for the safety concerns not specifically mentioned below - the applicant should discuss how each safety concern will be further characterised in the post-marketing setting. If applicable, additional pharmacovigilance activities (e.g. PASS) should be proposed and study synopsis should be submitted. (**OC**)*

*Moderate/severe renal and hepatic impairment have been included as missing information upon CHMP assessment. Studies investigating hepatic impairment (INCB 50465-108) and renal impairment (INCB 50465-109) are currently ongoing. In view of the limited data from the pivotal signal arm trial, the applicant is requested to include INCB 50465-108 and INCB 50465-109, pending the discussion on renal impairment, as a category 3 PASS, within the pharmacovigilance plan. The applicant should also submit study synopsis within annex 3 of the RMP. (**OC**)*

*Long-term safety is at this stage not known and this should be further characterised. Proposals for adequate pharmacovigilance activities should be made by the applicant. As the CHMP Rapporteur pointed out long term safety may be provided by the planned randomised, controlled phase III study. However, since parsaclisib is deemed to be a lifelong treatment in contrast to the limited follow up time in a clinical trial, the applicant is requested to discuss if long term safety can be sufficiently characterised within this RCT or if additional studies are warranted to characterise the long term safety. (**OC**)*

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the characterisation of safety specifications are still under evaluation. For each safety concern, the applicant should discuss how this can be best characterised in the post-marketing setting.

3.1.1. Risk minimisation measures

Routine Risk Minimisation Measures

The safety information in the proposed product information is aligned to the reference medicinal product.

3.1. Summary of risk minimisation measures from the RMP

Table 4: Proposal from applicant for risk minimisation measures

Safety concern	**Risk minimization measures (routine and additional)**	**Pharmacovigilance activities**
Serious infections (Important identified risk)	**Routine risk minimisation measures:** • SmPC section 4.2 • SmPC section 4.4 • SmPC section 4.8 • PL section 2 and 4 **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ● None **Additional pharmacovigilance activities:** • None

	• None	

PRAC Rapporteur Assessment Comment

*It is stated in RMP part V that "The safety information in the proposed product information is aligned to the reference medicinal product". As this is a full application, there is no reference medicinal product in place. The applicant is requested to remove this sentence form part V and all corresponding sections. (**OC**) Table part V.1. should remain within the RMP.*

The applicant did not propose any additional risk minimisation measures. This is in line with other PI3K-delta inhibitors. Currently Piqray (alpelisib) is the only PI3K inhibitor with aRMM in place. This aRMM consists of a prescribers guide for the risk of hyperglycaemia. However, hyperglycaemia is not considered a safety concern for parsaclisib.

The CHMP Rapporteur suggested aRMM linked to the safety concern "serious infections". In line with other PI3K inhibitors this is not considered warranted. Clear information on serious infections in the PI should be sufficient to mitigate this risk. Serious infections should however remain within the summary of safety concerns as important identified risk, as it will be further characterized with routine pharmacovigilance activities (see section 5.1).

*At this point the characterisation of the safety profile is ongoing. Pending the CHMP comments on the safety specification, the applicant should elaborate on the need for further risk minimisation measures, including the clinical consequences of the safety concerns, as well as management strategies and preventability measures should be discussed, both routine and additional risk minimisation measures. (**OC**)*

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted, was of the opinion that:

At this point the characterisation of the safety profile is ongoing. Pending the CHMP comments on the safety specification, the applicant should elaborate on the need for further risk minimisation measures.

3.1.1. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version **0.1** could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 5.

3.2. Pharmacovigilance

3.2.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.2.2. Periodic Safety Update Reports submission requirements

Not applicable

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The claimed therapeutic indication of parsaclisib is "in monotherapy for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL)".

MZL is the 3rd most common type of B-cell non-Hodgkin lymphoma, after DLBCL and FL. It is an indolent lymphoma with a median survival from 5 to 10 years depending of the subtype. Although outcomes are favorable for patients with MZL, advanced-stage disease remains incurable, and the relapsing nature of indolent lymphomas requires continued retreatment.

4.1.2. Available therapies and unmet medical need

No treatment in EU has a specific indication in relapse or refractory MZL. Only bendamustine is authorized locally in some countries to treat indolent NHL that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen.

