25 March 2021
EMA/CHMP/236249/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Copiktra

International non-proprietary name: **duvelisib**

Procedure No. EMEA/H/C/005381/0000

Note

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

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List of abbreviations

Abbreviation	Definition
AKT	Protein kinase B
ALC	Absolute lymphocytic count
AT	All Treated
BID	Twice daily
BOR	Best overall response
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CR	Complete response/remission
CRi	Complete response/remission with incomplete marrow recovery
CT	Computed tomography
CSR	Clinical study report
CSR-07	Clinical study report Study IPI-145-07
CSR-06	Clinical study report Study IPI-145-06
DE	Dose-escalation
DOR	Duration of response
EC	Expansion cohort
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ESMO	European Society of Medical Oncology
EWB	Emotion well-being
FACIT	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT	Functional Assessment of Cancer Therapy-General
FAS	Full analysis set
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FWB	Functional well-being

Abbreviation	Definition
HR	Hazard ratio
HRQoL	Health-related quality of life
IGHV	Ig heavy chain V-111
iNHL	Indolent non-Hodgkin lymphoma
IRC	Independent Review Committee
ITT	Intent-to-Treat
IV	Intravenously
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
IWG	International Working Group
LDH	lactate dehydrogenase
LNR	Lymph node response
LNRR	Lymph node response rate
MID	Minimal important difference
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
ORR	Overall response rate
OS	Overall survival
p-AKT	Phosphorylated protein kinase B
PD	Progressive disease/Pharmacodynamic
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	pharmacokinetic
PBMC	peripheral blood mononuclear cell
PO	By mouth
PP	Per-Protocol
PR	Partial response/remission
PRO	Patient Report Outcomes
PRwL	Partial response/remission with lymphocytosis

Abbreviation	Definition
PS	Performance Status
PT	Preferred Term
PWB	Physical well-being
QD	Once daily
QoL	Quality of life
RCT	Randomised Controlled Trial (Here: Study IPI-145-07)
RD	Responder Definition
RIT	Radioimmunotherapy
RP2D	Recommended Phase 2 dose
R/R	Relapsed/refractory
SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Stable disease/standard deviation
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPD	Sum of product of diameters
TLS	Tumour lysis syndrome
TOI	Trial Outcome Index
TTR	Time to response
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Verastem Europe GmbH submitted on 25 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Copiktra, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2019.

Copiktra (duvelisib), was designated as an orphan medicinal product EU/3/13/1125 on 26 April 2013 in the following condition: chronic lymphocytic leukaemia / small lymphocytic lymphoma and as EU/3/13/1157 on 17 July 2013 in the condition: follicular lymphoma. Both orphan designations were withdrawn from the EC register on 15 March 2021.

The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Copiktra

The applicant applied for the following indication "Relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) after at least one prior therapy with or without the presence of 17p deletion or *TP53* mutation; Relapsed or refractory follicular lymphoma (FL) after at least one prior systemic therapy".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0428/2019 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance duvelisib 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.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
19 September 2013	EMEA/H/SA/2604/1/2013/PA/III	Dr Alexandre Moreau, Prof. Brigitte Blöchl-Daum
20 February 2014	EMEA/H/SA/2604/3/2013/PA/II	Dr Armin Koch, Dr David Brown
23 July 2015	EMEA/H/SA/2604/3/FU/1/2015/PA/II	Dr Pierre Demolis, Prof. Brigitte Blöchl-Daum

The Protocol assistance pertained to the following non-clinical, and clinical aspects:

- the proposed nonclinical safety studies to support marketing authorisation;
- the design of the phase 3 study IPI-145-07, in particular, the proposed eligibility criteria, the choice of ofatumumab as comparator, the use of PFS as primary endpoint and schedule of assessments, the secondary endpoint and assessment analyses; the design of the extension study IPI-145-12, to receive IPI-145 or ofatumumab after documented disease progression; the size of safety database;
- the design of study IPI-145-08, in particular, the proposed eligibility criteria, the choice of rituximab in combination with placebo as comparator, the use of PFS as primary endpoint, the secondary endpoint and assessment analyses; the size of safety database;
- the non-inferiority design of studies IPI-145-21 and IPI-145-22 respectively, in particular, the proposed eligibility criteria, and choice of comparators, the choice of primary (PFS) and secondary endpoints; the statistical methodology, including the sample size, timing of interim analyses and error spending functions; the stratification factors.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	25 November 2019
The procedure started on	2 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	6 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 April 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	27 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 September 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	17 September 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	27 November 2020
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	25 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 February 2021
The CHMP agreed on a third list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	2 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 March 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Copiktra on	25 March 2021
The CHMP adopted a report on similarity of Copiktra with Gazyvaro and Imbruvica on	25 March 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication applied for was for relapsed or refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) after at least one prior therapy with or without the presence of 17p deletion or *TP53* mutation and relapsed or refractory follicular lymphoma (FL) after at least one prior systemic therapy.

2.1.2. Epidemiology

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukaemia in the Western world with an incidence of 4.2:100 000/year. The incidence increases to >30:100 000/year at an age of >80 years. The median age at diagnosis is 72 years. About 10% of the CLL patients are reported to be younger than 55 years (Eichhorst et al., 2015).

Non-Hodgkin lymphoma (NHL) is the twelfth most frequently diagnosed malignancy in Europe, with 115,118 cases estimated in 2018 (ECIS). Follicular lymphomas constitute approximately 8% of all NHLs (Sant et al., 2010) and is the most frequent indolent NHL and the second most common non-Hodgkin lymphoma in the United States and Europe (Casulo et al., 2015). The incidence of follicular lymphoma increases with age, with the median age at diagnosis between 60 and 65 years. The reported median age at diagnosis for FL is 64.9 years (Casulo et al., 2015).

2.1.3. Biologic features

CLL

CLL is a mature B-cell neoplasm characterised by an accumulation of monoclonal mature B cells (CD5+/CD19+) in the blood, bone marrow, and secondary lymph organs. The current World Health Organization (WHO) classification system recognises CLL/SLL as one disease but with distinct clinical presentations: CLL manifests as circulating tumour cells in peripheral blood and includes bone marrow infiltration, while SLL is primarily restricted to lymph nodes and other lymphoid compartments (Swerdlow, 2008). Historically, the treatment approach for CLL and SLL has been the same, with clinical trial enrolment inclusive of both diagnoses. European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up are published for CLL/SLL and recent drug approvals (Eichhorst et al., 2015) reflect CLL/SLL as a single indication.

FL

The genetic event characteristic of 90% of FL cases is a translocation involving the antiapoptotic BCL2 gene on chromosome 18 to the transcriptional enhancer of the immunoglobulin heavy chain gene locus on chromosome 14 (t14;18), resulting in a survival advantage from constitutive overexpression of BCL2 (reviewed by Casulo and Barr, 2019).

2.1.4. Clinical presentation, diagnosis

CLL

The natural history of CLL is variable although somewhat predicted by both clinical and genomic features. Many complications of the disease, such as anaemia and an impaired cellular and humoral immune system resulting in frequent infections and requiring supportive care, can lead to substantial socioeconomic costs and impaired quality of life. Since complete eradication of malignant clonal tumour cells is not possible with available therapeutic options, current treatment strategy seeks to prolong the suppression of these malignant cells. Although available regimens prolong progression-free survival (PFS) in the relapse setting, CLL remains incurable in most patients outside of the small subset of young or fit patients eligible for allogeneic stem cell transplant.

FL

FL in adults is generally an indolent B cell lymphoproliferative disorder of transformed follicular centre B cells, and is characterised by diffuse lymphadenopathy, bone marrow involvement, splenomegaly and less commonly other extra nodal sites of involvement (Freedman, 2018). The disease course is highly variable, with some patients asymptomatic for a long time, negating the need for therapy, while others require immediate intervention. Although sustained complete remissions can be achieved with various treatments, advanced indolent lymphomas are not curable with currently available therapies.

Patients with FL progressing within 24 months of initial immunochemotherapy with BR (bendamustine plus rituximab), R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab), or R-CVP (cyclophosphamide, vincristine, and prednisone plus rituximab), or within 12 months of single agent rituximab have *early treatment failure* (Parikh, 2018), although the definition may vary slightly.

2.1.5. Management

CLL

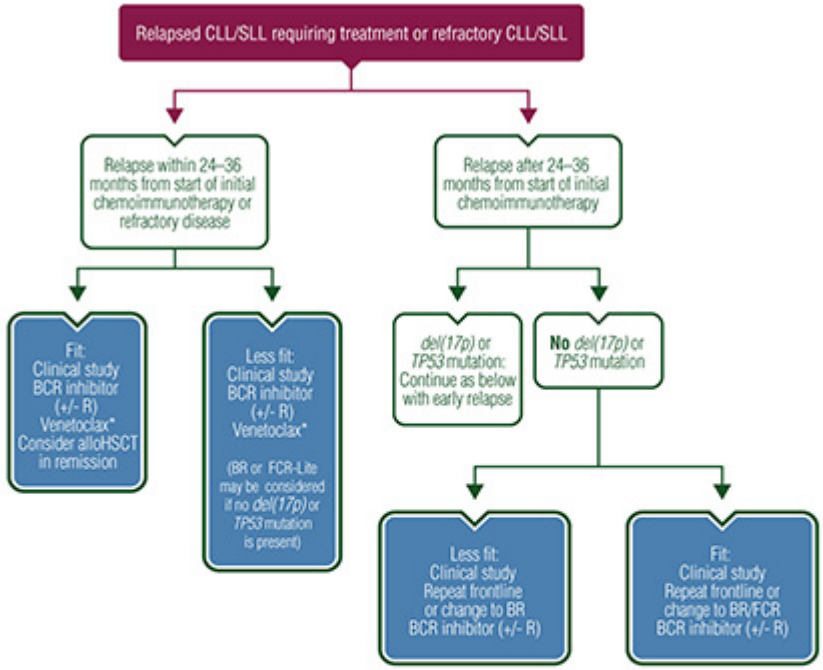
Treatment has evolved from monotherapy with alkylating agents (chlorambucil, bendamustine) and purine analogues (fludarabine) to immunotherapy (anti-CD52 monoclonal antibody alemtuzumab and anti-CD20 monoclonal antibody ofatumumab) and chemoimmunotherapy combinations (rituximab, ofatumumab as well as obinutuzumab in combination with purine and alkylating agents). Since 2014, novel targeted agents have been approved initially in the relapsed and some later in the previously untreated setting and include: Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor with the current indication (in CLL as a single agent or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and as a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy.

Idelalisib, a phosphoinositide-3-kinase (PI3K-δ) inhibitor with the current indication (in CLL): Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy or as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies.

Venetoclax, a BCL-2 inhibitor with the current indication in CLL: in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

Even with the availability of these novel treatments, most patients will eventually relapse, and many will succumb to their disease. Furthermore, not all patients tolerate or respond to these treatments, and resistance will emerge over time. In addition, the response rate tends to be lower and the duration of response (DOR) becomes progressively shorter with each subsequent line of therapy (Fischer et al., 2011; Carton et al., 2014; Keating et al., 2002, Wierda et al., 2010; Catovsky et al, 2007). There remains an unmet medical need for additional novel therapies, especially for patients with previously treated CLL.

Figure 1 ESMO guideline on CLL (eUpdate 2017)



*if failure to prior chemoimmunotherapy and BCR inhibitor OR if *del(17p)* or *TP53* mutation and failure or unsuitable for BCR inhibitor.
alloHSCT, allogeneic haematopoietic stem cell transplantation; BCR, B-cell receptor; BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; FCR-Lite, low-dose fludarabine, cyclophosphamide and high-dose rituximab; R, rituximab; SLL, small lymphocytic leukaemia; TP53, tumour protein p53

Follicular lymphoma (FL)

No curative treatments exist for iNHL, including FL, SLL and MZL. The standard of care is to administer various combinations of chemoimmunotherapy or radioimmunotherapy with diminishing effectiveness as patients progress through multiple lines of therapy or become refractory to treatment. The vast majority of patients treated for FL will have an initial response to therapy with 40 to 80 percent demonstrating a complete response, depending on the initial regimen used. However, conventional therapy for FL is not curative and most of these patients will ultimately develop progressive disease. In addition, less than 10 percent of patients treated with initial chemoimmunotherapy will not respond to treatment (ie, refractory disease). New treatment options for patients with relapsed iNHL who have not responded to or have progressed within 6 months of completing a rituximab and a chemotherapy regimen or RIT are needed.

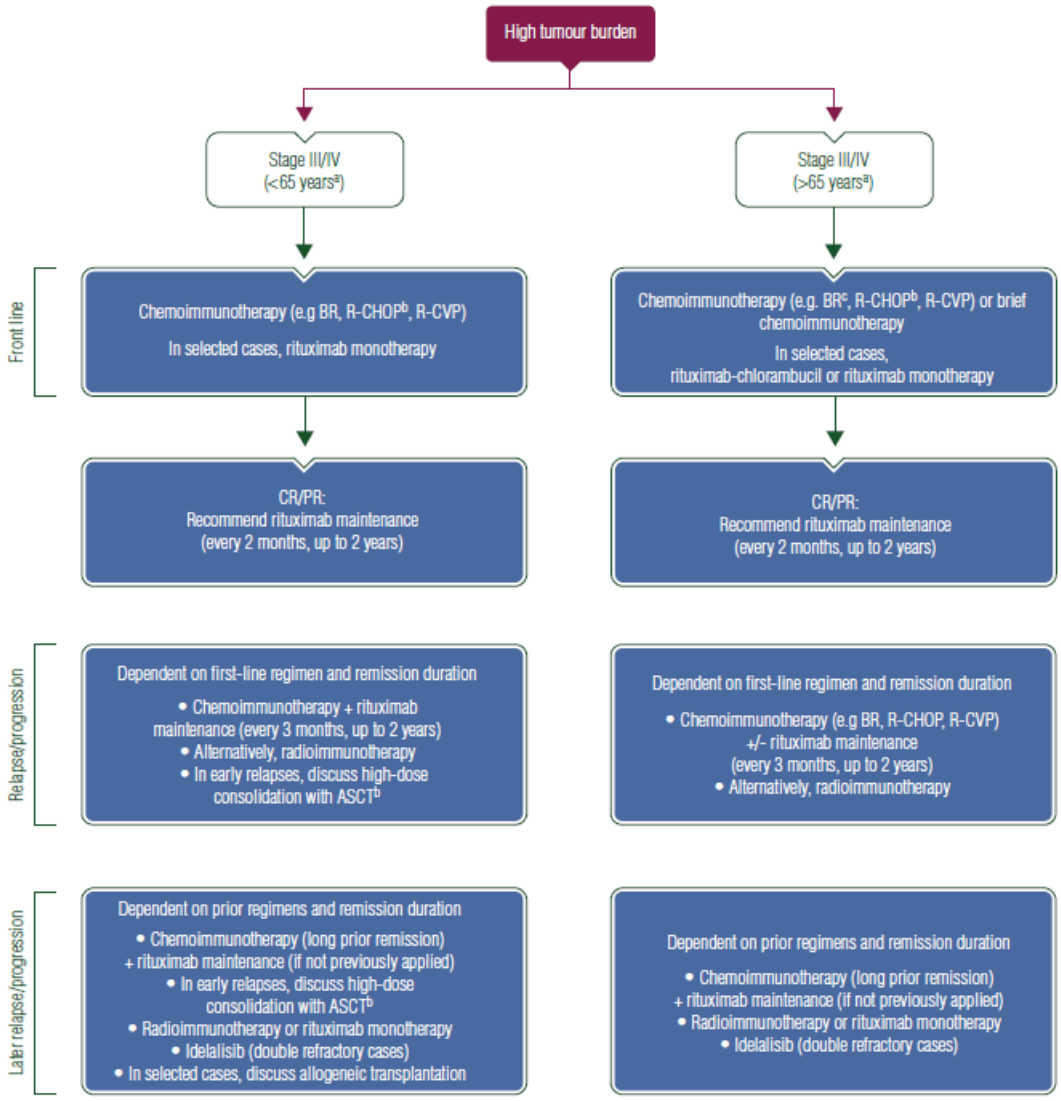
Rituximab, an anti-CD20 monoclonal antibody, as monotherapy or in combination with chemotherapy (cyclophosphamide and fludarabine; bendamustine; doxorubicin, vincristine, and prednisone (CHOP); and cyclophosphamide, vincristine, and prednisone (CVP)) has been the mainstay first- and second-line therapy for FL (Dreyling et al., 2016). In newly diagnosed patients, the median progression-free survival is 6 to 8 years, and the median overall survival is 12 to 15 years. Approximately 20% of patients with FL progress within two years of initial chemoimmunotherapy, a population that has shown a commensurately lower 5-year overall survival rate (50% vs 90% for patients without early progression) (Casulo et al., 2015).

Idelalisib, a PI3K- δ inhibitor was granted approval as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment based on the results of a single arm trial demonstrating durable complete and partial responses, (Study 101-09, DELTA, NCT01282424, Gopal et al., 2014) and extension Study 101-99, NCT01090414). In this single-arm study, idelalisib demonstrated an overall response rate (ORR) of 54.2% (8.3% complete response [CR], 45.8% partial response [PR]) in 72 FL subjects (see Zydelig SmPC). The median duration of response (DOR) for FL subjects was not reached. Confirmation of clinical benefit has not yet been reported in a randomised controlled setting. The ESMO Clinical Practice Guidelines for Newly Diagnosed and Relapsed Follicular Lymphoma include idelalisib as a recommended treatment option for later relapses providing an alternative monotherapy treatment for patients with FL that are refractory to rituximab or alkylating agents (Dreyling et al., 2016).

Another anti-CD20 antibody, obinutuzumab, was approved in April 2016 in combination with bendamustine followed by obinutuzumab maintenance in patients with FL who have relapsed or who are refractory to a rituximab-containing regimen by demonstrating improved progression-free survival.

Over the past several decades, substantial advances have been made in event-free survival, progression-free survival (PFS), and overall survival (OS) of patients with FL. These survival improvements are mostly attributed to progress in the delivery of effective anti-lymphoma therapies and improvements in supportive care (Casulo et al., 2015). Even with the newer available treatments, most patients with FL will eventually relapse or become intolerant to therapy. In addition, the rate of response and DOR progressively diminish with each subsequent line of therapy. Therefore, an unmet need exists in this condition.

Figure 2 Consensus-driven recommendations (ESMO 2016)



About the product

Duvelisib is an oral dual inhibitor of phosphoinositide 3-kinase (PI3K)- δ and - γ being developed as a monotherapy for the treatment of relapsed/refractory CLL/SLL and FL, diseases characterised by clonal proliferation and accumulation of malignant B cells in the blood and lymphoid tissues. PI3K- δ inhibition directly targets the survival and proliferation of malignant B cells, while PI3K-γ inhibition blocks the recruitment and differentiation of CD4+ T cells and macrophages which support the proliferation and survival of malignant B cells.

The drug substance duvelisib is a small molecule manufactured by a well described synthetic process, which has been developed applying quality by design principals. The finished product is formulated as an immediate release gelatine hard capsule.

The final indication following CHMP assessment is:

Copiktra monotherapy is indicated for the treatment of adult patients with:

- Relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies. (see section 4.4.and 5.1).
- Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies. (see section 4.4.and 5.1).

The recommended dose is 25 mg duvelisib twice daily. A cycle consists of 28 days. Treatment should be continued until disease progression or unacceptable toxicity.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 15 or 25 mg of duvelisib (as monohydrate).

Other ingredients are:

Capsule content: colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose.

Capsule shell: gelatin, titanium dioxide (E171) and iron oxide red (E172).

Composition of black ink: shellac glaze, iron oxide black (E172), propylene glycol and ammonium hydroxide.