However, ESMO and NCCN recommendations for relapse/refractory MZL in case systemic treatment is required are non-authorized treatment in MZL i.e. preferably an immunochemotherapy containing the anti-CD20 mAb (R-bendamustine, R-CHOP, R-CVP, R²).

In US, PI3K inhibitors (copanlisib, duvelisib, idelalisib) are recommended after 2 prior therapies with the exception of umbralisib which is recommended after at least one prior anti-CD20 mAb based regimen. It is to be noted that the only PI3K authorized in the US is umbralisib whose B/R in MZL is currently under reassessment by the FDA due to a safety signal (increased risk of death) in an ongoing clinical trial in CLL.

Few data are available in the relapse or refractory setting in patients with MZL due to the rarity of the disease making difficult to conduct a randomized trial. The applicant provided a SLR for this application, which shows that data available on patients who can be compared to those of the target indication are rare.

Although outcomes are favorable for patients with MZL, advanced-stage disease remains incurable, and the relapsing nature of indolent lymphomas requires continued retreatment. Therefore there is a need for additional authorized treatments in R/R MZL.

4.1.3. Main clinical studies

The main source of data for this application is provided by the results of the pivotal phase II clinical trial INCB 50465-204 (CITADEL-204). This is an ongoing, open-label, non-comparative study in subjects with relapse or refractory MZL, who received at least a prior anti-CD20 mAb. Patients received parsaclisib at 20 mg QD PO for 8 weeks followed by 20 mg once weekly PO (treatment A, n=28) or parsaclisib 20 mg QD PO for 8 weeks followed by 2.5 mg QD PO (treatment B, n=72) until disease progression, death, unacceptable toxicity, or consent withdrawal.

4.2. Favourable effects

Primary endpoint

At the intended posology, ORR (95% CI) was 59.7% (47.5, 71.1) with BOR of CR in 5.6 % (4 patients) and PR in 54.2 % (39 patients), SD was observed in 29.2 % (21 patients).

Among patients who responded, median time to response was 8.14 weeks (range: 5.0-36.1 weeks), corresponding to the first planned assessment of response.

ORR and BOR for patients who had 2 or more prior systemic therapies in cohort 2 according to IRC are overall consistent with the primary analysis. ORR (95% CI) at the intended posology is 53.8% (37.2, 69.9) with CR accounting for 5.1% (2 patients) and PR for 48.7% (19 patients).

Secondary endpoints

Median DOR (95% CI) at the intended dosing regimen was 13.57 months (8.05, 17.74), numerically superior to the median DOR in treatment arm A (9.26 months, 95% CI: 2.56, NE). The median follow-up time from the onset of CR or PR per the IRC to the data cutoff date was 22.87 months (range: 15.3-36.6 months).

Median PFS (95% CI) at the intended dosing regimen was 16.53 months (11.53, 20.63) with a median follow-up (min; max) was 25.53 months (15.8-40.9 months).

Median OS was not reached as 83% of patients were still alive at the data cut-off.

All 70 participants who had a baseline and at least a post baseline measurement of target lesion, had a reduction in the sum of product lesion diameter, of which 59 participant had best reduction > 50% from baseline.

4.3. Uncertainties and limitations about favourable effects

Data for this application of parsaclisib in monotherapy for patients with R/R MZL stand mainly on the pivotal phase 2 study CITADEL-204. The most important limitation about favourable effects is related to the design of this pivotal phase 2 single-arm, 2-cohort open-label study. Indeed, establishing efficacy in single-arm studies can be challenging due to the lack of comparator and the potential selection bias.

ORR which is an acceptable primary endpoint for this SAT, is supported by time-to-events secondary endpoints. These last endpoints are however difficult to interpret in the frame of such a single arm study design. In addition, PFS data have a low maturity and median OS was not reached which reinforces the uncertainties. PFS is therefore not considered to be statistically compelling and clinically relevant, and its description in the SmPC is therefore not endorsed. Finally, even if CR are observed, rates seem lower than those published in comparable settings.

Other uncertainties for the pivotal study relate to the lack of information regarding protocol deviations, differences in local versus central assessment of response, censoring approach used and the choice of the intended dose for maintenance which is not clearly justified.

The proposed MAIC is limited by several deficiencies, some related to the data available from the pivotal study and the published evidence, some more generally associated with the use of external controls. Therefore, it does not adequately address the main methodological concern of the phase 2 pivotal trial, i.e. the lack of a randomised comparator.