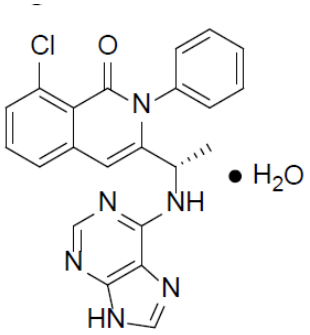
The product is available in PVC-PE-PCTFE / aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of duvelisib is (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one hydrate corresponding to the molecular formula $C_{22}H_{17}ClN_6O$ ($\bullet H_2O$). It has a relative molecular mass of 416.86 g/mol (as anhydrous form) and 434.88 g/mol (as monohydrate) with the following structure:

Figure 3: duvelisib monohydrate structure



Duvelisib is a chiral compound with a single chiral centre as (S) enantiomer. The duvelisib crystal structure indicates that the active substance is a channel hydrate containing eight water and eight duvelisib molecules in the asymmetric unit cell.

The chemical structure of duvelisib has been elucidated by a combination of elemental analysis, Fourier Transform Infrared Spectroscopy (FT-IR), Nuclear Magnetic Resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR) and mass spectrometry.

The active substance is a white to off-white crystalline solid which is practically insoluble in water, slightly soluble in simulated gastric fluid and exhibits pH-dependent solubility in aqueous buffers. Based on the solubility data in pH 1.2 hydrochloric solution (5.94 mg/mL), full dissolution is expected to be achieved in the stomach.

Duvelisib exhibits polymorphism. Multiple crystal forms of duvelisib active substance have been identified and characterised during extensive polymorphic screening studies. The polymorphic forms of duvelisib can be distinguished by XRPD. The manufacturing process followed and described is capable of consistently producing duvelisib.

Duvelisib polymorphic form does not adsorb moisture beyond its water of hydration between 0 and 80% relative humidity.

Manufacture, characterisation and process controls

Duvelisib is synthesised in 3 main stages using commercially available well-defined starting materials with acceptable specifications.

The synthetic manufacturing process consists of 3 stages.

Only one site is involved in the manufacture of the active substance. The designated starting materials have been satisfactorily justified. Proper specifications have been established for the respective starting materials and they are supported by comprehensive evaluation of potential impurities, which can be introduced to the process with the respective starting materials.

Overall, the control strategy for the manufacture of duvelisib is satisfactory. In support of the proposed control strategy, spike and purge studies have been performed to investigate the process capability to purge enantiomeric impurities.

Isolated intermediates formed during manufacturing process are sufficiently controlled. In addition, acceptable specifications for reagents, solvents and other materials used in the synthesis have been provided. Critical steps of the process were identified and are controlled by justified and appropriate in-process controls.

Process conditions have been optimised following DOE studies to reduce formation of side products while maintaining the desired yield.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Potential genotoxic impurities have been identified, their purge and fate studied in order to establish proper control strategy.

The information presented regarding potential impurities/degradation products controlled in the active substance is sufficient. Overall the defined control strategy is satisfactory. Changes introduced have been presented in sufficient detail and have been justified.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Duvelisib is packed in a LDPE bag placed inside a second LDPE bag and secured appropriately. The double LDPE bagged active substance is placed into a suitable secondary container (HDPE drum with a lid). This secondary container is used to provide mechanical strength to protect the LDPE bags during shipping and handling. The secondary container has no contact with the active substance. The primary packing material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), identification (FT-IR, HPLC, XRPD), assay (HPLC), impurities (HPLC), residual solvents (HS-GC), water content (KF), particle size distribution (Ph. Eur.), residue on ignition (Ph. Eur.), elemental impurities (ICP-MS) and microbiological enumeration (Ph. Eur.).

The specification limits for impurities/degradation products and residual solvents, are in accordance with the requirements of ICH guidelines Q3A and Q3C. The control strategy for potential genotoxic compounds has been satisfactorily justified.

All solvents used throughout the entire synthetic process, including those employed prior to the starting material, are routinely controlled in the specification and specified at levels below the ICH Q3C thresholds.

A suitable specification for particle size distribution is applied for the active substance based on the range of particle sizes used. The analysis for elemental impurities in duvelisib active substance is carried out in compliance with ICH Q3D.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. The specification of the finished product manufacturer is fully in line with the specification of the active substance manufacturer. Satisfactory information regarding the reference standards used has been presented.

The active substance specification is based on the active substance critical quality attributes (CQAs). The control strategy for duvelisib active substance was developed to ensure that the finished product consistently meets its CQAs and ultimately achieves the QTPP.

Batch analysis data from several pilot scale batches manufactured by the proposed commercial process, several commercial scale pre-validation batches and several commercial batches are provided, demonstrating compliance with the proposed specifications. The batch data provided is considered to be sufficient. Consistency and uniformity of the active substance quality have been demonstrated.

Stability

Stability data from several primary pilot scale stability batches and several commercial scale validation batches of active substance, from the proposed manufacturer, stored in the proposed container closure

system for up to 40 months and 36 months, respectively, under long term conditions (25°C/60% RH), and for up to six months under accelerated conditions (40°C/75% RH) according to the ICH guidelines were provided. 14-days temperature excursion studies were also conducted with samples stored at -20°C±5°C for 14 days followed by 14 days stored at 50°C±2°C, followed by 60 months at 25°C/60% RH for the long-term stability. These studies support physicochemical stability of the active substance.

All tested parameters were within the specification.

Forced degradation studies were conducted on duvelisib to assess the effect of extreme temperature excursions, light, acid, based, oxidation, heat and humidity. The data from these studies suggest duvelisib to be a stable compound and no special storage and handling instructions are warranted.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of the study indicate that upon direct exposure, the product is not sensitive to light. Therefore, it is concluded no special storage conditions with respect to light are required.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as immediate release hard capsules containing 15 mg or 25 mg of duvelisib (on anhydrous basis) as active substance.

Copiktra 15 mg hard capsules are opaque, pink, size 2 capsule with "duv 15 mg" printed in black ink on the body.

Copiktra 25 mg hard capsules are opaque, white body and Swedish orange cap, size 2 capsule with "duv 25 mg" printed in black ink on the body.

The composition of the capsule shells and black ink are presented below.

<u>Capsule content</u>
Duvelisib
Colloidal silicon dioxide
Crospovidone
Magnesium stearate
Microcrystalline cellulose

<u>Capsule shell</u>
Gelatin
Titanium dioxide (E 171)
Iron oxide red (E 172)

<u>Printing black ink</u>
Shellac glaze
Iron oxide black (E 172)
Propylene glycol
Ammonium hydroxide

The aim of the development of duvelisib capsule dosage form was to provide a stable formulation with the intended biopharmaceutical properties. The safety, efficacy and subject compliance requirements were also considered to set the dosage form design, primary packaging design, and critical attributes selection.

Appropriate QTPP product features were translated into product CQAs. These CQAs were subjected to initial risk assessment and further refined throughout the development, optimisation and finalisation of the manufacturing process.

As indicated in the active substance section, duvelisib is practically insoluble in water. In aqueous media at room temperature, duvelisib is slightly soluble in pH 1.2, very slightly soluble in buffers pH 2.2 and 3.0 and practically insoluble in pH range 4.0 to 7.4. Duvelisib is considered to be a Class IV compound in the Biopharmaceutical Classification System with low solubility and low permeability across physiological pH range. Excipients were chosen to provide an immediate release capsule formulation that is physiochemically stable for the intended period of storage, meeting the appropriate target requirements of QTPP: acceptable stability, immediate release and robust manufacturing process.

The excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the iron oxide black (E172) and butyl alcohol used in the composition of the black ink which are non-compendial excipients. Compliance with EU 231/2012 has been confirmed for iron oxides used in the gelatin capsules. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A compatibility study was performed to examine the interaction between the active substance and the proposed excipients. Binary mixtures of duvelisib and each excipient as well as the final formulation mixture were tested for at least 72 hours at 50°C and for at least 4 weeks at 40°C/75% RH. No detectable degradation was observed and duvelisib active substance was found to be compatible with the hard gelatin capsule shells and excipients.

During the procedure, the applicant has been requested to substantiate why the capsules should be swallowed as whole as claimed in SmPC section 4.2. Given the patient population likely to be taking this medicine will largely be elderly, the company was requested to investigate possibilities to administer the finished product to patients who have problems with swallowing the capsules. Based on the available clinical data, the bioequivalence between the product administrated as whole capsule and the capsule content suspended in soft food cannot be concluded. In addition, chemical stability studies of the active substance in different types of soft food are missing. In the absence of studies to verify the compatibility of the duvelisib powder if added to food or drink, the recommendation remains to not open the capsules and/or mix capsule contents with food or drink. The applicant agreed to investigate alternative methods of administration for patients with swallowing difficulties as post marketing activity. When supportive data is obtained, a variation application will be submitted to revise the Product Information regarding additional advice on the method of administration. The proposed commitment is accepted.

The dissolution method is performed in accordance with Ph. Eur Sink conditions are met during testing of both capsule strengths.

Development work was performed with the 25 mg strength, which included evaluation of media pH, rotation speed and media volume. The addition of surfactants was not evaluated since adequate dissolution was achieved by adjusting the pH of the medium. The final proposed acceptance criteria for duvelisib hard

capsules 25 mg was determined. The discriminatory power of the dissolution method has been demonstrated with respect to active substance particle size and post-lubrication blending time.

The manufacturing process development has been adequately described. Based on the initial risk assessment CQAs have been addressed over the development from development to commercial batch sizes. Normal Operational Ranges have been set and examined. An overall control strategy has been established.

The primary packaging is a Child-resistant PVC-PE-PCTFE / Aluminium blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by only one manufacturer. The manufacturing process main steps are blending and encapsulation. The process is considered to be a standard manufacturing process.

The manufacturing process has been described in sufficient detail and the in-process controls are adequate for hard capsules.

The manufacturing process for duvelisib capsules, 25 mg and 15 mg is considered as a standard process and traditional process validation has been performed with three consecutive batches of each strength manufactured at the commercial manufacturing site. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The finished product release and shelf-life specifications **Error! Reference source not found.**include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), assay (duvelisib content) (RP HPLC), content uniformity (RP HPLC), related substances (RP HPLC), water content (KF,Ph. Eur.), dissolution (RP HPLC), microbiological enumeration test (Ph. Eur.), specified microorganisms- E. coli (Ph. Eur.).

The potential presence of class 1 and 2A elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data was provided. The information on the control of elemental impurities is satisfactory.

Following a major objection raised during the evaluation, a risk assessment on the potential presence of nitrosamine impurities in the finished product based on the combined recommendations from health authorities, including EMA communication EMA/189634/2019 was presented. The nitrosamine impurities risk assessment of the finished product included evaluating contributions from duvelisib, excipients, finished product manufacturing facilities, and packaging components. It was concluded that there is no risk related to the presence of nitrosamine impurities in the product. Therefore, no changes to the control strategy for Copiktra are necessary to mitigate potential contamination by nitrosamines.

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

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

Stability of the product

Stability data from 3 primary stability batches of 15 mg capsules stored for up to 36 months at long-term (30°C/75% RH, Zone IVb) and up to 6 months stability data at accelerated conditions (40ºC/75% RH) according to the ICH guidelines were provided; and three production scale batches of 25 mg capsules stored for up to 60 months under long term conditions (30°C/65% RH, Zone IVa and 30°C/75% RH, Zone IVb), and up to 6 months under accelerated conditions (40ºC/75% RH). Samples were packaged in thermoform blisters.

In addition, several batches of the 25 mg strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, packaged in thermoform blisters. Unpacked samples along with the same samples protected from light (dark control) were studied. The results of the study indicate that upon direct exposure, the product is sensitive to light. The storage restriction "Store in the original package in order to protect from light" is therefore applied.

A forced degradation study was also carried out on duvelisib 25 mg capsules. The results obtained confirm the stability indicative nature under humidity, acid hydrolysis, base hydrolysis and oxidation conditions. Based on available stability data, the proposed shelf-life of 48 months for Copiktra 15 mg hard capsules or 60 months for Copiktra 25 mg hard capsules, with the storage conditions "store below 30°C" and store in the original package in order to protect from light" as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product for manufacture of the capsule shells. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture is provided.

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure a major objection was raised with respect to the risk assessment on the potential presence of nitrosamine impurities in the finished product. The applicant has satisfactorily addressed this major objection and it was concluded that there is no risk related to the presence of nitrosamine impurities in the product.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product regarding possibilities to administer the finished product to patients who have problems with swallowing the capsules. A recommendation has been issued.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of

the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Given the patient population likely to be taking this medicine will largely be elderly, the applicant is requested to investigate possibilities to administer the finished product to patients who have problems with swallowing the capsules taking into-account the Reflection paper on the pharmaceutical development of medicines for use in the older population EMA/CHMP/QWP/292439/2017 (October 2020).

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacology-testing plan for duvelisib was designed to delineate the role of PI3K-δ and PI3K-γ inhibition in haematologic malignancies and to provide the scientific rationale for the use of duvelisib in the proposed indications. The pharmacology evaluation included biochemical, cellular, and whole blood assays to assess the binding to and inhibition of PI3K isoforms by duvelisib and its major metabolite, IPI-656. Duvelisib and IPI-656 specificity was assessed using a diverse panel of kinases, as well as a panel of G protein coupled- receptors (GPCRs), ion channels, and transporters.

Single dose pharmacokinetics of duvelisib has been studied in BALB/c mice, Sprague Dawley rats, beagle dogs, and cynomolgus monkeys. PK after repeated dose and IPI-656 were determined in the Sprague-Dawley rats, New Zealand White rabbits, and cynomolgus monkeys, which were the animal species and strains used in toxicological evaluation of duvelisib. All of the pivotal safety pharmacology studies, toxicology studies and bioanalytical assays for duvelisib and metabolite IPI-656 were conducted in compliance with GLP in OECD member countries.

2.3.2. Pharmacology

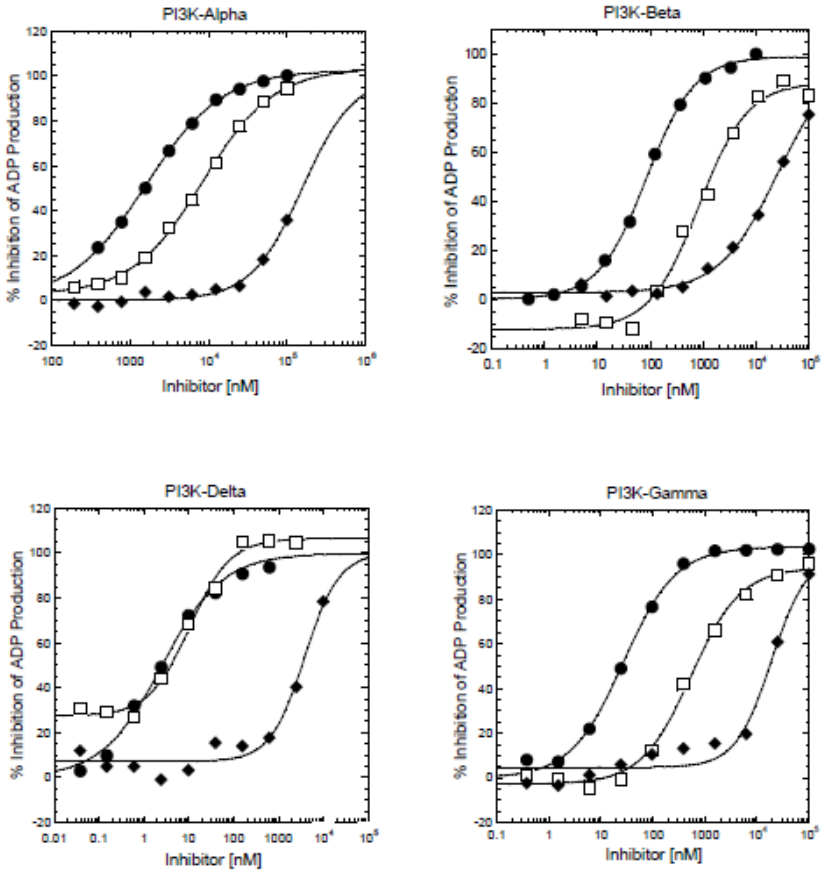
Primary pharmacodynamic studies

Duvelisib was shown in isoform selective enzymatic assays to selectively inhibit PI3K-δ, and PI3K-γ at low nM concentrations (IC50 values of 1.3 and 31.4 nM respectively), whereas the major metabolite IPI-656 showed much less selectivity, with much higher IC50 values (the lowest being PI3K-δ with a IC50 value of 3827.1 nM). Idelalisib (CAL-101) was included as a PI3K-δ isoform specific inhibitor. IC_{50} values were determined in an endpoint assay run in the presence of 3.0 mM ATP (ie, physiological levels), quantitating the concentration-dependent decrease in [α-32P] ADP formation as a function of increasing concentrations of duvelisib. Results showed that duvelisib potently inhibits PI3K-δ and PI3K γ, with IC50 values of 2.5 nM and 27.4 nM, respectively.

Table 1 IC_{50} Values of PI3K-α, β, δ and γ isoforms by IPU-145, CAL-101 and IPI-656

Compound	PI3K Isoform IC_{50} Values (nM)			
	α	β	δ	γ
IPI-145	1811.5	84.4	1.3	31.4
CAL-101	8486.5	837.5	10.5	545.7
IPI-656	>100000.0	26060.0	3827.1	19034.0

Figure 4 IC_{50} Values of PI3K-α, β, δ and γ isoforms by IPU-145, CAL-101 and IPI-656



IPI-145 (●), CAL-101 (□) and IPI-656 (◆)

To determine the affinity of duvelisib for PI3K-δ, PI3K-γ, and PI3K-β, the individual rate constants (kon and koff) were measured, yielding the dissociation constant (Kd). For PI3K-α, the koff was too rapid to determine experimentally, and the Kd was measured directly by equilibrium fluorescence titration. A summary of the binding rate constants and Kd values for each PI3K isoform is presented below (Winkler et al 2013).

Table 2 Summary of Kd values of duvelisib for Class I PI3K isoforms

Duvelisib Binding Data	PI3K-δ	PI3K-γ	PI3K-β	PI3K-α
K_{off} (s^{-1})	0.000365	0.000832	0.00426	0.109
K_{on} (10^6 M^{-1} s^{-1})	15.6	3.43	2.73	4.20
$t_{1/2}$ (min)	31.6	13.8	2.7	0.10
K_d (nM)	0.023	0.24	1.56	25.9

Activity of duvelisib and IPI-656 in PI3K Isoform-Selective Cellular Assays (Study report IPI-145-015). PI3K-α, β, γ, and δ inhibitory activity of IPI-145 and IPI-656 was measured in SKOV-3, 786-O, RAW264.7, and RAJI cells, respectively. The four cellular assays were pre-incubated with varying concentrations of test article and inhibition of phosphorylation of AKT at Ser473 was monitored by ELISA. Percent inhibition of AKT phosphorylation was measured, and the concentration of inhibitor needed to inhibit 50% (IC50) of AKT phosphorylation was calculated.

Table 3 Activity of Duvelisib and IPI-656 in Class I PI3K Isoform-Selective Cellular Assays

Cell Line	Isoform Activity	Stimulus	Duvelisib IC_{50} ± SDM (nM) [n]	IPI-656 IC_{50} (nM) [n]
RAJI (human lymphoma)	PI3K-δ	Anti-IgM	0.36 ± 0.09 [15]	2608 [2]
RAW 264.7 (murine macrophage-like)	PI3K-γ	C5a	19.5 ± 9.1 [30]	>10000 [2]
786-O (human renal cancer)	PI3K-β	None	26.2 ± 10.2 [6]	>8333 [4]
SKOV-3 (human ovarian cancer)	PI3K-α	None	1410 ± 1090 [6]	>10000 [2]

In vitro activity of duvelisib

To evaluate the cellular potency of duvelisib in the presence of human blood constituents, whole blood assays using PI3K-δ, PI3K-γ, and PI3K-β specific stimuli were developed.

The PI3K pathway plays a critical role in the activation of basophils by relaying signals from cell-surface receptors to downstream mediators leading to degranulation (Cushing 2012, Puri 2012).

In basophils, stimulation via the immunoglobulin E (IgE) Fc receptor by the addition of anti-FcεR1 antibody occurs through PI3K-δ, whereas stimulation with formyl-methionyl-phenylalanine (fMLP) occurs primarily through PI3K-γ. When these two basophil stimuli were used in whole blood, duvelisib inhibited PI3K-δ-specific basophil degranulation with an average IC50 of 96.1 nM, and PI3K-γ-specific degranulation with an average IC50 of 1028 nM (Winkler et al, 2013).

At higher concentrations, duvelisib showed activity in PI3K-β-selective biochemical and cellular assays. To determine the effect of duvelisib on PI3K-β activity in whole blood, platelet GPIIb/IIIa activation was measured after stimulation with a thrombin peptide (a PI3K-β-dependent effect). The average IC50 for duvelisib in this PI3K-β-specific assay was 4700 nM, indicating an approximately 4.5-fold window between PI3K-γ and PI3K-β inhibition in whole blood. The assay results for duvelisib are summarised below.

Table 4 Activity of Duvelisib in Whole Blood Assays, from Winkler et al, 2013

Cell Type	Isoform	Stimuli	Readout	IC_{50} ± STM (nM) [n]
Basophils	PI3K-δ	anti-FcεR1	degranulation	96.1 ± 75.7 [7]
Basophils	PI3K-γ	fMLP	degranulation	1028 ± 803 [16]
Platelets	PI3K-β	Thrombin peptide	GPIIb/IIIa activation	4700 ± 1800 [10]

In a number of *in vitro* studies performed in support of the current application as well as a number of publications submitted, the effect of duvelisib on primary malignant B-cell survival, as well as proliferation and migration signals in malignant B cells were shown. Dong et al. (2014) showed that duvelisib, at a concentration range (0.25 to 5 µM) that covers clinically relevant plasma concentrations for the patients who received duvelisib 25 mg twice daily, a modest induction of CLL cell cytotoxicity was observed, which was time- and concentration-dependent. The cytotoxic effect was independent of the patients' Ig heavy chain variable region mutational status.

The effect of duvelisib varied across the cell lines screened, with no B-cell lymphoma subtype cell line being universally more sensitive to the compound. However, several of the cell lines failed to achieve a Growth Inhibition level of fifty percent including: GRANTA-519, KARPAS-299, OCI-Ly7, OPM-2, RL, and RPMI-8226. The most sensitive cell lines to IPI-145 were TMD-8 and WSU-NHL, which had GI50 values of 0.5nM and 7.5nM, respectively. Other cell lines with GI50 values at sub-micromolar range included: DOHH-2, Farage, HH, KARPAS-422, and SU-DHL-4.

Duvelisib inhibited the macrophage colony-stimulating factor (MCSF1) and interleukin-4 (IL-4) driven M2 polarisation of murine BMDM, as measured by Arg1 expression, in a dose-dependent manner. IPI-549, a PI3K-γ selective inhibitor, also inhibited Arg1 expression in a dose-dependent manner; however, IPI-3063, a potent PI3K-δ selective inhibitor, did not inhibit Arg1 expression when used at PI3K-δ-selective concentrations (1 to 100 nM).

Table 5 Activity Comparison of Duvelisib and PI3K Isoform-Selective Inhibitors in Class I PI3K Isoform-Selective Cellular Assays

Compound	Cell Type	Isoform	Stimuli	Readout	IC_{50} (nM)
Duvelisib	RAJI (Human Lymphoma)[a]	PI3K-δ	Anti-IgM	pS473-Akt	0.36
	RAW 264.7 (Murine Macrophage like)[a]	PI3K-γ	C5a	pS473-Akt	19.5
IPI-3063	RAJI (Human Lymphoma)[b]	PI3K-δ	Anti-IgM	pS473-Akt	0.1
	RAW 264.7 (Murine Macrophage like)[b]	PI3K-γ	C5a	pS473-Akt	418
IPI-549	RAJI (Human Lymphoma)[c]	PI3K-δ	Anti-IgM	pS473-Akt	175.8
	RAW 264.7 (Murine Macrophage like)[c]	PI3K-γ	C5a	pS473-Akt	1.2

[a] Report IPI-145-015
[b] Winkler et al, 2013

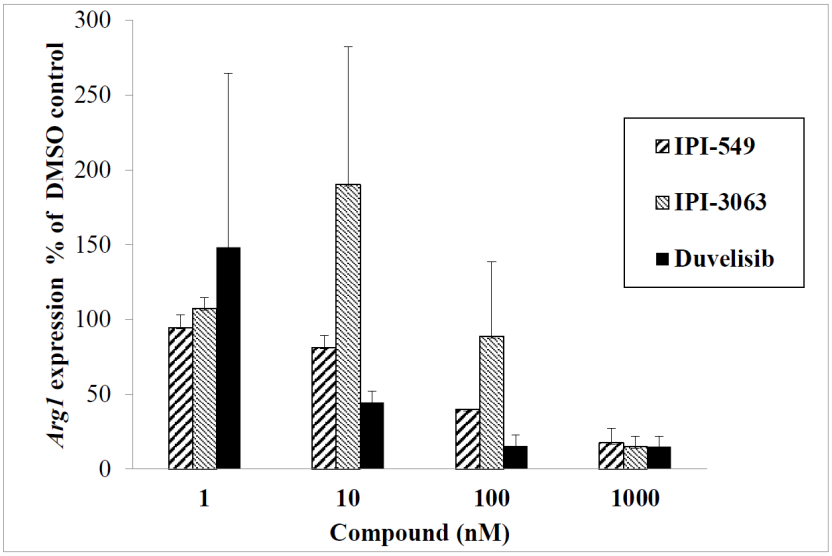
[c] Report IPI-145-019

Peripheral blood mononuclear cells obtained from CLL patients (n = 3) were used to evaluate the effect of PI3K inhibition on T cell migration in response to CXCL12 (C-X-C Motif Chemokine Ligand 12 protein coding gene). Both PI3K δ (IPI 3063) and PI3K- γ (IPI-549) selective inhibitors were used to delineate the PI3K isoform-dependency on this migration. Results showed that CXCL12-induced T cell migration was most potently inhibited by the PI3K-γ selective inhibitor, IPI-549, with an average EC50 of 17 nM compared with IPI-3063, a PI3K-δ-selective inhibitor, that was the least active with an average EC50 of 630 nM.

*Table 6**: Activity of Duvelisib and PI3K Isoform-Selective Inhibitors in the CXCL12-Induced T Cell Migration Assay***

Compound	Mean EC_{50} (nM) ± SD
Duvelisib	128 ± 39
IPI-3063 (PI3K-δ inhibitor)	630 ± 71
IPI-549 (PI3K-γ inhibitor)	17 ± 17

Figure 5 Arg1 expression in duvelisib IPI-549, IPI-3063 treated macrophages (1 to 1000 nM dose range)



In the *in vitro* studies of PI3K-γ inhibition, the migration of tumour-supportive T cells in response to CXCL12 in peripheral blood mononuclear cells (PBMCs) obtained from CLL patients showed an IC50 of 128 nM and the inhibition of MCSF1 and IL-4 driven M2 polarisation of murine bone marrow-derived myeloid cells showed an IC50 of 4 – 15 nM.

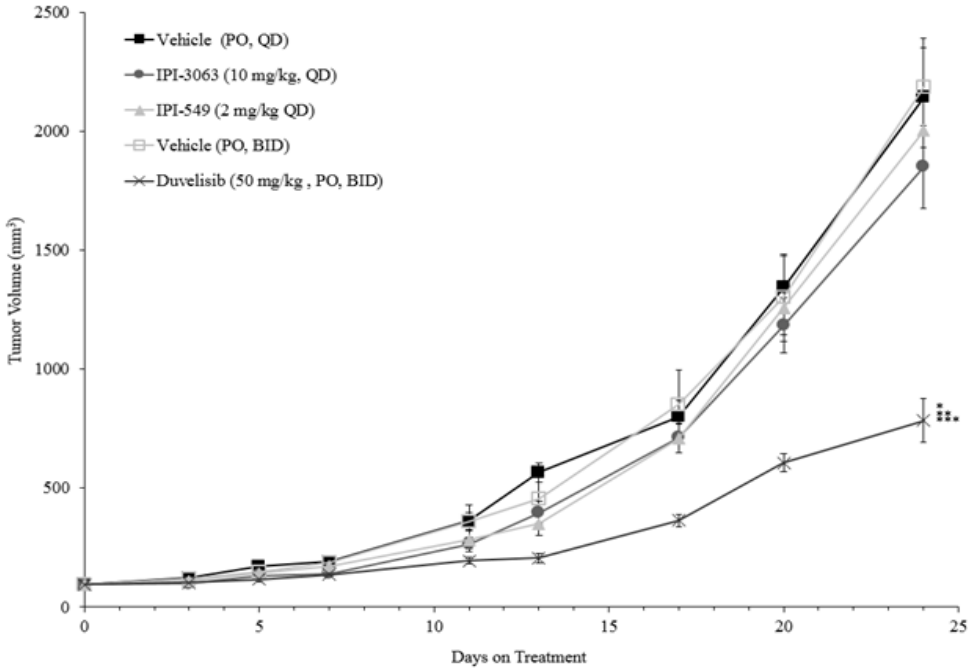
The *in vivo* inhibition of tumour volume in the DoHH2 murine xenograft model showed an inhibition of tumour volume of about 66% at a free Cmax serum level of 140 nM duvelisib. The unbound duvelisib plasma Cmax of 47 nM would be sufficient to inhibit macrophage polarisation (IC50 = 4-15 nM), which is a PI3K-γ-mediated function.

In the whole blood assay, the IC50 for inhibition of PI3K-γ in basophils was 1.03 µM (429 ng/mL), which is below the reported clinical Cmax of 3.6 µM, and also below the Cmax of 2.3 µM based on the PopPK simulations.

In vivo proof of concept

Only one proof of concept *in vivo* study was submitted. In Study report IPI-145-021, it was shown in a DoHH2 human transformed follicular lymphoma murine xenograft model, that duvelisib at 50 mg/kg po BID gave a significant inhibition of tumour growth, compared to either a PI3K-δ inhibitor (IPI-3063) or PI3K-γ inhibitor (IPI-549) administered alone (PO, at 10 mg/kg or 2 mg/kg respectively).

Figure 6 Anti-Tumour Activity of Duvelisib, IPI-3063, and IPI-549 in the DoHH2 Murine Xenograft Model



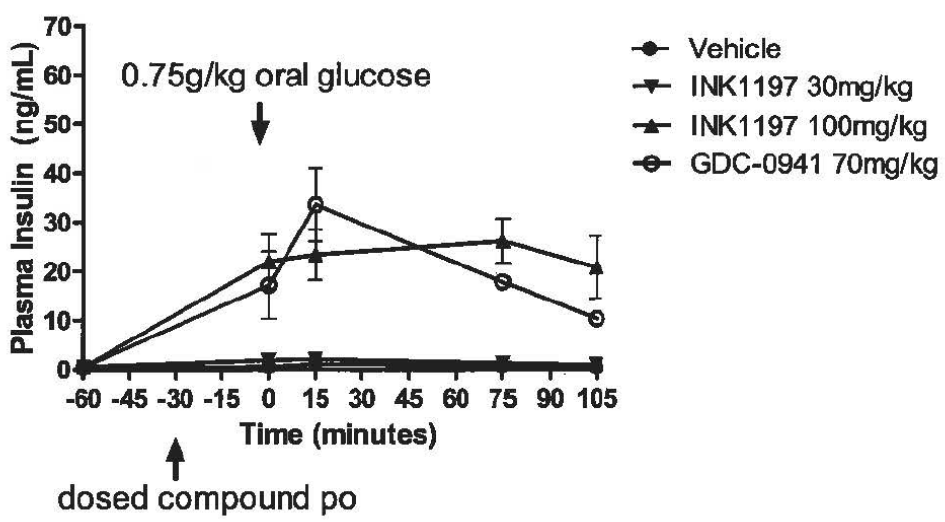
*Student's t-test p-value < 0.0001 compared to vehicle (BID or QD)
** Student's t-test p-value < 0.0001 compared to IPI-3063
*** Student's t-test p-value < 0.0001 compared to IPI-549

Secondary pharmacodynamic studies

Duvelisib and the major metabolite IPI-656 were tested against a broad panel of kinases, where duvelisib primarily showed activity against PI3K and no other kinases tested. IPI-656 showed slight binding to ALK, however, in a subsequent study, no binding was observed at concentrations up to 30μM.

PI3K inhibitors (especially PI3K-α and PI3K-β) have been shown to elevate blood glucose and blood insulin levels in rats. Therefore, duvelisib was tested in rats at 30 and 100 mg/kg/day following single administration or administration on 5 consecutive days. No effect on plasma glucose or insulin levels were observed at the 30 mg/kg/day dose level, whereas at 1000 mg/kg/day, or following administration of a PAN-PI3K-inhibitor, increased blood glucose or blood insulin levels were observed following OGTT. Similarly, hyperglycaemic and hyperinsulinaemic response was observed following IGTT. The observation of hyperglycaemic and hyperinsulinaemic effects were at duvelisib exposure levels where all PI3K-receptors (including PI3K-α and PI3K-β) were all inhibited to some extent, whereas at the lower dose, where PI3K-δ, PI3K-γ were selectively inhibited, no such effects were observed.

Figure 7 Plasma insulin levels after an oral Glucose tolerance test (OGTT) in rats post single dose of INK1197



Safety pharmacology programme

In vitro hERG channel inhibition was studied for both duvelisib and the major human metabolite IPI-656. hERG potassium inhibition IC50 values for duvelisib and IPI-656 was found to be 49.8µM and >100µM respectively. Based on the free fraction of duvelisib and IPI-656 in the clinical setting following administration of 25 mg BID, the applicant calculated safety margins of 1060- and 2600-fold respectively.

Core battery safety pharmacology was performed in rats (CNS and respiratory systems) at a single oral dose of duvelisib of 0, 5, 50, and 350 mg/kg. The dose levels administered were the same as those used in the GLP 4-week repeat-dose toxicity study in the rat.

No duvelisib-related effects were observed in the FOB parameters for up to 24 hours post dose. However, in the high dose group (350 mg/kg), significant decreases in locomotor activity was observed in the figure 8 maze at 2 hours post dose, however, no concurrent effects were observed in locomotor activity or arousal in the FOB arena at 2 hours post dose.

No duvelisib-related effects on respiratory parameters, including respiratory rate, tidal volume, and minute volume was observed at any dose level in male rats.

The *in vivo* cardiovascular safety study was performed in non-naïve telemetered cynomolgus monkey receiving duvelisib at an oral dose of 0, 5, 30, and 150 mg/kg. No statistically significant treatment related effects were observed on cardiovascular parameters. Toxicokinetic data from the GLP 4-week study was used to describe the exposures achieved in the *in vivo* safety pharmacology studies.

Pharmacodynamic drug interactions

No studies or discussion on pharmacodynamic drug interactions were included (see discussion on non-clinical Pharmacology).

2.3.3. Pharmacokinetics

Analytical methods

Bioanalytical methods were developed for the GLP general toxicity and reproduction toxicity studies. The bioanalytical method for duvelisib (IPI145) based on a solvent extraction procedure followed by LC-MS/MS (rat, monkey, rabbit) was successfully validated. All four pivotal general toxicity studies included ISR, which came out with 87.8-100% acceptance.

The LC-MS/MS methods used to determine duvelisib in the single dose pharmacokinetics in mice and dogs and in the repeated dose pharmacokinetics in the mouse (for studying the anti-tumour activity of duvelisib in the B-cell lymphoma subcutaneous xenograft model; see section on pharmacodynamics) have been described in the individual studies. The LC-MS/MS methods for the determination of duvelisib in plasma of mice and dogs provided acceptable precision and accuracy for the calibration standards. Repeated dose studies have not been performed in dogs.

^{14}C-Labeled duvelisib was used in in-vitro and *in vivo* metabolism and distribution studies. Metabolite characterisation was accomplished by LC-MS/MS in conjunction with liquid scintillation counting.

Permeability and transport

Duvelisib exhibited moderate membrane permeability. In a Caco-2 cell monolayer assay, the apparent permeability values at 10 µM were 2.5 x 10^{-6} cm/sec and 31 x 10^{-6} cm/sec for A>B and B>A assays, respectively. A concentration-dependent active B to A efflux with efflux, ratios ranging from 13 to 4.2 was observed over a concentration range of 3 to 100 µM duvelisib. Duvelisib is a substrate of P-gp. Therefore, intestinal absorption is expected to be affected by concomitantly given P-gp inhibitors.

Pharmacokinetics

The single dose pharmacokinetics of duvelisib has been studied in BALB/c mice, Sprague Dawley rats, beagle dogs, and cynomolgus monkeys. Duvelisib was rapidly absorbed after oral administration in mice, rats, dogs and monkeys.
In mice, the bioavailability of duvelisib was low (7%) and T_{max} was 0.08 h. Following IV administration, duvelisib was rapidly eliminated, with a high clearance (5.25 L/h/kg) and a short plasma half-life (0.22 h). The volume of distribution at steady state (Vss) was moderate (1.14 L/kg), which is two times greater than total body water (0.6 L/kg). This indicates that in mice duvelisib is not extensively distributed into tissues.

In rats, duvelisib was rapidly absorbed following oral administration with T_{max} values that ranged from 1 to 4 hours. The bioavailability was moderate to high (57%). C_{max} and overall exposure ($AUC_{0\text{-}last}$) increased approximately dose proportionally in the dose range of 30 to 300 mg/kg.Following IV administration, duvelisib was rapidly eliminated, with a clearance of 1.83 L/h/kg and a plasma half-life of 0.73 h. The Vss was moderate (1.66 L/kg), which is 2.7 times greater than total body water (0.6 L/kg). This indicates that also in rats duvelisib is moderately distributed into tissues.

In dogs, the oral absorption of duvelisib was rapid. Duvelisib in solution (5% NMP [N-methyl-2-pyrrolidine], 60%PEG 400 and 35% water) showed a bioavailability of 97% and a T_{max} of 3 hours, whereas in duvelisib in

suspension (5% NMP and 95% water) showed a bioavailability of 40% and a T_{max} of 1 hour. Following intravenous administration, duvelisib in an aqueous NMP/cyclodextrin solution showed a low clearance (0.85 L/h/kg), a small volume of distribution (0.13 L/kg) and an elimination half-life of 2 hours. Duvelisib in an aqueous PEG 400 solution showed a clearance of 3.23 mL/min/kg, a small volume of distribution (0.49 L/kg) and an elimination half-life of 1.83 hours.

In monkeys, the bioavailability was 40%. T_{max} was 1.5 hours. From 30 to 300 mg/kg, C_{max} and overall exposure ($AUC_{0\text{-last}}$) increased approximately dose proportionally. At the tested oral dose of 5 mg/kg, the administration duvelisb in a capsule formulation led to a three times lower plasma exposure and C_{max} values. The clearance was low (0.4 L/h/kg), the volume of distribution was moderate (1.27 L/kg) and the elimination half-life was 5 to 6 hours.

There were no relevant differences between males and females in pharmacokinetic parameters.

In human, duvelisib showed a bioavailability of about 40%, a T_{max} of 1 to 2 hours and a low volume of distribution (12.3 L, ~0.18 L/kg) for healthy subjects. In subjects with advanced hematologic malignancies, the apparent volume of distribution (Vss/F) was 28.5 L (~0.44 L/kg) (see clinical assessment report).

The repeated dose pharmacokinetics of duvelisib and IPI-656 were determined in the Sprague-Dawley rats, New Zealand White rabbits, and cynomolgus monkeys, which were the animal species and strains used in toxicological evaluation of duvelisib.

In rats, after repeated oral administration, exposure was generally greater than dose proportional.
In the 5 days study, the exposure to duvelisib was dose proportional in males or slightly greater than dose proportional in females over the tested doses of 25 and 50 mg/kg. The exposure to the metabolite IPI-656 was proportional or less than dose proportional. Exposure to duvelisib was about 2-fold higher in females compared to males but exposure to IPI-656 was about 2-fold higher in males compared to females. The IPI-656/duvelisib exposure ratios were less than 0.01 in males and females indicating low exposure of IPI-656 relative to duvelisib.