Finally, although the provided supportive study is consistent with pivotal studies results, with even more important benefit observed in patient with FL, it should be interpreted with caution as it has been previously seen that benefit in FL does not always transpose into a benefit in MZL. Nevertheless, this supports an activity of parsaclisib in iNHL.

4.4. Unfavourable effects

The median duration of exposure for patients with iNHL (MZL and FL) treated with parsaclisib monotherapy (N = 181) at the recommended dose was 9.7 (0.36, 35.3) months. The number of patients enrolled is quite limited with only 72 patients with R/R MZL and an overall 181 iNHL patients treated at the chosen dose of 20 mg QD for 8 weeks followed by a reduced dose-intensity maintenance dose of 2.5 mg QD.

In both iNHL and B-cell malignancies pool, demographics and baseline characteristics were generally comparable, also between doses subgroups.

In the iNHL Pool, 97.8% of participants reported general medical history, mostly vascular disorders, GI disorders and metabolism and nutrition disorders confounding numerous cases reporting similar clinical manifestations. The most frequently reported medical history was hypertension (over 40%). Antibacterial and antiviral therapies where the most frequently reported concomitant treatments, often permitted within protocols' recommendations.

The most common AEs in the iNHL pool were reported for the gastrointestinal disorders SOC with a cumulative incidence of 71.3%. The most commonly reported PTs were diarrhoea (47%), nausea (21%) and constipation (9.9%). The second most reported SOC was infections and infestations with a cumulative incidence of 58.6% with pyrexia and neutropenia presented as most reported PTs for this SOC with 18.8% and 14.9% of incidence respectively. Other SOCs are also largely represented within the safety reviews submitted as follows: General disorders and administration site conditions SOC (50.8%); Skin and subcutaneous tissue disorders SOC (43.1%); Respiratory, thoracic, and mediastinal disorders SOC (41.4%) and metabolism and nutrition disorders SOC (40.3%).

Adverse events of special interest included the following PTs: febrile neutropenia, pneumonitis, pneumonia, PJP, diarrhea, colitis, rash, exfoliative dermatitis, CMV infection, herpes simplex, varicella zoster virus infection, and intestinal perforation.

Safety data shows high number of TEAEs leading to dose interruption at the recommended dose (50.5%). A relevant number of patients had treatment related TEAE of anaemia and hemoglobin decreased was observed for 183 patients (33.5%) in the B-Cell Malignancy total pool. Substantial number of subjects had treatment related TEAEs of pruritus, urinary tract infections, abdominal pain and acute kidney injury events.

Overall, data reported within arm B (recommended dose) of cohort 2 (BTKi naïve R/R MZL) of the pivotal study and within the B-cell malignancies pool are comparable to those reported in the iNHL pool.

Regarding the haematological parameters, the applicant reported significant rates of the iNHL patients experiencing an AE related to a haematological parameter of any grade with neutropenia being the dominant AE (48.6%). Unsurprisingly, events of chemistry laboratory abnormalities were driven by increased ALT (29.8%) and increased AST (26%) events.

4.5. Uncertainties and limitations about unfavourable effects

Parsaclisib is assumed to be a next generation, highly potent PI3Kσ inhibitor which is meant to improve the safety profile of PI3K inhibitors. This affirmation does not seem to be justified by the safety data provided from the different parsaclisib studies as the data presented above can show even though it is very difficult to draw clear conclusions since no comparison to SoC or another PI3K inhibitor is possible considering the open label design of the studies and the absence of a historical control.

The number of patients enrolled is quite limited with only 72 patients within the sought indication; the median duration of exposure is 9.7 months (0.36, 35.3), making it very difficult to draw clear conclusions

for the long-term safety profile of parsaclisib. Moreover, there is a data gap that should be addressed with regards to the proportion of patients in each treatment line, disease burden and baseline characteristics for the safety population.

The use of prior systemic anti-cancer therapies was quite different between the patients pooled within the different studies since patients enrolled within the pivotal study INCB 50465-204 (CITADEL-204) with R/R MZL had received at least 1 prior anti-CD20-based regimen when patients included within the supportive study INCB 50465-203 (CITADEL-203) with R/R FL had received at least 2 prior lines of therapy. The proportion of each treatment line, disease burden and baseline characteristics are not detailed by histology group for all patients enrolled within the iNHL pool.