In the 28-day study, exposure was greater than dose proportional. Modest accumulation of duvelisib was noted with $AUC_{0\text{-}24\,h}$ ratios of 2 and 1.4 for males and 2 and 1.3 for females for doses of 5 and 50 mg/kg/day, respectively. In the 13-week study, the exposure to duvelisib was much greater than dose proportional over the tested doses of 0.5, 5 and 25 mg/kg/day. For a 10-fold increase in dose between 0.5 and 5 mg/kg/day exposure increased by more than 20-fold, and for 5-fold increase in dose between 5 and 25 mg/kg/day exposure increased by more than 10-fold except for the female rats on Days 28 and 91 where the increase in exposure was dose proportional. Minor accumulation (≤2.0-fold) was observed and the steady-state exposure (28 days) in females was approximately 2-fold the exposure observed in males.

In pregnant rabbits at 75 mg/kg, the IPI-656/duvelisib exposure ratio was approximately 0.71 indicating that the exposure to IPI-656 was only slightly lower than that of duvelisib in the rabbit. In a definitive EFD study in rabbits over gestational Days 7 through 20, duvelisib exposure increased with increasing dose on gestation Day 7 with accumulation ratios of 19, 8, and 4 for dose levels of 10, 25, and 75 mg/kg/day, respectively, on gestation Day 20.

In monkeys, after daily repeated administration for 5 days, duvelisib exposure increased in a generally dose proportional manner, but not for IPI-656 for which C_{max} was less than dose proportional. Duvelisib and IPI-

656 showed some accumulation (up to 2-fold). Exposure was slightly higher in males compared to females. Exposure to the metabolite was generally higher (up to 2-fold) than to the parent.
In the 28-days study, duvelisib exposure increased more than dose-proportionally over the 5 mg/kg to 30 mg/kg dose range and less then proportionally over the 30 mg/kg to 150 mg/kg dose range. Accumulation ratios ranging from 2.7 to 6.1. In the 13-weeks study, at dose levels of 0.2 to 5 mg/kg/day, accumulation ratios ranged from 0.9 to 2.2 for the low and mid dose groups (0.2 and 1 mg/kg/day) up to 7 to 10 for the high dose group (5 mg/kg/day). No consistent gender difference was noted in duvelisib plasma exposure.

Plasma protein binding

Duvelisib is highly bound to plasma proteins, with unbound fractions being dependent on species and concentration ranging from 1-100 µM. The concentration-dependence of the unbound fraction in plasma was high in monkeys (8.0–23.2%) and rabbits (3.8-12.2%) and less marked in rats (11.1-14.2%) and mice (5.5-8.4%). At 10 µM, the duvelisib free fraction was 13.4% in monkeys, 9.6% in rabbits, 11.4% in rats, 6.0% in mice.

The percent free fraction of duvelisib in humans is estimated to be 1.3%. There was no concentration dependency in protein binding over the clinically relevant concentration range of 1 to 10 µM.

IPI-656 is more highly protein-bound than duvelisib. At 1 µM, the free fraction was 5.2% rabbits, 4.5% in rats, 3.1% in mice, 0.4% in monkeys and 1.3% in humans. Concentration dependency was only observed in the monkeys.

Tissue distribution

The tissue distribution of duvelisib was investigated in Sprague Dawley rats (non-pigmented) and Long-Evans Rats (pigmented).

The results showed that duvelisib is distributed to most tissues, with the exception of the brain and lens. The highest concentrations were observed in tissues that are involved in the metabolism and excretion of duvelisib, including the contents of the gastrointestinal tract and urinary bladder, the lining gastrointestinal mucosa, the urinary bladder and bladder wall, the liver and bile duct, followed by the kidney cortex and medulla. In pigmented rats, there was an increased concentration of duvelisib in the uveal tract of the eye and some retention of duvelisib in pigmented tissue, which suggests that duvelisib binds to melanin.

Duvelisib did not exhibit significant partitioning into red blood cells (RBCs) *in vitro* or *in vivo* in rat, monkey or human.

The potential of duvelisib to cross the placenta and the potential excretion into milk have not been studied. These studies are not warranted for anti-cancer drugs.

Metabolism

In vitro studies

The primary metabolic pathways were phase I oxidation and phase II glucuronidation.

CYP3A4 was the primary enzyme in phase I metabolism of duvelisib. CYP1A2, CYP2B6 and/or CYP2C8 may be involved to a lesser extent in the formation of duvelisib metabolites. Glucuronidation, as a major part of

phase II metabolism of duvelisib, was primarily mediated by UGT1A4 with minor contribution by UGT1A3 and UGT1A9. Duvelisib has a low propensity to form reduced forms of glutathione-conjugated metabolites in rat and human liver microsomes in the presence NADPH regenerating system. In liver microsomes and cryopreserved hepatocytes, duvelisib was metabolised slowly by rat, moderately by dog and human, and extensively by mouse and monkey. Across all species, twenty metabolites were identified (M1 up to M20).

No disproportionate or human-specific metabolites were identified. With the exception of M7 and M10 (both N-glucuronide conjugates of duvelisib), all metabolites detected in human hepatocyte incubations were also detected in at least two animal hepatocyte incubations, including at least one of the toxicology species (rat and monkey). M7 and M10 were not unique human metabolites, since they were also seen *in vivo* in ^{14}C-duvelisib mass balance studies: M7 and M10 in rats and M7 in monkeys.

In in-vitro incubations with hepatocytes, duvelisib exhibited moderate to high hepatic extraction (extraction ratio >0.3) in the dog and mouse, and low to moderate hepatic extraction in the rat, monkey, and human (extraction ratio ≤0.3).

In-vivo studies

IPI-656 (M17) is the major metabolite of duvelisib in plasma of rats, monkeys and human. This metabolite, which is a mono-oxidation product, has no pharmacologically relevant activity (Section 2.1 Pharmacodynamics).

The concentration of duvelisib and its metabolites in plasma were determined following oral administration of ^{14}C-duvelisib in rats and monkeys at doses of 5 mg/kg and in heathy humans at 25 mg (≈0.4 mg/kg).

In rats, ^{14}C-duvelisib accounted for 88.5% and 88.1% of the circulating radioactivity in plasma of male and females, respectively. The two main circulating metabolites were M17 at levels of 1.39% in males and 0.79% in females and M4 (glutathione related) at levels of 1.66% in males and 1.15% in females.

In monkeys, ^{14}C-duvelisib accounted for 16.7% and 20.3% of the circulating radioactivity in plasma of males and females, respectively. There were three main circulating metabolites, including were M17 (18.3% in males and females), M24 (7.69% in males, 4.12% in females) and unknown peak 1 (UNK1) (purine-related, 7.61% in males, 7.99% in females). Although unambiguous identification could not be made, it is thought that the metabolites comprising this region are polar metabolites potentially originating from liberation of the adenine motif from duvelisib with subsequent processing through purine metabolic pathways.

In human, duvelisib accounted for 37.7% of the circulating radioactivity following a single oral dose of 25 mg duvelisib (+ 2.8 µg ^{14}C-duvelisib) intravenously. The major circulating metabolite was M17 (45.8%), followed by the minor metabolite M7 (3.99%) which is a glucuronate conjugate of duvelisib.

Excretion

The primary clearance mechanism of duvelisib was CYP450-mediated metabolism. The major elimination pathway for duvelisib and duvelisib metabolites (including IPI-656) was the faeces via the hepatobiliary route.
In the rat, monkey, and human, the mean percentage of administered radioactivity excreted in the faeces was 94%, 78%, and 79%, respectively, with the remaining radioactivity recovered in the urine. (3%, 4% and 14%, respectively). The primary duvelisib-related residues in the plasma and faeces were duvelisib and IPI-656.

In bile duct-cannulated rats, a majority of absorbed duvelisib-related radioactivity was excreted in the bile. Duvelisib accounted for 1-1.5 % of the dose in bile (males and females) and for 22.3% (males) and for 42.5% (females) in faeces. This indicates that enterohepatic circulation of duvelisib does not play a relevant role.

2.3.4. Toxicology

Single dose toxicity

One exploratory single dose study was performed in the cynomolgus monkey. The study also included a phase with 7 days administration, which is discussed below in the repeat dose study section.

Table 7 Single dose toxicity study of duvelisib

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
Report 1634-021	Cynomolgus monkey 1 M/ 1 F	0, 50, 150, 300 and 500 mg/kg PO at 5 ml/kg in vehicle of 0.5% (w/w) high viscosity carboxymethylcellulose (CMC) and 0.05% (w/w) TWEEN® 80 in deionised	C_{max} 4745 ng/mL $AUC_{0\text{-last}}$ 44678.5 ng*h/mL MTD (500 mg/kg)	No treatment-related clinical findings or effects on body weight or glucose levels were observed at any dose level during Phase A. The MTD following a single oral administration of duvelisib in monkeys was the highest dose evaluated, which was 500 mg/kg.

Single administration of duvelisib at doses of up to 500 mg/kg/day was well tolerated.

Repeat dose toxicity

In the repeat dose studies, the rat and cynomolgus monkey were selected as the nonclinical species. The cynomolgus monkey was chosen as the non-rodent species, due to the metabolite profile appearing more comparable to the human, than dog. In rats, 14 days treatment (non GLP study), 28 days and 13-week studies were performed, the latter two according to GLP. With regards to dose selection in the rodent studies, the dose levels selected for the subsequent 28-day study in rats, appear above the MTD in the 14-day study, as extensive clinical signs as well as mortality of high dose animals in the 14-day study (Study SDI00004) was observed following 7 and 8 days of administration of 300 mg/kg duvelisib. However, a change of vehicle was also introduced, which would amount in less exposure than the vehicle used in the shorter duration study, which is why the high dose level selected in the consecutive 28-day GLP study (Study No 805097) was even higher (350 mg/kg/day). Although lower exposures were anticipated, and hence the clinical signs would be expected to be less severe, dosing was discontinued by day 6 or 7, due to mortalities and moribundity (10 animals found dead, and 8 additional being euthanised).

In cynomolgus monkeys, the single dose study also included a 7-day fixed dosing period, and the results are presented below in the table.

In the rodent GLP repeat-dose studies the following parameters and end points were evaluated: clinical observations/signs, body weights, food consumption, ophthalmology, clinical pathology (haematology, coagulation, clinical chemistry, urinalysis), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathologic examinations.

In the cynomolgus monkey GLP repeat-dose studies the following parameters and end points were evaluated: morbidity, mortality, clinical observations/signs, body weights, food evaluation, ophthalmology, ECG, clinical pathology (haematology, coagulation, clinical chemistry, urinalysis), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathologic examinations. In the 13-week study, in addition to the standard study endpoints, immunophenotyping and TDAR analyses were conducted during the main and recovery study phases.

Table 8 Summary of repeat dose studies of duvelisib

Study ID	Species/ Sex/ Number/ Group	Dose/Route		Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
	Rats, Sprague Dawley					
SDI00004 Non GLP	Sprague Dawley 5 M/F	0, 30, 100, 300 mg/kg/day At 5 ml/kg/day Vehicle 5% NMP and 95% PEG 400		14 days	100 mg/kg/day Plasma concentration M 17,720 and F 17,400 ng/mL, at 2 hours post-dose and M 9,816 and F 15,498 ng/mL, at 8 hours post-dose	≥ 30: Lymphoid depletion in spleen, thymus, other lymphoid structures; adrenal cortical cell hypertrophy with or without single cell necrosis and vacuolar change of cortical cells in some animals; ↑granulocytic cells in the mucosa and submucosa of the small intestine ≥ 100: Hyperplasia of bone marrow; hypertrophy and hyperplasia of pancreatic islet cells 300 mg/kg/day: Mortality All females dead on day 7 All males dead on Day 8 Increased faecal and urine staining of fur, few and small faeces, thin appearance, unkempt appearance, dark material around facial area, piloerection, dehydration, rapid/shallow breathing, wobbly gait, decreased activity, hypothermia, salivation, hunched posture, closed eyelids (F) Decreased bodyweight (day 5, 17.6% M, 6.7% F) Decreased food consumption (49.0% M, 5.2% F) coagulative hepatocellular necrosis, activation of Kupffer cells in the liver; vasculopathy in the small intestine; hypocellular bone marrow

805097 GLP *	Sprague Dawley Main study 10 M/F Recovery 5 M/F TK 3 M/F 0 mg/kg 9 M/F	0, 5, 50 and 350 mg/kg/day PO at 10 ml/kg/day Vehicle 0.5% (w/v) Carboxymethyl-cellulose (low viscosity) and 0.05% (v/v) TWEEN® 80 in ultrapure Water		28 days Treatment with 14 days recovery period	5 mg/kg/day Cmax values were 362 and 700 ng/mL and the AUC0-24 values were 1,780 and 3,330 ng*hr/mL for males and females, respectively, on Day 28.	<u>≥ 5 mg/kg/day</u> Histological findings: increased cellularity of white pulpa in spleen <u>≥ 50 mg/kg/day</u> Increased neutrophil count Minimal to marked decreases in RBC, HB, HT (F), decreased MCV, MCHC, Marked decreased PLT (1F) Increased ASAT (F), increased urea, decreased albumin Histological findings: Lymphoid atrophy/necrosis in spleen and thymus, testicular seminiferous epithelial atrophy, uterine atrophy Bone marrow: mild increase in M:E ratio in 1M and 1F. increased myeloid cellularity, pyknotic cells 1F, 14 day recovery: marked adverse erythroid hypoplasia, shift in myeloid cells (2F), marked megakaryocyte hypoplasia (1F) <u>350 mg/kg/day</u> The above findings, and additionally; Mortality (10 animals) 8 animals euthanised Clinical signs; Reduced activity, partially closed eyes, hunched posture, reduced muscle tone, reduced faecal output associated with dehydration - Clinical signs recovered following cessation of treatment Dosing stopped on day 6 or 7 Significantly reduced mean body weight (compared to control), body weight loss. - compensatory body weight gain following end of treatment in surviving animals Reduced food consumption (Day 1-15) Minimal to marked decreases in RBC, HB, HT (M +F) Marked decreased PLT (1F) Increased ASAT, ALAT, ALP, TP, , globulin Decreased albumin, calcium and phosphorous level and Na, K, CL Ophthalmological findings: Small bilateral multifocal anterior cortical lens opacities in 2/3 F, considered secondary to hyperglycaemia Histological findings: Multiple lesions in haemolymphoid system, atrophy, extensive necrosis lymphoid atrophy/necrosis in lymph nodes, GALT, Haemorrhage in lymph nodes, spleen, thymus,

						Adrenal cortical degeneration and necrosis, testicular seminiferous epithelial atrophy, uterine atrophy. Bone marrow: Necrosis and erythroid hypocellularity, erythroid hypoplasia, megakaryocytic hyperplasia 1F. 21-day recovery: slight reactive decrease in M:E ratio (few surviving males), changes in WBC and minimal decrease in red cell mass parameters with evidence of regeneration 35 days recovery: No changes in bone marrow cell proliferation and maturation in surviving females
805592 GLP	Sprague Dawley Main study 15 M/F Recovery 10 M/F TK 3 M/F 0 mg/kg 9 M/F	0, 0.5, 5, 25 mg/kg/day PO at 10 ml/kg/day Vehicle 0.5% (w/v) Carboxymethyl-cellulose (low viscosity) and 0.05% (v/v) TWEEN® 80 in ultrapure Water		13 weeks treatment with 4 weeks recovery period	Applicant and study director: 25 mg/kg/day, due to reversibility of most findings Cmax values ng/mL 3300 (M) 3950 (F) mean AUC0-24 values M 14300 ng*h/mL F 14000 ng*h/mL on Day 91	<u>Negative control animals;</u> Histology: Pancreas; multifocal changes (M), including inflammation, increased incidence of islet hyperplasia, with or without interstitial fibrosis. These findings were mainly in male animals in all groups (control and treated), and were considered to be secondary reactive response due to increased insulin response. <u>≥ 5 mg/kg/day</u> Dose dependent reversible changes in haematology, clinical chemistry and coagulation parameters Decreased lymphocyte count Decreased organ weight of pancreas, spleen and thymus (M) Histology: Pancreas; multifocal inflammation (M), lymphoid depletion of spleen; PALS hyperplasia and reduced cellularity of marginal zone of thymus, <u>25 mg/kg</u> As above, but also changes observed in some female animals Testes; decreased weight, minimal degeneration/atrophy of seminiferous epithelium
	Cynomolgus monkeys					

1634-021 Phase B Non-GLP	Cynomolgus monkey 1 M/1 F	0, 30, 100 and 300 mg/kg/day PO 0.5% (w/w) carboxymethyl cellulose (high viscosity), 0.05% (w/w) TWEEN® 80 in deionised water		7 days	30 mg/kg/day	<u>≥ 30 mg/kg/day</u> Minimal/mild vascular inflammation Minimal vascular necrosis in the liver <u>≥ 100 mg/kg/day</u> Decreased phosphorous <u>300 mg/kg/day</u> Decreased RBC, HB, HT, ASAT, ALAT Increased neutrophils, platelets (M) Lymphoid depletion, Lymph nodes, spleen and GALT Lymphoid depletion and necrosis in thymus Bone marrow: decreased cell numbers; erythroid, myeloid, lymphoid and megakaryocytes

905098 GLP	Cynomolgus monkey 6 M/F (4 main study animals and 2 recovery animals)	0, 5, 30, 150 mg/kg/day PO in 5 ml/kg Vehicle 0.5% (w/v) Carboxymethyl-cellulose (low viscosity) and 0.05% (v/v) TWEEN® 80 in ultrapure Water		28 days 14 days recovery	**HNSTD** 5 mg/kg Cmax values M 1940 and F 890 ng/mL mean AUC0-24 values M 8920 and F 5120 ng*h/mL	<u>≥ 5 mg/kg/day</u>: Decreased retic, Increased WBC/neutrophils Increased M:E ratio (F, reversible) Increased fibrinogen Decreased Albumin, TP Histology: Lymphoid depletion/necrosis with secondary opportunistic infection and inflammation (protozoa [cryptosporidia and giardia], yeast [candida], bacterial infection in stomach) associated lesions; alveolar/interstitial inflammation in the lungs; neutrophilic cell inflammation in spleen, lymph nodes, liver, gallbladder, GIT, kidney, adrenal gland, testis and epididymis; macrophage hyperplasia/accumulation and/or hypertrophy in spleen, lymph nodes, liver and GIT; vascular inflammation in the liver, ileum and epididymis; and several other lesions in the GIT (oedema, haemorrhage, erosion, ulceration) and necrosis in the liver Bone marrow: erythroid hypoplasia/necrosis <u>≥ 30 mg/kg/day</u>: Decreased lymphocyte count, RBC, HB, HT, Increased M:E ratio reversible Increased ALAT, ASAT, TRIG Increased urinary protein, Decreased phosphorous, K Na, CL (secondary to GI loss) <u>150 mg/kg:</u> 2 animals euthanised on Day 28 and 33, respectively, due to opportunistic infections associated with lymphoid depletion Decreased MCV, Increased WBC, neutrophils, retic Increased M:E ratio – not completely reversible

805593 GLP	Cynomolgus monkey Main study 4 M/F in control and high dose groups 3 M/F in low and mid dose Recovery 3M/F in control and high dose 2 M/F in low and mid dose groups	0, 0.2, 1, 5 mg/kg/day PO in Vehicle 0.5% (w/v) Carboxymethyl-cellulose (low viscosity) and 0.05% (v/v) TWEEN® 80 in ultrapure Water		13-week 6-week recovery	NOAEL 5 mg/kg/day Cmax values were 786 and 471 ng/mL and mean AUC0-24 values were 3830 and 4200 ng*h/mL for males and females, respectively, on Day 91	<u>≥ 0.2 mg/kg/day</u>: Decreased retic, Anti-KLH IgM and IgG detected Minimal lymphoid depletion in GALT Minima/moderate hypertrophy of smooth muscle in duodenum/jejunum/ileum <u>≥ 1 mg/kg/day</u>: Opportunistic GI infections Decreased B-lymhpocyte count Decreased K and Cl Decreased TDAR Decreased thymic weight, minimal to marked lymphoid depletion in thymus, GALT and lymph nodes, histiocytosis in lymph nodes Minimal/slight inflammation of caecum/colon <u>5 mg/kg/day</u>: Increased retic, WBC, neutrophils, PLT Increased fibrinogen Decreased urea Bone marrow: increased M:E ratio, myeloid hypercellularity Slight lymphoid depletion spleen, slight neutrophil cell infiltration Minimal goblet cell hyperplasia (jejunum/ileum), inflammation of gallbladder and rectum, femorotibial joint inflammation in (1/14 animals)

RBC- red blood cell/erythrocytes, HB haemoglobin, HT haematocrit, ASAT aspartate aminotransferase, PLT platelets, MCHC Mean corpuscular haemoglobin concentration, MCV mean corpuscular volume, ALAT alanine aminotransferase, PALS peri-arteriolar lymphoid sheath, GIT gastrointestinal tract, M:E ratio myeloid:erythrocyte ratio, TDAR T-cell dependent antibody response,
*Bioanalysis in study 805097 was provided by contributing scientist, Study director not claiming GLP for this part of the study.