Uncertainties are raised regarding safety queries for hepatotoxicity events, making it impossible to adjudicate on the assertion as parsaclisib could have an improved hepatic safety profile compared to other PI3K inhibitors.

More than 50% of the enrolled iNHL patients treated with parsaclisib at the recommended dose had at least 1 SAE, which is a high frequency and of big concern taking into consideration the indolent disease course. Furthermore, pneumonia is one of the most frequently reported SAE also reported as one of the frequent causes of death in this treatment setting. This is a known risk within the therapeutic class, however, guidance should be added in the SmPC section 4.2 for parsaclisib interruption in case of grade 3 and higher pneumonia as it is the case for PJP. Permanent discontinuation of parsaclisib in case PJP is confirmed should be considered while interruption should be recommended until pneumonia is resolved.

A further point is that, at this stage, it is unclear if the AEs observed with parsaclisib occurred with the same trends and frequencies throughout the different treatment periods (induction period vs maintenance dose regimens, first 3 months vs end of treatment (one year cut-off could be chosen)…). A discussion of the incidence and trends in AEs taking into considerations these variables is expected. Moreover, The applicant states that the assessment of safety and efficacy data from Study INCB 50465-101 (A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB050465 and INCB039110 in Subjects With Previously Treated B-Cell Malignancies) has highlighted a marked late-onset of some AEs, especially colitis and diarrhea in few patients and that most of the responses occurred approximately at week 9. An induction-maintenance regimen was then introduced (20 mg QD for 8 weeks followed by a reduced dose-intensity maintenance dose of 2.5 mg QD) in order to find a balance between efficacy and safety, preserve rapid onset of response and reduce the incidence of late-onset AEs. In order to substantiate this hypothesis, the applicant submitted no safety analysis that could possibly support the superiority of the chosen dose regimen from a global BR perspective, in the contrary, it seems that the majority of toxicities are reported more frequently within the recommended dose regimen arm with more toxicities (about 4 times higher) leading to parsaclisib discontinuation. More broadly, the applicant should provide life-table method analysis for all identified AESIs (excluding the few ones already provide).

Furthermore, numerous risks should be better reflected in the SmPC, in terms of frequency but also severity and management recommendations. In addition, some antibacterial and antiviral therapies where allowed during clinical trials with parsaclisib. The Rapporteur believes that this should be mirrored in the SmPC.

A significant rate of the iNHL patients experienced an AE related to a haematological parameter of any grade with neutropenia being the dominant AE. These results are of most importance and concerns since parsaclisib is deemed to be a lifelong treatment in contrast to the very limited exposures in the clinical development settings.

To conclude and considering that the studies that are part of this CMA are ongoing, long-term safety is at this stage not known. These types of results will hopefully be provided by the planned randomised, controlled phase III study if uncertainties regarding its conduct are dispelled.

4.6. Effects Table

Table 34 Effects Table for parsaclisib in R/R MZL in study CITADEL-204 (data cut-off:14 may 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR (95% CI)	Overall Response Rate CR + PR by IRC	%	59.7 (47.5, 71.1)	NA		
CR (95% CI)	Complete Response	%	5.6 (1.5, 13.6)	NA		
PR	Partial Response	%	54.2	NA		
Median PFS (95% CI)	Progression-free survival	Months	16.53 (11.53, 20.63)	NA	Low maturity of data	
Median DOR (95% CI)	Duration of Response	Months	13.57 (8.05, 17.74)	NA		
Median OS	Overall survival	Months	Not Reached	NA	83% of patients still alive at the data cut-off	
Unfavourable Effects						
Patients having a treatment related AEs	incidence	%	83,3	NA		
Serious AEs	incidence	%	55,6	NA		
Diarrhea	incidence	%	52,8	NA		
Rash	incidence	%	18,1	NA		
Pneumonia	Incidence	%	9,7	NA		

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Data for this application of parsaclisib in monotherapy for patients with R/R MZL stand mainly on the pivotal phase 2 study CITADEL-204. ORR (95% CI) which was the primary endpoint (59.7%, 47.5, 71.1) with 5.6 % CR and 54.2% PR. Median (95% CI) DOR and PFS were 13.57 months (8.05, 17.74) and

16.53 months (11.53, 20.63) respectively. Relevance of the low rate of CR in the context of an indolent disease needs to be addressed and the limitations related to the design of the single arm pivotal study due to the lack of comparator and the potential selection bias prevent from a proper assessment of the B/R. The provided supportive data (a phase II single arm in FL and a MAIC) are of limited value.