In general, in both rat and cynomolgus monkey, the primary, on-target effects of duvelisib were observed at all dose levels. Findings involve the immune system characterised by depletion of lymphoid cells in the lymphoid tissues, e.g. spleen, thymus, lymph nodes and gut associated lymphoid tissue (GALT) and decreased immune function, obvious especially in the monkey as many opportunistic infections were observed in both the 28-day and 13-week studies. Severe toxicity was observed at dose levels at 50 mg/kg and above in rat, and at 5 mg/kg and above in monkey.

Exposure margins for the findings related to duvelisib has been summarised with Cmax and AUC values and compared to human exposure at the MHRD, resulting in exposure margins. Similarly, exposure of the major metabolite IPI-656, at the NOAEL in the pivotal toxicity studies have been presented.

For most findings related to duvelisib treatment, the exposure margins were relatively low, especially considering the total exposure, whereas somewhat higher exposure margins were achieved when free duvelisib was considered, due to high plasma protein binding in the clinical setting. With regards to the exposure to the major metabolite IPI-656 at the NOAEL levels of the pivotal toxicity studies, both free and total exposure margins were mostly below 1, e.g. the exposure to IPI-656 is higher in the clinical setting.

Table 9 Nonclinical overview summarising the key findings in the toxicity studies of duvelisib

Key Findings	Lowest-Effect Dose	AUC_{0-24}[a] (ng*h/mL)	AUC_{0-24} Exposure Multiple[b]	
			Total	Free
Mortality/Moribundity Associated with weight loss, ↓food consumption, ↑neutrophils and monocytes, lymphoid depletion, atrophy/ necrosis, bone marrow necrosis, inflammation/ulceration of gastrointestinal tract, necrosis of liver	**Rat** 350 mg/kg/day (28-day study)	**Rat**[c] 252000 (M) 477000 (F)	**Rat** 16-fold 30-fold	**Rat** 149-fold 282-fold
Mortality/Moribundity Deteriorating clinical conditions attributed to opportunistic infections associated with immunosuppression	**Monkey** 150 mg/kg/day (28-day study)	**Monkey** 480000	**Monkey** 30-fold	**Monkey** 546-fold
Lymphoid depletion, atrophy and/or necrosis of lymphoid tissues, decreased lymphocytes	**Rat** 50 mg/kg/day (28-day study)	**Rat** 34900 (M) 73400 (F)	**Rat** 2-fold 5-fold	**Rat** 21-fold 43-fold
Lymphoid depletion, atrophy and/or necrosis of lymphoid tissues, decreased lymphocytes; associated with opportunistic infections, inflammation, and/or degenerative changes in various organs	**Monkey** 30 mg/kg/day (28-day study)	**Monkey** 167000	**Monkey** 11-fold	**Monkey** 152-fold
Decrease in TDAR	**Monkey** 1 mg/kg/day (13-week study)	**Monkey** 157	**Monkey** 0.01-fold	**Monkey** 0.06-fold
Decrease in B cells	**Monkey** 5 mg/kg/day (13-week study)	**Monkey** 4015	**Monkey** 0.25-fold	**Monkey** 1.72-fold
Red cell mass Decrease due to necrosis and/or erythroid hypoplasia of bone marrow	**Rat** 50 mg/kg/day (28-day study) **Monkey** 30 mg/kg/day (28-day study)	**Rat** 34900 (M) 73400 (F) **Monkey** 167000	**Rat** 2-fold 5-fold **Monkey** 11-fold	**Rat** 21-fold 43-fold **Monkey** 152-fold

Key Findings	Lowest-Effect Dose	AUC_{0-24}[a] (ng*h/mL)	AUC_{0-24} Exposure Multiple[b]	
			Total	Free
Testes Seminiferous tubule atrophy	**Rat** 50 mg/kg/day (28-day study) 25 mg/kg/day (13-week study)	**Rat** 34900 (M) 14300 (M)	**Rat** 2-fold 0.9-fold	**Rat** 21-fold 8.4-fold
Pancreas Islet cell hypertrophy, inflammation, acinar cell atrophy	**Rat** 5 mg/kg/day (13-week study)	**Rat** 1190 (M) 2100 (F)	**Rat** 0.1-fold 0.1-fold	**Rat** 0.7-fold 1.2-fold
Embryo-fetal Toxicity Decreased fetal body weight, total resorptions and/or post-implantation loss (see Section 4.4)	**Rat** 50 mg/kg/day (GLP DRF) **Rabbit** 100 mg/kg/day (GLP DRF)	**Rat**[d] 73400 (F) **Rabbit**[e] ND	**Rat** 5-fold **Rabbit** 4.2-fold[f]	**Rat** 43-fold **Rabbit** 31-fold[f]
Phototoxicity Cutaneous erythema, edema following UVR exposure (see Section 4.5)	**Rat** 350 mg/kg/day (in vivo phototoxicity study)	**Rat**[g] 252000 (M) 477000 (F)	**Rat** 16-fold 30-fold	**Rat** 149-fold 282-fold

DRF = dose range-finding; EFD = embryo-fetal development; F = female; GLP = Good Laboratory Practice; M = male; ND = not done; NOAEL = no observed adverse effect level; RBC = red blood cells; TDAR = T-cell-dependent antibody response; UVR = ultraviolet radiation

[a] AUC_{0-24} on the last day of dosing, unless specified; AUC_{0-24} value is the combined mean (males and females), except in cases where there was a gender difference in exposure

[b] Exposure multiples are based on an estimated average AUC_{0-24} value of 15776 ng*h/mL in humans at the 25 mg BID duvelisib clinical dosage for the target indication. The free fraction of duvelisib in human plasma is 1.3% (Module 2.6.4 Section 4.2). Therefore, the expected free AUC_{0-24} value is approximately 205 ng*h/mL. The free fraction of duvelisib in the rat is 12.1%; free fractions of duvelisib in the monkey are 23.3% (150 mg/kg dose), 18.7% (30 mg/kg dose), 8.8% (5 mg/kg dose), and 8.0% (1 mg/kg dose)

[c] Exposure data are from Day 1 due to mortality and cessation of dosing at 350 mg/kg

[d] Plasma exposure determinations were not conducted in the GLP rat EFD dose range-finding study; exposure multiple was calculated using exposure from 50 mg/kg/day dose in GLP 28-day study (Report 805097)

[e] Plasma exposure determinations were not conducted in the GLP rabbit EFD dose range finding study

[f] AUC_{0-24} exposure multiple calculated using rabbit exposure data at 75 mg/kg/day from the GLP rabbit EFD study (Report WIL-692023). The NOAEL in rabbits was 75 mg/kg/day, and the AUC0-24 was 66200 ng*h/mL. The free fraction of duvelisib in rabbits is 9.6% (75 mg/kg dose)

[g] Plasma exposure determinations were not calculated in the GLP rat phototoxicity study; exposure values are from Day 1 of the 28-day rat toxicology study (Report 805097)

Genotoxicity

The genotoxicity of duvelisib was assessed in two *in vitro* tests as well as one *in vivo* test. The AMES's test showed that duvelisib did not cause gene mutation in the bacteria strains tested, at concentrations of up to 5000µg/plate. The two chromosome aberrations tests performed (on *in vitro* in human PBL) and one *in vivo* study in rats treated with duvelisib for 3 consecutive days, showed no or a slight increase in micronuclei in the *in vivo* test. In the *in vivo* micro nucleus test in rats, duvelisib tested weakly, but significantly positive in males only at the 350 mg/kg/day dose ($p<0.05$) for percentage of micronuclei. This was not observed in

female rats, for which exposure tends to be approximately 2-fold higher than in male rats in the repeat-dose toxicity studies. In addition, the free plasma exposure multiple at this dose was more than 200 fold exposure at MRHD. The increase was also within the historical negative control of the laboratory, constituted a slight increase and was only observed at the high dose.

Carcinogenicity

No carcinogenicity studies have been performed, (see discussion on non-clinical aspects).

Reproduction Toxicity

Reproductive toxicity has only been examined in embryo-foetal development studies. The lack of fertility and early embryonic development as well as any pre-and post-natal development or juvenile studies is acceptable based on the intended patient population and advanced cancer indication. Effects on testes were observed in the repeat dose toxicity studies, please see above.

Embryo-foetal developmental toxicity studies were performed in rats and rabbits, according to ICH S5(R2). Toxicokinetic sampling were included in both DRF and definitive rabbit studies, and in the definitive rat study. Animals showed exposure. In both DRF studies, the higher dose groups showed unacceptable maternal toxicity, including mortality or animals euthanised in extremis (doses of 150 and 275 mg/kg/day in rat, and 100 and 200 mg/kg/day in rabbits). In the rat, doses of 50 mg/kg/day gave rise to decreased body weights (4,7%) on GD20, lower gravid uterus weight, and decreased mean foetal weights (-16.7-18,4%), as well as a few skeletal variations and anasarca in one foetus, all of which was considered to be incidental findings within expected background findings.

As of the above results, final dose levels in the rat was set at 5, 10, 35 mg/kg/day, and at 10, 25 and 75 mg/kg/day in the rabbit. In the rat, the only finding of the study was slightly lower mean foetal weights at the high dose of 35 mg/kg/day, of 7.7% M, 5.6% F, 5.4% M+F when compared to concurrent control. The body weights observed were however, within historical controls.

In the rabbit study, similarly almost no adverse findings were observed, apart from one high dose female, which aborted on GD 18. Prior to the abortion, a number of clinical observations were made, including; body weight loss, severely reduced food consumption, decreased defecation, brown material around anogenital area, red material in the cage pan prior to abortion. However, as the animal was the only one exhibiting clinical signs and aborted, the findings regarding this animal was considered to be incidental by the study director, as all other treated animals' parameters were generally similar to control animals. The exposure margins have been based on the DRF studies (dose levels of 50 mg/kg and 100 mg/kg, for rat and rabbit respectively).

Toxicokinetic data

A human $AUC_{0\text{-}24h}$ of 15.776 µg.h/mL was used to establish animal/human exposure margins. This value was extrapolated from the human $AUC_{0\text{-}12h}$ of 7.888 µg.h/mL observed in study 02. In addition, exposure margins were corrected for the free fraction in plasma (10.9% (rat), 6.7% (rabbit), 8.8% (monkey), and 1.3% (human)). In the repeat-dose toxicity studies in rat exposure multiples at the NOAEL were below free plasma concentration duvelisib at MRHD of 25mg BID for males and between 2-7-fold for females. In cynomolgus monkeys, exposure margins were well below free plasma concentration duvelisib at MRHD. Main effects

observed to establish the NOAEL were related to the expected pharmacology of duvelisib. In addition, effects on testes were observed in male rats. At the same dose level, in female rats exposure was often approximately 2-fold exposure in male rats.

Other toxicity studies

Metabolites

The human major metabolite IPI-656 was also present in the nonclinical species used. The ratio of IPI-656 to duvelisib in rats, monkeys, and rabbits was 0.01, 1.43, and 0.71, respectively. Albeit in most instances the exposure margins obtained for IPI-656 was less than 1X clinical setting at the NOAEL or HNSTD.

Impurities

There are 4 impurities discussed in the nonclinical part of the dossier. The proposed limit of 1.0 % of the R enantiomer of duvelisib (IPI-490473) has been sufficiently justified. The R-enantiomer was present at 5.6 or 0.8 % in the repeat-dose toxicity studies (4-week and 13-week duration respectively) in both nonclinical species. It was furthermore present at a level of 5.3% in the test article lot used for the genotoxicity studies. The three impurities 2-ETHP, 2-HTHP and IPI490506 were all tested in AMES test, following equivocal results in the *in-silico* analysis for these three compounds. All three impurities/starting material were found to be negative in the AMES tests, hence as a result, IPI-490506 is treated as non-mutagenic impurity (ICH M7 Class 5). This approach is supported and the proposed limit of ≤ 0.15% w/w, is accepted, as it does not exceed the limits for impurity qualification based on ICH Q3A.

Phototoxicity

Duvelisib was tested both *in vitro* and *in vivo* due to absorption of light between wavelengths of 290 and 700 nm and distributes to both skin and eyes based on whole body autoradiography study results in male Long-Evans rats. The *in vitro* 3T3 assay indicate that duvelisib has phototoxic potential. In the *in vivo* study, duvelisib was administered to rats at 5, 50 and 350 mg/kg/day for three days. A subsequent single exposure to 10 J/cm2 of UVA, elicited cutaneous reactions indicative of phototoxicity (erythema, oedema) in the lightly and/or darkly pigmented skin sites in the 350 mg/kg/day group with UVR exposure. No adverse cutaneous reactions were observed in the low- or mid-dose duvelisib groups. There was no evidence of ocular phototoxicity, either by ophthalmologic evaluation or histopathologic evaluation, at any duvelisib dose. The NOAEL for phototoxicity in this study is the mid-dose of 50 mg/kg/day.

2.3.5. Ecotoxicity/environmental risk assessment

The stepwise refinement of the Fpen in order to achieve a PECsurfacewater below the trigger value of 0.01µg/L was performed. Phase I calculations result in a refined PECsw of 0.0111 µg/L. This value is just above the trigger value. The LogKow value of 2.57 was determined with the shake flask method, hence no further PBT assessment of duvelisib is triggered.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

The refinement of the Fpen is not supported. The applicant agreed to perform a Phase II assessment post-authorisation and will submit an updated ERA once the required studies have been performed and provide the expected submission date. A timeline of 24 months was given for completion of the studies specified below.

The following studies must be committed to:

- Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge;
- Ready biodegradability test (OECD 301);
- Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);
- Algal growth inhibition test (OECD 201);
- Daphnia sp. reproduction test (OECD 211, use version 2012);
- Fish, Early Life Stage Toxicity Test (OECD 210);
- Activated sludge, respiration inhibition test (OECD 209, use version 2010)
-

For all studies the original study report must be submitted. Please note that from all requested chronic toxicity studies and the OECD 209 test, a NOEC and/or EC10 is needed for the risk assessment. In case a limit test is performed, the OECD guidelines should be followed: if the limit test results in a statistically significant effect, a new test to determine a dose-response relationship should be performed, from which a NOEC and/or EC10 should be reported. Depending on the outcome of Tier IIA, the following additional studies might be required for Tier IIB:

- Aerobic and anaerobic transformation in soil (OECD 307);
- Soil Micro-organisms: Nitrogen Transformation Test (OECD216);
- Terrestrial Plants, Growth Test (OECD 208);
- Earthworm, Acute Toxicity Test (OECD 207);
- Collembola, Reproduction Test (ISO 11267)
- Effects on a sediment dwelling organism: Hyalella sp; Lumbriculus sp. (OECD 225) or Chironomus sp. (OECD 218 or 219)

2.3.6. Discussion on non-clinical aspects

Duvelisib is a dual inhibitor of class I phosphoinositide-3-kinase (PI3K)-δ and PI3K-γ. However, the inhibition of PI3K-β is in the same order as that of PI3K-γ, and both are much lower than that of PI3K-δ. According to the Clinical Study Report IPI-145-02, the Cmax of duvelisib in humans at the intended dose of 25 mg BID is 3.6 µM, of which the free fraction is 47 nM. This is well above the Kd of PI3K-β (1.56 nM), relatively close to the enzymatic IC50 (85 nM) and well above the IC50 of the 786-O cellular assay. Therefore, the high specificity suggested by the applicant of duvelisib for only PI3K-γ and PI3K-δ seems questionable, and the inhibition of PI3K-β may also play a role in the complicated effects of duvelisib.

Two *in vitro* assays and one *in vivo* assay showed specific PI3K-γ inhibition by duvelisib, however, the effects were shown at only slightly lower or even higher free concentrations of duvelisib than the free Cmax concentration in humans of approximately 47 nM. Therefore, it is suspected that the contribution of the PI3K-γ related effects will possibly be less than of the PI3K-δ related effects. In the murine xenograft model of transformed follicular lymphoma, the tumour growth is only decreased by about a half, at a free Cmax of about 140 nM, which is higher than the free Cmax of 47 nM in humans. These results suggest that duvelisib is not a very potent anticarcinogen. Although the proof of concept has been shown through *in vitro* and *in vivo* studies, the true potential of duvelisib as an anticancer drug has to be determined on the basis of clinical efficacy data.

Measurements with a large panel of diverse kinases, G-protein-coupled receptors, ion channels and transporters, revealed no possible effects on other targets besides inhibition of PI3K-γ and PI3K-δ by duvelisib. Furthermore, there are no non-clinical safety pharmacology issues found. In safety pharmacology studies, the *in vitro* hERG test showed a potential for hERG potassium inhibition. However, when taking into consideration the free fraction of duvelisib, safety margins were calculated to be in excess of 1000 and 2600 for duvelisib and the major metabolite IPI-656 respectively. *In vivo* cardiovascular studies in cynomolgus monkeys did not reveal treatment related effects.

Duvelisib distributed to very large extent to the small intestinal wall (100 times higher than plasma radioactivity). Other organs with relatively high radioactivity was liver and kidney with tissue/plasma ratios of 24-41 for the liver and 9 in kidney after 1 hour. This should be seen in context of very common adverse reactions associated diarrhoea/colitis grade 3 or more as well as hepatotoxicity observed as transaminase increased grade 3 or more observed as common and all grades as very common adverse reactions to duvelisib (SmPC). To put this into context for the benefit/risk assessment, distribution studies in rat show that duvelisib may be present in wall of the small intestines at up to 100 times higher concentration as compared to the target organs of pharmacological effect, namely blood and bone marrow.

Overall, the primary pharmacodynamic studies provided adequate evidence that the dual PI3K-δ and PI3K-γ inhibitory effect of duvelisib may synergistically inhibit tumour growth, when compared to PI3K-δ or PI3K-γ inhibition alone.

From a pharmacokinetic point of view, the choice of rat and cynomolgus monkey considered appropriate for the nonclinical efficacy and safety studies. Duvelisib distributed to very large extent to the small intestinal wall (100 times higher than plasma radioactivity), which may correlate with the high frequency of GI adverse effects observed in the clinical setting.

The Cynomolgus monkey was chosen over the dog as a non-rodent species for repeat-dose toxicity testing, due to the metabolite profile of the monkey being more comparable to the human.

Brief summary of findings in the repeat-dose toxicity studies, including adverse effects related to expected pharmacology was added to section 5.3 of the SmPC. The toxicology studies performed, conform with the guidance given in ICH S9, for advanced cancer indications.