Additional data could help to resolve some uncertainties. To provide comprehensive data, the applicant proposes to conduct a confirmatory double-blind, randomized, placebo-controlled, multicenter Phase III study (INCB Study 50465-302) in patients with MZL R/R in the same clinical setting as the pivotal Phase 2 study for this request in a CMA setting. However, several questions regarding the feasibility of this study are raised.

Related to the low CRR in the pivotal study, the choice of the maintenance dose should be justified with respects to pharmacokinetic, efficacy and safety data.

It is quite difficult to draw clear conclusions regarding the safety profile of parsaclisib since no comparison to SoC or another PI3K inhibitor is possible considering the open label design of the studies and the absence of a historical control. The AEs trends are dominated by diarrhoea/colitis, infections mostly pneumonia, neutropenia and skin reactions. Uncertainties are raised regarding safety queries for hepatotoxicity events, making it impossible to adjudicate on the assertion as parsaclisib could have an improved hepatic safety profile compared to other PI3K inhibitors. More than 50% of the enrolled iNHL patients treated with parsaclisib at the recommended dose had at least 1 SAE, which is a high frequency and of big concern taking into consideration the indolent disease course and that parsaclisib is supposed to be a lifelong treatment in contrast to the very limited exposures in the clinical development settings.

4.7.2. Balance of benefits and risks

Results of parsaclisib currently do not support an indication in R/R MZL. Several major issues need to be addressed including the unmet medical need. Moreover, efficacy data are based solely on the pivotal phase 2 study CITADEL-204. The uncertainties due to the limitations related to the design of the single arm pivotal study due to the lack of comparator and the potential selection bias need to be resolved by comprehensive data.

Moreover, relevance of the low rate of CR in the context of an indolent disease with guidelines providing several recommendations for treatment of 2L+ MZL is questioned together with a justification of the proposed maintenance dose.

The safety profile of Parsaclisib is as it can be expected for a PI3K inhibitor. Severe diarrhoea/colitis, pneumonitis, neutropenia and severe skin reactions were the most important AEs reported. Uncertainties regarding the long term safety profile, the recommended dose regimen choice and hepatotoxicity queries are raised. No major safety issues were identified even though no comparison is possible at this time being given the uncontrolled nature of the submitted studies and the absence of historical data.

From a quality point of view, the overall B/R of parsaclisib has to be evaluated as negative as two major objections have been raised regarding definition of starting materials and manufacturing process validation. In addition to the two major objections, numerous other concerns related to the drug substance and the drug product were identified.

4.7.3. Additional considerations on the benefit-risk balance

Based on the above, the clinical data are not considered comprehensive.

Conditional marketing authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition the product is designated as an orphan medicinal product. However, the applicant should addressed several issues

- The benefit-risk balance is negative at the present time at stated above.
- The claim that parsaclisib can fulfil an unmet medical need in MZL and its major therapeutic advantage (MTA) over existing therapies should be further justified. The proposed phase III study to provide comprehensive study plans a control arm in 2L+ similarly to the intended indication. The ability to identify a control arm in 2L+ is not consistent with the notion of unmet medical need. In addition, several recommendations are actually provided by NCCN and ESMO guidelines in 2L+MZL
- It is likely that the applicant will be able to provide comprehensive data. The applicant plans to conduct a confirmatory phase 3, double blind, randomized, placebo controlled multicentre study (Study INCB 50465-302) in patients with R/R MZL in the same clinical setting than the pivotal phase 2 study for this application. The ability of this study to enrol patient with R/R MZL is currently uncertain. Indeed, provided the CMA is granted, patient with R/R MZL will be able to receive marketed parsaclisib in the same clinical setting than proposed in the phase III study. It can be expected that patients would be less willing to participate in the study. Moreover, while the results of a comparison study will allow to further assess the B/R, the relevance of the control arm is still questioned. Related to this issue, the clinical trial application (CTA) for this phase III which has been submitted in CZ, ES, PL, IT, HU and FR has been withdrawn in CZ, FR, IT, ES and refused in HU at the time of this assessment. Therefore, recruitment of patient with MZL expected to be challenging.

4.8. Conclusions

The overall benefit /risk balance of parsaclisib in sought indication is negative at the present time.