In the general toxicity studies, the primary effects of duvelisib observed included lymphoid depletion with a functional impact (decrease in B cells in peripheral blood, decrease in TDAR, and occurrence of secondary infections/inflammation), decreased erythropoiesis, and testicular degeneration/atrophy. Pancreatic, vascular, and hepatic changes were also noted in some duvelisib toxicology studies. The nonclinical toxicities observed in rats and monkeys following duvelisib administration are consistent with the reported nonclinical effects of the PI3K-δ inhibitor, idelalisib, which is approved in the treatment of CLL and FL. The findings are reflected in the SmPC.

In the 28-day repeat dose study in rats, severe toxicity was observed in the high dose group of 350 mg/kg/day. This resulted in the cessation of dosing in this group, following 10 animals being found dead, and a further 8 moribund animals being euthanised. However, this study was preceded by a 14-day study, where similar severe toxicities were observed, in the high dose group, where the animals received only) 300 mg/kg/day.

Regarding reproductive toxicity studies, the definitive embryofoetal development studies did not show any toxicity towards. However, embryofoetal toxicity was observed in the preliminary studies, in presence of severe maternal toxicity (dose levels above 150 mg/kg/day in rats, and 100 mg/kg/day in rabbits), but only

at exposures above 25-fold the MHRD. The findings are suggested not to be presented in the SmPC, due to the findings only being present at high exposure multiples, based on free duvelisib. This approach is in line with the ICH S5 (3) guideline.

Overall the toxicology studies revealed that duvelisib had effects on the immune system, characterised by depletion of lymphoid cells in spleen, lymph nodes, thymus and GALT, and decreased immune function was especially obvious in the cynomolgus monkey where many opportunistic infections were observed. The preliminary (EFD) studies showed severe maternal toxicity, resulting mortality, as well as complete resorption of foetuses or abortions in rats and rabbits respectively. These changes were observed at exposures (based on free fraction) at 25-fold or above the clinical exposure at the MHRD. In the definitive EFD studies, no significant toxicity to reproduction was observed, at dose levels corresponding to approximately 33 and 22 - fold the clinical exposure (high dose groups in both rat and rabbit studies respectively). Hence the observed reproductive toxicity is at exposures above what is considered clinically relevant, according the ICH S5(R3).

In repeat-dose toxicity studies in rat and cynomolgus monkey, adverse effects were mainly related to expected exaggarated pharmacology, including adverse effects on lymphoid tissues, bone marrow and haematology parameters at exposures of free duvelisib at 8 to 16 fold, corresponding to total duvelisib at 2 to 11 fold Maximum Recommended Human Dose (MRHD) of 25 mg BID in human.

The genotoxicity of duvelisib was assessed in two *in vitro* tests as well as one *in vivo* test. The AMES's test showed that duvelisib did not cause gene mutation in the bacteria strains tested, at concentrations of up to 5000µg/plate. In the *in vivo* micro nucleus test in rats, duvelisib tested weakly, but significantly positive in males only at the 350 mg/kg/day dose ($p<0.05$) for percentage of micronuclei; the increase was also within the historical negative control of the laboratory, constituted a slight increase, was only observed at the high dose and could be related to indirect PI3K inhibition effects, as this has been associated with bone marrow toxicity characterised by erythroid hypoplasia and pyknotic erythroid cells with nuclear fragments that were consistent with apoptosis. Inhibition of PI3K has previously been associated with apoptosis of erythroid progenitors *in vitro*, and the process of apoptotic nuclear fragmentation (karyorrhexis/pyknosis) is similar to that of erythrocyte enucleation, which may lead to apoptotic fragments in a small number of cells described as micronuclei resulting from chromosome breakage. Taken together with the evidence provided, it is agreed that the results from the *in vivo* genotoxicity test are to be considered negative. Carcinogenicity studies have not been conducted with duvelisib, which is acceptable in accordance with the ICH S9 guidance.

In dose range finding and pivotal embryo-foetal developmental toxicity studies in rat and rabbit, duvelisib (free fraction) induced embryo-foetal developmental toxicity only at free plasma exposures margins of >25 fold of 25 mg BID in human (MRHD), corresponding to 4 to 5 fold total plasma concentrations).

Fertility studies with duvelisib were not conducted. Histological findings in male and female rats were observed in the repeat dose toxicity studies and included testis (seminiferous epithelial atrophy, decreased weight, soft testes), and epididymis (small size, oligo/aspermia) in males and ovary (decreased weight) and uterus (atrophy) in females.

The ERA provided concluded that the PECsw exceeded the action limit of 0.01 µg/L.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical aspects of duvelisib are sufficiently studied and the main findings are reflected in the SmPC section 5.3.

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation: Submission of a Phase II ERA assessment in a timeline of 24 months covering:

- Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge;
- Ready biodegradability test (OECD 301);
- Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);
- Algal growth inhibition test (OECD 201);
- Daphnia sp. reproduction test (OECD 211, use version 2012);
- Fish, Early Life Stage Toxicity Test (OECD 210);
- Activated sludge, respiration inhibition test (OECD 209, use version 2010)

Depending of the outcome of Tier IIA, the following additional studies might be required for Tier IIB:

- Aerobic and anaerobic transformation in soil (OECD 307);
- Soil Micro-organisms: Nitrogen Transformation Test (OECD216);
- Terrestrial Plants, Growth Test (OECD 208);
- Earthworm, Acute Toxicity Test (OECD 207);
- Collembola, Reproduction Test (ISO 11267)
- Effects on a sediment dwelling organism: Hyalella sp; Lumbriculus sp. (OECD 225) or Chironomus sp. (OECD 218 or 219)

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 10 Tabular overview of clinical studies

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
5.3.1 REPORTS OF BIOPHARMACEUTIC STUDIES							
5.3.1.1 Bioavailability (BA) Study Reports							
IPI-145-05 Phase 1 Sponsor: Infinity	Evaluate ADME and absolute BA of duvelisib	Healthy adult male subjects	Open Label, 2-Period	**Period 1 (BA)** Single dose duvelisib oral capsule, 25 mg + Single dose [^{14}C]IPI-145, 2.8 µg IV	6	1 day	Complete; Full CSR
				Period 2 (ADME) Single dose [^{14}C]IPI-145, 25 mg oral suspension		1 day	
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports							
IPI-145-15 Phase 1 Sponsor: Infinity	**Part 1:** Evaluate BE of duvelisib market image formulation to clinical trial formulation;	Healthy adult subjects	Randomized, Open Label, 2-Part	**Part 1, Cohort 1** Single dose duvelisib oral capsule, 25 mg market image formulation, fasted + Single dose duvelisib oral capsule, 25 mg clinical trial formulation, fasted	32	2 days	Complete; Full CSR
	Assess safety and tolerability			**Part 1, Cohort 2** Single dose duvelisib oral capsule, 5 mg market image formulation, fasted + Single dose duvelisib oral capsule 5 mg clinical trial formulation, fasted	52	2 days	
	Part 2: Assess FE on PK of duvelisib; Assess safety and tolerability			**Part 2, Cohort 3** Single dose duvelisib oral capsule, 25 mg market image formulation, with high-fat meal + Single dose duvelisib oral capsule, 25 mg market image formulation, fasted	20	2 days	
				TOTAL:	**104**		
5.3.2 REPORTS OF STUDIES PERTINENT TO PHARMACOKINETICS USING HUMAN BIOMATERIALS							
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies							
IPI-145-14 Phase 1 Sponsor: Infinity	Evaluate PK of duvelisib in subjects with chronic hepatic impairment compared to matched healthy subjects; Assess safety and tolerability	**Group 1:** Adults with mild hepatic impairment	Non-randomized, Open Label, Parallel Group	Single-dose duvelisib oral capsule, 25 mg, fasted	6	1 day	Complete; Full CSR
		Group 2: Adults with moderate hepatic impairment			6		
		Group 3: Matched healthy subjects			6		

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
		Group 4: Adults with severe hepatic impairment			6		
				TOTAL:	**24**		
5.3.3 REPORTS OF HUMAN PHARMACOKINETIC (PK) STUDIES							
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports							
IPI-145-01 Phase 1 FIH Sponsor: Infinity	Evaluate safety, tolerability, PK, PD, FE, and effect of ketaconazole on PK of duvelisib	Healthy adult subjects	**Part 1 (SAD)** Randomized, Double Blind, Placebo-Controlled	Duvelisib oral capsule, range of 1 to 30 mg single dose OR matching placebo	36	1 day	Complete; Full CSR
			Part 2 (MAD) Randomized, Double Blind, Placebo-Controlled	Duvelisib oral capsule, range of 1 to 5 mg BID and 10 mg QD OR matching placebo	48	14 days	
			Part 3 (FE) Randomized, Open Label, 2-way Crossover	Duvelisib oral capsule, 25 mg single dose in each period	6	2 treatment periods, each 2 days	
			Part 4 (DDI) Non-randomized, Open Label	Days 1 and 6: Duvelisib oral capsule, 10 mg Days 3 to 7: Ketoconazole oral tablet 200 mg BID	16	2 days	
				Total:	**104**		
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports (Continued)							

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
M15-412 Phase 1 Sponsor: AbbVie	Evaluate PK of duvelisib in Japanese healthy adult male subjects; Assess safety and tolerability	Japanese healthy adult male subjects	**Part 1 (SAD):** Randomized, Double-Blind, Placebo-Controlled	**Cohort 1:** Single-dose duvelisib oral capsule, 5 mg OR placebo	8	1 day	Complete; Abbreviated CSR
				Cohort 2: Single-dose duvelisib oral capsule, 20 mg OR placebo	8		
				Cohort 3: Single-dose duvelisib oral capsule, 30 mg OR placebo	8		
			Part 2 (MAD): Non-randomized, Open-Label	**Cohort 4:** Duvelisib oral capsule, 10 mg QD	9	14 days	
				TOTAL:	**33**		
M15-789 Phase 1 Sponsor: AbbVie	Evaluate PK of duvelisib in Chinese healthy adult subjects; Assess safety	Chinese healthy adult subjects	Open-Label	**Cohort 1:** Single-dose duvelisib oral capsule, 25 mg	3	1 day	Terminated; Synoptic CSR
				Cohort 2: (30 days post Part 1) Single-dose duvelisib oral capsule, 25 mg	9		
				TOTAL:	**12**		

Table **5.3.3.2 Patient PK and Initial Tolerability Study Reports**

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
IPI-145-02 Phase 1 Sponsor: Infinity	Determine MTD of duvelisib and recommend a dose and schedule for subsequent studies in subjects with advanced hematologic malignancies; Examine PK; Assess potential biological activity	Adults with advanced hematologic malignancies	**Dose Escalation, Accelerated Phase:** Open-Label, 1 patient at each level	Duvelisib oral capsule, 8 mg or 15 mg BID	30	BID in 28-day cycles until disease progression or unacceptable toxicity	Complete; Full CSR
			Dose Escalation, Standard Phase: Open-Label, 3+3 at each level	Duvelisib oral capsule, range of 25 to 100 mg BID			
			Expansion Phase: Open-Label	Duvelisib oral capsule, 25 mg BID	220		
				Duvelisib oral capsule, 75 mg BID			
				TOTAL:	**250**		
M15-460 Phase 1 Sponsor: AbbVie	Evaluate safety and PK of duvelisib in Japanese subjects with R/R lymphoma	Japanese subjects with R/R lymphoma	Open Label, Single arm	Duvelisib oral capsule, 25 mg BID	6	BID in 28-day cycles until DP or unacceptable toxicity	Terminated; Abbreviated CSR
5.3.3.4 Extrinsic Factor PK Study Reports							
IPI-145-10 Phase 1	Evaluate effect of duvelisib on PK of	Healthy adult subjects	Non-randomized,	**Period 1 (Day 1)** Single dose MDZ oral, 2 mg, fasted	14	1 day	Complete; Full CSR

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
Sponsor: Infinity	midazolam (MDZ)		Open Label, 2-period	**Period 2 (Days 2 – 6)** Duvelisib oral capsule, 25 mg BID, fed except with single dose MDZ oral, 2 mg on Day 6 morning, fasted		5 days	
IPI-145-11 Phase 1 Sponsor: Infinity	Evaluate effect of rifampin on PK of duvelisib	Healthy adult subjects	Non-randomized, Open Label, 2-period	**Period 1 (Day 1)** Single dose duvelisib oral capsule, 25 mg	14	1 day	Complete; Full CSR
				Period 2 (Days 3 – 9) Rifampin oral, 600 mg QD Single dose duvelisib oral capsule, 25 mg on Day 9		1 day	
VS-0145-131 Phase 1 Sponsor: Verastem	Evaluate effect of etravirine on PK of duvelisib	Healthy adult subjects	Non-randomized, Open Label, 2-period	**Period 1 (Day 1)** Single dose duvelisib oral capsule, 25 mg	20	1 day	Complete; Full CSR
				Period 2 (Days 3 – 12) Etravirine oral, 200 mg BID but only a single dose on Day 3 evening and Day 12 morning Single dose duvelisib oral capsule, 25 mg on Day 12		1 day	
5.3.4 REPORTS OF HUMAN PHARMACODYNAMIC (PD) STUDIES (None provided)							
5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES – Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)							
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication							

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
IPI-145-07 Phase 3 Sponsor: Infinity/Verastem	Evaluate efficacy of duvelisib monotherapy vs. ofatumumab monotherapy in subjects with R/R CLL or SLL	Adult subjects with R/R CLL/SLL with at least 1 prior therapy	Randomized, Controlled, Parallel Arm, Open-Label, Active Comparison Cross-over allowed to Study IPI-145-12	**Arm 1:** Duvelisib oral capsule, 25 mg BID	~150	BID until DP or unacceptable toxicity	Ongoing; enrollment complete with subjects in long-term follow-up; Full CSR with safety & efficacy data as of 19MAY2017
				Arm 2: Ofatumumab IV Initial dose of 300 mg IV on Day 1, followed by 7 weekly doses of 2000 mg IV; then 2000 mg IV once a month for 4 months	~150	6 months	
				TOTAL:	**~300**		
5.3.5.4 Other Study Reports							
IPI-145-12 Phase 3 Sponsor: Infinity/Verastem	Evaluate efficacy of duvelisib or ofatumumab monotherapy in subjects who experience disease progression after treatment in IPI-145-07	Adults subjects with R/R CLL/SLL previously treated in Study IPI-145-07	Open-Label, Optional roll-over study from Study IPI-145-07 All subjects to receive opposite study drug than that received in Study IPI-145-07	**Arm 1:** Duvelisib oral capsule, 25 mg BID	~75	BID until DP or unacceptable toxicity	Enrollment ongoing; Full CSR with available safety & efficacy data as of 19JUL017
				Arm 2: Ofatumumab IV Initial dose of 300 mg IV on Day 1, followed by 7 weekly doses of 2000 mg IV; then 2000 mg IV once a month for 4 months	~75	6 months	
				TOTAL:	**150**		

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES – Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)							
5.3.5.4 Other Study Reports (Continued)							
IPI-145-18 Phase 1b Sponsor: Infinity	Evaluate safety of duvelisib in combination with obinutuzumab; Expansion phase to assess clinical activity	Adult subjects with CLL/SLL previously treated with a BTK inhibitor	**Safety Lead-in Phase:** Open-Label, Single Arm, Dose Escalation of duvelisib	Duvelisib oral capsule, BID, 25 mg to 75 mg, starting Day 2 of Cycle 1 Obinutuzumab IV, administered according to approved product labeling	6	28 day cycles until DP or unacceptable toxicity	Terminated after 3 patients enrolled in Lead-In Phase; Protocol only, no CSR will be provided; Safety data included in ISS
			Expansion Phase: Open-Label, Single Arm	Duvelisib regimen as determined in Safety Lead-in Phase; Obinutuzumab IV, administered according to approved product labeling	40		
				TOTAL:	**46**		
IPI-145-23 Phase 2 Sponsor: Infinity/Verastem	Collection of long-term safety, clinical activity, and OS data	Adult subjects with hematologic malignancies who received treatment with duvelisib or participated in the survival follow-up phase in a previous duvelisib study	Long-term, Continued Treatment, Open Label	Duvelisib, oral capsule, Subjects will continue on the same dose level they last received in their previous duvelisib study; Two dose reductions are permitted	Dependent on number of eligible subjects from previous duvelisib studies	Until DP or voluntary drop out	Enrollment ongoing; Protocol only, no CSR will be provided; Safety data included in ISS

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
VS-0145-328 Phase 3 Sponsor: Verastem	Reporting of long-term safety data	Adult subjects with hematologic malignancies who received duvelisib 25 mg BID in studies IPI-145-02, IPI-145-6 IPI-145-7 or IPI-145-12	Long-term, Open Label	N/A	442	N/A	Reporting ongoing; CSR as of 19 July 2019 data provided
5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES – Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)							
5.3.5.4 Other Study Reports (Continued)							
IST-145-01/ HEMREF34 (5.3.5.4) Phase 1b Sponsor: IST	Evaluate tolerability, initial safety profile, and MTD of duvelisib in combination with rituximab and/or bendamustine	Adult subjects with CD20+ NHL or CLL with at least one prior therapy	**Dose Escalation Phase:** Non-randomized, Open Label, 3+3 dose escalation	**Arm 1 (D+R):** Duvelisib oral capsule, 25 mg BID + rituximab, IV, 375 mg/m^2 QWK	3 to 6	**D:** Up to 12 cycles, each 28 days **R:** 2 cycles, each 28 days	Complete; Protocol only, no CSR will be provided; Safety data included in ISS
				Arm 2 (D+BR): Duvelisib oral capsule, 25 mg QD to 75 mg BID + bendamustine, IV, 90 mg/m^2 on Days 1 -2 + rituximab, IV, 375 mg/m^2 on Day 1	3 to 6	**D:** Up to 12 cycles, each 28 days **BR:** Up to 6 cycles, each 28 days	
				Arm 3 (D+B) *Removed in Amendment 2*	*N/A*	*N/A*	
			Dose Expansion Phase:	**Arm 1, Cohort A (NHL)** Duvelisib oral capsule, 25 mg BID + R	~10	**D:** Until DP, unacceptable	

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
			Non-randomized, Open Label	**Arm 1, Cohort B (CLL)** Duvelisib oral capsule, 25 mg BID + R	~10	toxicity, or subject refusal	
				Arm 2, Cohort A (NHL) Duvelisib oral capsule, 25 mg BID + BR	~5		
				Arm 2, Cohort B (CLL) Duvelisib oral capsule, 25 mg BID + BR	~10		
				TOTAL:	**~41 to 47**		
5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES – Follicular Lymphoma (FL)							
5.3.5.2 Study Reports of Uncontrolled Clinical Studies							
IPI-145-06 Phase 2 Sponsor: Infinity/Verastem	Evaluate antitumor activity of duvelisib in subjects with iNHL refractory to rituximab and to either chemotherapy or RIT	Adult subjects with refractory iNHL (FL, SLL, or MZL)	Open-Label, Single Arm	Duvelisib oral capsule, 25 mg BID	120	28-day cycles until DP or unacceptable toxicity	Ongoing; enrollment complete; Full CSR with available safety & efficacy data as of 07APR2016
5.3.5.4 Other Study Reports							

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
IPI-145-08 Phase 3 Sponsor: Infinity	Evaluate the efficacy of duvelisib in combination with rituximab (D+R) vs. placebo + rituximab (PBO + R) in previously treated subjects with CD20+ FL	Adult subjects with previously treated CD20+ FL	Randomized, Double-Blind, Placebo-Controlled	**Arm A (D+R):** Duvelisib oral capsule, 25 mg BID + rituximab (375 mg/m^2) once weekly for 4 weeks, then once on Day 1 of Cycles 4, 6, 8, and 10	200 (study terminated; n=6 enrolled)	28-day cycles for 27 cycles Subjects may continue additional cycles of duvelisib up to 5 years with documented evidence of response	Terminated; Synoptic CSR
				Arm B (PBO + R): Placebo + rituximab (375 mg/m^2) once weekly for 4 weeks, then once on Day 1 of Cycles 4, 6, 8, and 10	200 (study terminated; n=7 enrolled)		
				TOTAL:	**400 (terminated ; n=13 enrolled)**		
5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES – Follicular Lymphoma (FL)							
5.3.5.4 Other Study Reports							
IPI-145-19 Phase 1b/2 Sponsor: Infinity	Evaluate the safety and clinical activity of duvelisib in combination with rituximab or obinutuzumab in subjects with previously untreated CD20+ FL	Adult subjects with previously untreated CD20+ FL	Open Label, Two-part (Safety Lead-in followed by Simon-Two Stage design)	**Arm 1 (D + R)** Duvelisib oral capsule, 25 mg BID + rituximab IV, 375 mg/m^2 for 4 weekly doses and then every 2 cycles for a total of up to 16 doses	~30	28 day cycles up to 2 years	Complete; Abbreviated CSR
				Arm 2 (D + O) Duvelisib oral capsule, 25 mg BID + obinutuzumab IV, 1000 mg for 4 weekly doses, then every 2 cycles for a total of up to 16 doses	~25	28 day cycles up to 2 years	
				TOTAL:	**55**		

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES – Rheumatoid Arthritis (RA)							
5.3.5.4 Other Study Reports							
IPI-145-04 (5.3.5.4) Phase 2 Sponsor: Infinity	Evaluate efficacy of multiple dose levels of duvelisib vs. placebo in patients with moderate-to-severe RA taking a stable dose of methotrexate (MTX)	Adult subjects with moderate-to-severe RA taking a stable dose of MTX	Randomized, Double-Blind, Placebo-Controlled, Parallel Cohort	**Cohort 1:** Duvelisib oral capsule, 0.5 mg BID	79	12 weeks	Complete; Full CSR
				Cohort 2: Duvelisib oral capsule, 1.0 mg BID	79		
				Cohort 3: Duvelisib oral capsule, 5.0 mg BID	79		
				Cohort 4: Placebo BID	79		
				TOTAL:	**316**		
5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES – Asthma							
5.3.5.4 Other Study Reports							
IPI-145-03 Phase 2a Sponsor: Infinity	Examine the effects of multi-dose regimens of different dose strengths of duvelisib on lung function in mild	Adult subjects with mild asthma	Randomized, Double-Blind, Placebo-Controlled, 2-way Cross-over	**Cohort 1:** Crossover, duvelisib oral capsule, 1 mg or placebo, Q12h	15	2 treatment periods of 14 days, with 7 to 12 day washout in between	Complete; Full CSR
				Cohort 2: Crossover, duvelisib oral capsule, 5 mg or placebo, Q12h	15		

Study Identifier	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Planned	Duration of Treatment	Study Status; Type of Report
	asthmatic subjects following allergen challenge			**Cohort 3:** Crossover, duvelisib oral capsule, 25 mg or placebo, Q12h	15	2 treatment periods of 5 days, with 16 to 21 day washout in between	
				TOTAL:	**45**		

B = Bendamustine; BTK = Bruton's Tyrosine Kinase; CLL = Chronic Lymphocytic Leukaemia; CSR = Clinical Study Report; D = Duvelisib; DDI = Drug Drug Interaction; DP = Disease Progression; FE = Food effect; FIH = First in Human; FL = Follicular Lymphoma; ISS = Integrated Summary of Safety; IST = Investigator Sponsored Trial; IV = Intravenous; MAD = Multiple Ascending Dose; MTD: Maximum Tolerated Dose; MTX = Methotrexate; MZL = Marginal Zone Lymphoma; N/A = Not applicable; NHL = Non-Hodgkin's Lymphoma; O = obinutuzumab; PD = Pharmacodynamics; PK = Pharmacokinetics; QWK = Every week; R = Rituximab; R/R = Relapsed/Refractory; SAD: Single Ascending Dose; SLL = Small Lymphocytic Lymphoma

2.4.2. Pharmacokinetics

Table 11 overview of the studies and their assessments supporting duvelisib clinical pharmacology

Study No. (n)	Objectives/Design	Doses Studied	PK
Studies in Healthy Subjects			
IPI-145-01 (n = 106)	Part 1: SAD safety, tolerability, PK, and PD Part 2: MAD safety, tolerability, PK, and PD Part 3: Food effect (clinical-trial formulation) Part 4: Ketoconazole DDI	Part 1: Duvelisib 1-30 mg Part 2: Duvelisib 1-5 mg BID and 10 mg QD × 14 days Part 3: Duvelisib 25 mg fed and fasted Part 4: Duvelisib 10 mg with and without ketoconazole 200 mg BID × 5 days	Intensive PK

IPI-145-05 (n = 6)	Mass balance/ADME and absolute BA	[^{14}C]-duvelisib 25 mg (suspension) Duvelisib 25 mg capsule Microdose of [^{14}C]-duvelisib 2.8 µg IV	Intensive PK
IPI-145-10 (n = 14)	DDI study with a sensitive CYP3A4 substrate Midazolam	Duvelisib 25 mg BID × 5 days Single-dose MDZ 2 mg with or without duvelisib (Day 5)	Intensive PK
IPI-145-11 (n = 14)	DDI study with Rifampin, a strong CYP3A4 inducer	Rifampin 600 mg QD × 7 days Single-dose duvelisib 25 mg with and without rifampin (Day 7)	Intensive PK
IPI-145-14 (n = 24)	Hepatic Impairment (Child-Pugh)	Duvelisib 25 mg, single dose, in subjects with mild, moderate, or severe hepatic impairment	Intensive PK
VS-0145-131	DDI study with Etravirine, a moderate CYP3A4 inducer	Duvelisib 25 mg single dose, 10 days of etravirine 200 mg BID + duvelisib on day 10.	Intensive PK
IPI-145-15 (n = 80)	BE: Comparison of market-image to clinical-trial formulation FE: Effect of food on market-image formulation	BE: Duvelisib 5 mg and 25 mg, single dose FE: Duvelisib 25 mg, single dose	Intensive PK
M15-412	PK, safety, and tolerability in Japanese healthy subjects	SAD: 5, 20, and 30 mg MAD: 10 mg QD	Intensive PK
M15-789	PK and safety in Chinese healthy subjects	SAD: 25 mg	Intensive PK
Studies in Subjects with Advanced Hematologic Malignancies			
IPI-145-02 (n =210)	Phase 1 Dose Escalation: MAD safety, tolerability, PK, and PD in subjects with advanced hematologic malignancies Phase 1 Dose Expansion: Selected duvelisib 25 mg and 75 mg BID doses for safety, tolerability, PK, and PD in subjects with hematologic malignancies	Phase 1 Dose Escalation: Duvelisib 8-100 mg administered on continuous BID schedule in 28-day cycles Phase 1 Dose Expansion: Duvelisib 25 mg and 75 mg BID doses administered on continuous BID schedule in 28-day cycles	Intensive and Sparse PK
IPI-145-06 (n = 129)	Phase 2, open-label, single-arm safety and efficacy study in subjects with iNHL, including FL, marginal zone lymphoma, and SLL, whose disease is refractory to rituximab and either chemotherapy or radioimmunotherapy	Duvelisib 25 mg administered on continuous BID schedule in 28-day cycles	Sparse PK

Study No. (n)	Objectives/Design	Doses Studied	PK
IPI-145-07 (n ~ 160 treated with duvelisib)	Phase 3 study of duvelisib vs ofatumumab in subjects with relapsed or refractory CLL/SLL	Duvelisib 25 mg administered on continuous BID schedule in 28-day cycles	Sparse PK
M15-460	Safety and PK profile of duvelisib in Japanese subjects with relapsed or refractory lymphoma	Duvelisib 25 mg administered on continuous BID schedule in 28-day cycles	Intensive PK
IPI-145-19	Phase 1b/2 study of duvelisib in combination with rituximab or obinutuzumab in FL	Duvelisib 25 mg BID with rituximab or obinutuzumab in 28-day cycles	Sparse PK

ADME = absorption, distribution, metabolism, and excretion; BA = bioavailability; BE = bioequivalence; BID = twice daily; CLL = chronic lymphocytic leukemia; DDI = drug-drug interaction; FE = food effect; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; IV = intravenous; MAD = multiple ascending dose; MDZ = midazolam; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; SAD = single ascending dose; SLL = small lymphocytic lymphoma

Methods

- Bioanalytical analysis

PK blood samples were collected and analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for quantification of plasma duvelisib and its metabolite IPI-656. The methods for duvelisib and IPI-656 analysis in plasma and urine were adequately validated in accordance with the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

- Non-compartment data analysis

Noncompartmental analyses (NCA) were used for the estimation of plasma duvelisib and IPI-656 PK parameters in all studies except the two pivotal studies, IPI-145-06 and IPI-145-07.

- Population pharmacokinetic analysis

The provided population PK analysis utilised pooled PK data collected from 13 studies and included a total of 806 subjects with 16737 concentration records. The purpose of the population PK model and analyses was to estimate population PK parameters, inter- and intra-subjective variabilities, covariates, and to characterise exposure-response relationships.

- Physiologically-based pharmacokinetic model-based analysis

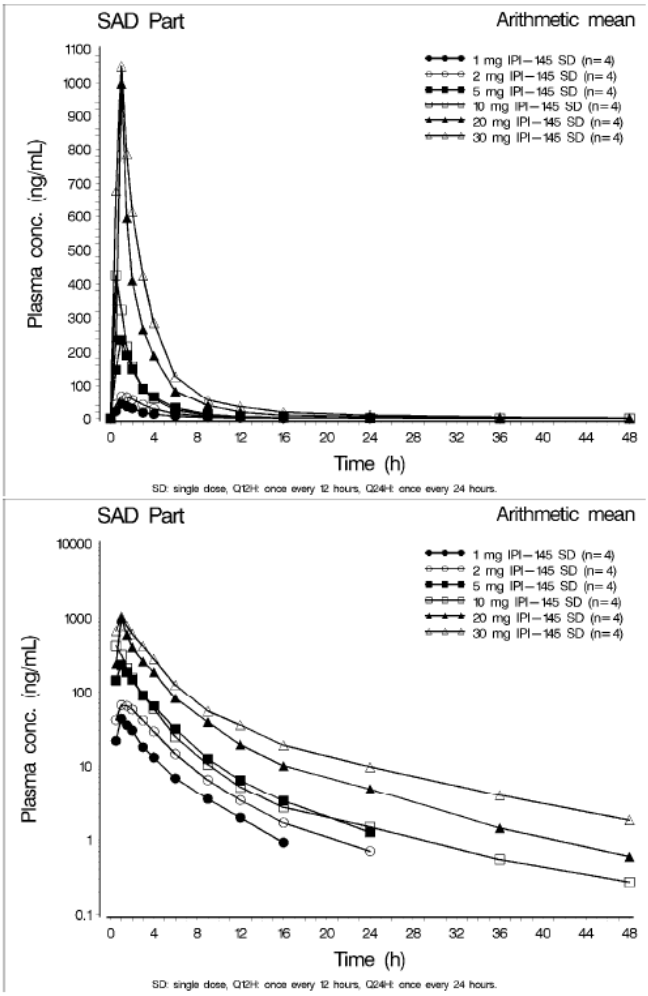
PBPK modelling and simulations using Simcyp were aimed to support dosing recommendation for co-medication of duvelisib with strong CYP3A4 inhibitors. In addition, the PBPK model was also used to assess the inhibition potential of duvelisib and IPI-656 on CYP3A4 or CYP2C8 substrates. PBPK modelling was further used to estimate the exposure of duvelisib and IPI-656 at steady-state in subjects with hepatic impairment. PBPK modelling using GastroPlus was used to estimate the effect of co-medication of proton pump inhibitors on the exposure of duvelisib.

PBPK modelling was used to support the proposed dosing reduction to 15 mg BID if strong CYP3A4 inhibitors are co-administered with duvelisib. After thorough assessment, the PBPK model has been deemed adequate for the various simulations for which it has been used.

Absorption

A tmax of ~1 hour was demonstrated in healthy subjects following single-dosing of duvelisib in a dose range of 1-30 mg, indicating rapid absorption of this drug.

Figure 8 mean IPI-145 plasma concentration-time profiles following administration of increasing single doses of IPI-145 in healthy subjects (Study IPI-145-01)



When comparing duvelisib administered as an oral capsule with duvelisib administered as an IV infusion (study IPI-145-05), the absolute bioavailability of duvelisib was estimated to be 42%.

Duvelisib exhibited moderate membrane permeability in Caco-2 cells and was shown to be a substrate for Pgp and to lesser extent also a substrate for BCRP. Duvelisib is a weak base with pKa values of 3.65 and 9.93 and has a pH-dependent solubility profile with low solubility at pH>3. In simulated gastric fluid the solubility of duvelisib was high 4.52 mg/ml based on a dose of 25 mg.

Influence of food

A food effect was observed in terms of a reduction in Cmax of 10-37% and a delay in tmax from 1 to 3-4 hours, whereas a minimal impact on AUC for duvelisib was evident.

Table 12 Geometric LS Means and 90% CI for Duvelisib Following Fed or Fasted Conditions in Healthy Subjects in Study IPI-145-01

	Geometric LS Means			
Parameter	**Fed**	**Fasted**	**Ratio**	**90% CI**
C_{max} (ng/mL)	699	776	0.90	0.61-1.34
$AUC_{0\text{-}last}$ (ng•h/mL)	3388	3127	1.08	0.87-1.34
$AUC_{0\text{-}\infty}$ (ng•h/mL)	3440	3158	1.09	0.88-1.34

$AUC_{0\text{-}last}$ = area under the concentration vs time curve from 0 to last observed plasma concentration; $AUC_{0\text{-}\infty}$ = area under the concentration vs time curve from 0 to infinity; CI = confidence interval; Cmax = maximum observed plasma concentration; LS = least squares

Source: Study IPI-145-01 CSR Table 18 (modified)

Table 13 Geometric LS Means and 90% CI of Food Effect for Duvelisib Pharmacokinetic Parameters – Cohort 3, 25 mg in Study IPI-145-15

	Geometric LS Means			
Parameter	**Market-Image, Fed**	**Market-Image, Fasted**	**Ratio**	**90% CI**
C_{max} (ng/mL)	561.5	897.8	0.63	0.55-0.71
$AUC_{0\text{-}last}$ (ng•h/mL)	2653.6	2698.6	0.98	0.92-1.05
$AUC_{0\text{-}\infty}$ (ng•h/mL)	2790.6	2964.8	0.94	0.88-1.01

$AUC_{0\text{-}last}$ = area under the concentration vs time curve from 0 to last observed plasma concentration; $AUC_{0\text{-}\infty}$ = area under the concentration vs time curve from 0 to infinity; CI = confidence interval; Cmax = maximum observed plasma concentration; LS = least squares

Note: The AUC and C_{max} analyses were performed on ln-transformed parameters using a linear mixed-effect model with treatment, period, and sequence as fixed effects, and subject as a random effect. The analyses were based on subjects without missing data.

Source: Study IPI-145-15 CSR Table 16 (modified)

The food effect was also addressed in the provided population PK analysis, and overall, the food effect was described to cause a modest decrease in Cmax with minimal impact on expected AUC (see section 2.1.8 of this AR). As no clinically meaningful food effect seems to be evident in terms of overall duvelisib exposure, the omission of precautions with respect to concomitant food intake is considered acceptable.

Bioequivalence

The duvelisib capsule formulation was changed during the clinical development. Duvelisib drug product A (DP-A "clinical-trial formulation") was developed initially and used in Phase 1 and 2 clinical studies, including a pivotal Phase 2 clinical study (Study IPI-145-06). Duvelisib drug product B (DP-B "market-image

formulation") was developed later and used in Phase 1, 2, and 3 clinical studies (including pivotal Study IPI-145-07), bioequivalence Study IPI-145-15, and primary (registration) stability studies. No bioequivalence (BE) studies have been conducted to compare the proposed intermediate strength 15-mg duvelisib capsule with the clinically used 5-mg strength duvelisib capsule, which has been addressed in the Quality AR.

Duvelisib 25 mg

For the 25 mg dosing, the market-image formulation was demonstrated to be within the equivalence range of 80% to 125% compared to the clinical-trial formulation in terms of AUC, whereas the upper bound of the 90% CI for Cmax (104.04% to 133.10%) exceeded the standard upper limit of 125%. The geometric mean ratio (GMR) and 90% confidence interval (CI) between the Test formulation (market image) and the Reference formulation (clinical-trial) for duvelisib PK parameters of interest (AUClast, AUCinf, and Cmax) are given in Table 6.

Table 14 Statistical Analysis of Bioequivalence for Duvelisib Pharmacokinetic Parameters – Cohort 1, 25 mg in Study IPI-145-15

Parameter	Statistic	Market-image (Test)	Clinical-trial (Reference)
AUC_{inf} (h*ng/mL)	N	28	26
	Geometric LS Mean	3336.0	3303.5
	Geometric LS Mean Ratio (%)	100.98	
	90% CI of Ratio (%)	(96.89, 105.25)	
AUC_{last} (h*ng/mL)	N	32	32
	Geometric LS Mean	3028.3	2887.6
	Geometric LS Mean Ratio (%)	104.87	
	90% CI of Ratio (%)	(98.42, 111.75)	
C_{max} (ng/mL)	N	32	32
	Geometric LS Mean	1114.9	947.4
	Geometric LS Mean Ratio (%)	117.68	
	90% CI of Ratio (%)	(104.04, 133.10)	

CI = confidence interval; LS = least squares; PK = pharmacokinetic; n = number of subjects in subset
Note: The AUC and C_{max} analyses were performed on ln-transformed parameters using a linear mixed-effect model with treatment, period, and sequence as fixed effects, and subject as a random effect. The analyses were based on subjects without missing data.
Source: Study IPI-145-15 CSR Table 11

Duvelisib 5 mg

Bioequivalence in terms of Cmax and AUC were adequately demonstrated between the market-image and the clinical-trial formulation for the 5 mg dosing, see Table 8 below.

Table 15 Statistical Analysis of Bioequivalence for Duvelisib Pharmacokinetic Parameters – Cohort 2, 5 mg in Study IPI-145-15

Parameter	Statistic	Market-image (Test)	Clinical-trial (Reference)
AUC_{inf} (h*ng/mL)	N	49	51
	Geometric LS Mean	581.1	562.6
	Geometric LS Mean Ratio (%)	103.28	
	90% CI of Ratio (%)	(99.25, 107.47)	
	N	50	51

Parameter	Statistic	Market-image (Test)	Clinical-trial (Reference)
AUC_{last} (h*ng/mL)	Geometric LS Mean	571.4	552.4
	Geometric LS Mean Ratio (%)	103.44	
	90% CI of Ratio (%)	(99.46, 107.58)	
C_{max} (ng/mL)	N	50	51
	Geometric LS Mean	209.2	217.0
	Geometric LS Mean Ratio (%)	96.41	
	90% CI of Ratio (%)	(88.88, 104.58)	

CI = confidence interval; LS = least squares; PK = pharmacokinetic; n = number of subjects in subset
Note: The AUC and C_{max} analyses were performed on ln-transformed parameters using a linear mixed-effect model with treatment, period, and sequence as fixed effects, and subject as a random effect. The analyses were based on subjects without missing data.
Source: Study IPI-145-15 CSR Table 14

Distribution

The mean Vss at steady state following IV dosing in healthy subjects were estimated to 12.3 L (Study IPI-145-05) and the mean apparent volume of distribution (Vss/F) was 28.5 L at 25 mg twice daily (BID) in subjects with advanced hematologic malignancies (Study IPI-145-02). Steady state plasma concentration for duvelisib (BID dosing) was reached on or prior to day 11.

The estimated whole blood to plasma duvelisib ratio of ~0.5 from the same study indicates a limited distribution to blood cells.

In vivo protein binding of duvelisib was comparable in plasma obtained from subjects with hematologic malignancies and healthy subjects (Report IPI-145-016). There was a tendency of a higher free fraction of duvelisib in subjects with severe hepatic impairment (2.1%) compared to healthy subjects (1.0%) (Report IPI-145-014).

Elimination

In healthy subjects, mean clearance (CL) was estimated to 4.1 L/h with a half-life (t½) of 9 hours. Following oral dosing in patients with advanced hematologic malignancies, mean duvelisib apparent clearance and terminal $t_{½}$ for 25 mg BID were 4.2 L/h (57% CV) and 4.7 h (57% CV), respectively.

Excretion
Duvelisib and its metabolites are primarily excreted in faeces with minimal renal excretion. The total recovery of administered radioactivity (mean ± SD) was 92.5 ± 2.2%; with 79.0 ± 2.2% and 13.5 ± 1.8% in faeces and urine, respectively. In faeces, 10.9% of the radioactivity was recovered as unchanged duvelisib (Report RPT03070) and less than 1% of the administered dose was excreted in urine as unchanged duvelisib.

Metabolism
CYP3A4 is the primary cytochrome P450 in the metabolism of duvelisib. In addition, CYP1A2, CYP2B6 and/or CYP2C8 may to a lesser extent be involved in the formation of selected IPI-145 metabolites, whereas duvelisib is not metabolised by CYP2C9, 2C19, 2D6, or 2E1.

Metabolite profiling (report RPT03070) of plasma, urine and faeces was conducted in study IPI-145-05 following administration of 25 mg ^{14}C-duvelisib. More than 85% of the radioactivity in plasma has been identified with IPI-656 (45.8%), duvelisib (37.7%) and M7 (4.0%), a glucuronide metabolite. These three moieties were the most abundant in urine ranging 1 to 2% of the administered dose. More than 25 radioactivity peaks or regions were observed in faeces. Even though duvelisib and IPI-656 were the most abundant moieties, they accounted for ~12% and 17.7% of the administered dose in the excreta, respectively. The mono-oxygenated metabolite M20 and the glucuronide metabolite M7 appear to be the less important pathways with recoveries of 7.4% and 3.8% respectively, while many more metabolites were recovered at low levels 2-3% or less (CYP1A2, 2B6 and 2C8 involvement).
Mean metabolite (IPI-656) to parent (M/P) ratio based on AUC varied between 0.88 to 1.3 in healthy subjects following single dose and between 0.99 and 1.21 at steady-state (studies IPI-145-01, IPI-145-05, M15-412). In patients, metabolite to parent (M/P) ratio at steady-state was 0.95 and 1.0 for 25 mg bid and 1.10 for 75 mg bid (study IPI-145-02 and M15-460).

Inter-conversion
As no metabolic transformation occurs at or near the stereocentre of duvelisib, metabolism-dependent chiral conversion is considered unlikely.

Pharmacokinetics of metabolite IPI-656
In vitro investigations have demonstrated IPI-656 to be pharmacologically inactive ((7244-fold less potent against PI3K-δ compared to duvelisib) at relevant exposure levels in terms of effect on PI3K-δ, and thus, of limited clinical relevance.
Pharmacokinetics of IPI-656 has been evaluated in most studies alongside the pharmacokinetics of duvelisib. IPI-656 appeared slowly in the systemic circulation. IPI-656 median Tmax was approximately 4-6 h. After reaching peak levels, mean IPI-656 concentration values declined in an apparent mono-exponential manner. Mean t1/2 ranged from 13.7 to 15.7 h. Following multiple oral administrations of duvelisib IPI-656 exhibited flat plasma concentration-time profiles. IPI-656 plasma exposure AUC0-12 was approximately 3 to 4 fold higher at steady state compared to first administration but there was no indication for a time dependent pharmacokinetics of IPI-656 (study IPI-145-02).

Dose proportionality and time-dependency

Exposure (measured as Cmax and AUC) increased proportionally over a dose range of 1 to 30 mg (single dose) and 1 to 5 mg BID (multiple dose) in healthy subjects. The mean IPI-145 plasma concentration-time profiles on Days 1 and 14 showed a dose-dependent increase in plasma concentrations following administration of increasing multiple doses of IPI-145.
Dose-proportionality was explored by plotting the

Figure 9 Dose-normalised exposure parameters Cmax and AUC0-tau vs 1, 2 and 5-mg BID dosing regimens

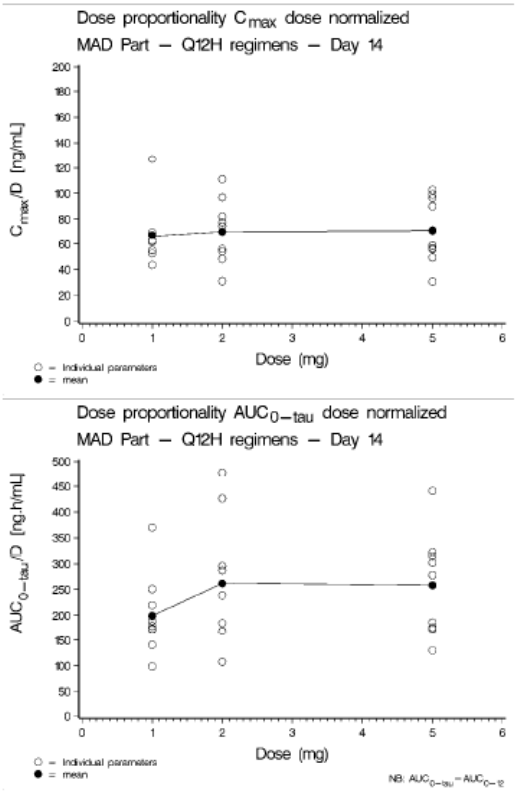
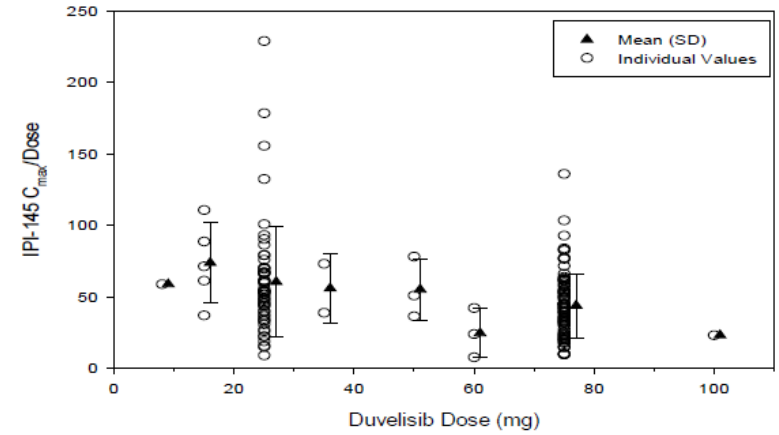
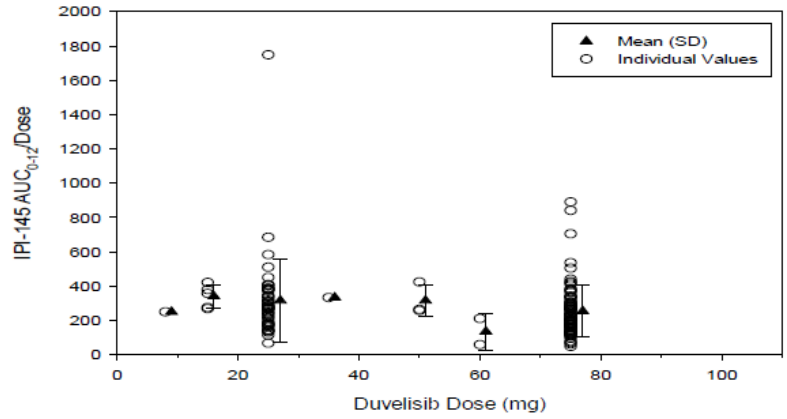


Figure 10 Individual and mean-dose normalised PK parameters Cmax and AUC 0-12 of duvelisib vs dose following multiple oral dose administration of duvelisib on cycle 2, day 1 to subjects with advanced haematologic malignancies in study IPI – 145 -02

C_{max}/Dose vs Dose



AUC_{0-12}/Dose vs Dose



AUC_{0-12} = area under the concentration vs time curve from 0 to 12 hours; C_{max} = maximum observed plasma concentration; SD = standard deviation
Source: Report INFI-PCS-108 Figure 5

Duvelisib exposure increased upon BID dosing (AUC0-12ss:AUC0-12 first dose); an increase of 1.65 to 1.83 was observed in healthy subjects over the dose range 1-5 mg (study IPI-145-01) and a 1.9 fold increase was determined for patients treated with 25 mg duvelisib BID (study IPI-145-02).

Intra- and inter-individual variability

Mean pharmacokinetic Cmax and AUC values of duvelisib are consistent between studies and formulations. Between-subject variability (CV%) of AUC and Cmax was moderate to high 33% to 51% and 34% to 49%, respectively, for groups with 10 subjects or more.

PopPK analysis estimated a between-subject variability (CV%) of AUC and Cmax at 50 to 70% in subjects with haematological malignancies.

Pharmacokinetics in target population

Pharmacokinetics of duvelisib in subjects with advanced hematologic malignancies was investigated by non-compartmental analysis in study IPI-145-02 and study M15-460 (Japanese patients, N=7) and by population PK analyses.

Table 16 PK parameters of duvelisib for the 25 mg and 75 mg dose (study IPI-145-02)

	25 mg duvelisib		75 mg duvelisib	
	Single dose	Multiple dose	Single dose	Multiple dose
Number of subjects	N=65	N=57	N=122	N=90
AUC0-12 (ng.h/mL)	4784 (71%)	7888 (77%)	12313 (65%)	19059 (59%)
AUC0-inf (ng.h/mL)	7098 (104%)	-	19153 (81%)	-
Cmax (ng/mL)	1062 (70%)	1511 (64%)	2630 (60%)	3294 (51%)
Tmax (h)	2.0 (0.5-6.0)	1.4 (0.5-6.0)	1.2 (0.5-25)	1.1 (0.0-8.0)
t1/2 (h)	6.8 (46%)	4.7 (57%	7.7 (45%)	6.5 (202%)
Cl/F (L/h)	5.6 (70%)	4.2 (56%)	6.8 (86%)	5.3 (61%)
Vss/F (L)	4.7 (78%)	29 (62%)	64 (104%)	41 (71%)
Rac [a]		1.94 (51%)		2.03 (68%)
LI [b]		1.40 (45%)		1.33 (53%)

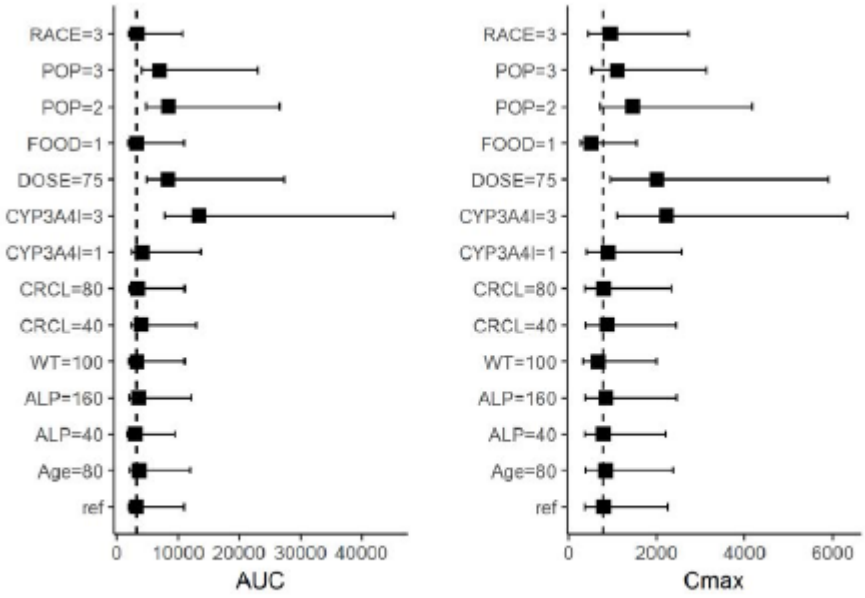
a) Rac = AUC0-12ss:AUC0-12 first dose

b) LI = AUC0-12ss:AUC0-inf first dose

Special populations

The potential impact of various intrinsic factors, including age, gender, race and bodyweight as well as renal or hepatic impairment populations have been examined by the use of population PK analyses. In addition, a dedicated clinical study has examined the pharmacokinetics of duvelisib in patients with impaired hepatic function, and furthermore, a PBPK model was applied for the estimation of impact of hepatic impairment on the exposure of IPI-145 and its primary metabolite IPI-656 following multiple oral doses of IPI-145 25 mg BID.

Figure 11 Simulated AUC and Cmax for typical population (steady state)



ref - reference population: healthy (POP=1), Caucasian (RACE=1), age=50 yrs, body weight = 70kg, ALP=80, CRCL=100, CYP3A4I=0 (No), DOSE=25, FOOD=0 (fasted).

Hepatic impairment

Study IPI-145-014 was an open-label study to evaluate the effect of hepatic function on the pharmacokinetics of duvelisib. Twenty-four (24) subjects were enrolled into 4 hepatic groups (n = 6/group) based on Child-Pugh classification. The groups were healthy, mild, moderate, or severe hepatic impairment. All subjects had hepatic impairment > 1 year with an aetiology of chronic alcoholism and/or chronic viral hepatitis (B or C). Subjects received a single dose of duvelisib 25 mg. PK blood samples were collected up to 72 hours.

Geometric mean $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were minimally changed in subjects with hepatic impairment compared to healthy subjects. When compared to healthy subjects, $AUC_{0\text{-}\infty}$ values represented an 11%, 6%, and 19% decrease in subjects with mild, moderate, and severe hepatic impairment, respectively. The ratio of metabolite to parent AUC decreased with increased degree of hepatic impairment (mild: 1.03, moderate: 0.81, severe: 0.72).

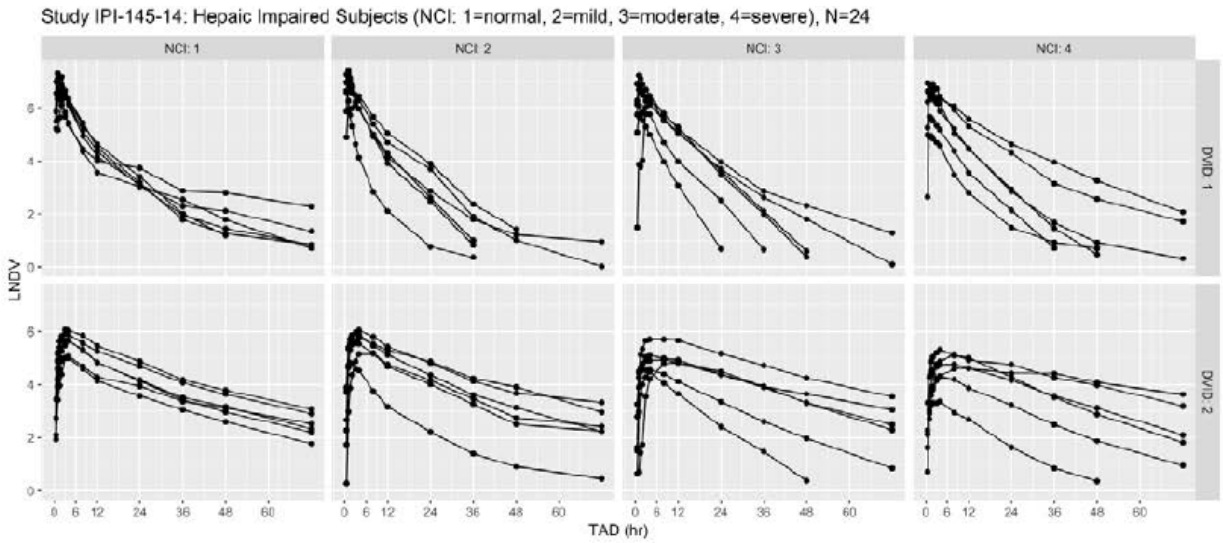


Figure 12 Hepatic impairment (study IPI-145-14). Duvelisib (upper panel) and metabolite IPI-656 (lower panel) mean plasma concentrations versus time (individual log (plasma concentrations)

Using PBPK modelling duvelisib exposure following multiple dosing was predicted. The PBPK model developed to predict the exposure of IPI-145 and IPI-656 following oral administration and the effect of ketoconazole on the pharmacokinetics of duvelisib, was used together with the Cirrhosis module of SimCYP. PBPK modelling predicted increases in geometric mean AUC for IPI-145 in subjects with mild, moderate and severe HI relative to healthy age matched subjects were consistent with observed data; predicted values were 0.98-, 1.08- and 1.03-fold, respectively, *versus* observed values of 0.89-, 0.94- and 0.81-fold, respectively. Predicted geometric mean AUC ratios for IPI-656 in mild, moderate and severe HI relative to healthy age matched subjects were 1.05, 0.67 and 0.41, respectively. These were similar to the observed values of 0.91, 0.75 and 0.48, respectively.
The PBPK model was then applied prospectively to predict the systemic exposure of IPI-145 and IPI-656 during multiple oral dose administration of IPI-145 25 mg BID in subjects with mild, moderate and severe HI. Geometric mean Cmax and AUC ratios for IPI-145 (relative to healthy aged matched subjects) were 0.83 and 0.89, 0.76 and 0.91, and 0.60 and 0.76, respectively. Geometric mean AUC ratios for IPI-656 (relative to healthy aged matched subjects) were 1.03, 0.65 and 0.40, respectively.

Renal impairment
No specific PK study has been performed in subjects with renal impairment (see Discussion on Clinical Pharmacology).

Gender, bodyweight, race, and age
The results from the population PK analysis point to no clinically significant differences in the PK parameters Cmax and AUC across subjects based on gender, bodyweight, race or age, which is considered reassuring.

Table 17 Older patients included in the clinical pharmacology studies

	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 (N=158)	64/158	44/158	3/158
Non-controlled trials (N=284)	102/284	52/284	5/284

Interactions

Human clinical DDI studies investigating the impact of ketoconazole (CYP3A4 inhibitor), rifampin and etravine (CYP3A4 inducers) on duvelisib PK as well as the impact of duvelisib on midazolam (CYP3A4 substrate) conducted were:

- Effect of a strong CYP3A4 inhibitor (ketoconazole) on single dose duvelisib (study IPI-145-01)
- Effect of a strong CYP3A4 inducer (rifampicin) on single dose duvelisib (study IPI-145-11)
- Effect of a moderate CYP3A4 inducer (etravirine) on single dose duvelisib (study IPI-145-131)
- Effect of duvelisib at steady-state on a CYP3A4 substrate (midazolam) (study IPI-145-10)

In addition, PBPK simulations were performed to evaluate the impact of CYP3A4 inhibitors and CYP3A4 inducers on duvelisib PK as well as the impact of duvelisib on CYP3A4 and CYP2C8 substrates under steady-state conditions.

CYP3A4 inhibitors

Physiologically-based PK (PBPK) simulations were performed to predict the impact of cytochrome P450 (CYP) 3A4 inhibitors and inducers on duvelisib PK under steady-state conditions. The predicted mean AUC ratio of IPI-145 after a single oral dose of 10 mg in healthy subjects as a consequence of co-administration of ketoconazole (200 mg BID) was 3.45, which was consistent with the observed value of 3.95 in the DDI study. Multiple oral doses of 25 and 75 mg BID IPI-145 in oncology patients with concomitant ketoconazole (200 mg BID) was predicted to cause increases in IPI-145 exposure of approximately 1.59- and 1.45-fold, respectively, whereas predicted mean AUC ratios of IPI-145 at doses of 25 and 75 mg BID after coadministration the moderate CYP3A4 inhibitor fluconazole (200 mg QD) were 1.34- and 1.29-fold, respectively.

CYP3A4 inducers

The predicted mean AUC ratio of IPI-145 after a single oral dose of 25 mg in healthy subjects as a consequence of co-administration of the strong CYP3A4 inducer rifampicin (600 mg QD) was 0.29, which was reasonably consistent with the observed value of 0.18.

CYP3A4 substrates

Application of the IPI-145 and IPI-656 models to predict the increase in exposure of midazolam (CYP3A4 substrate) after a single oral dose of 2 mg in healthy subjects as a consequence of coadministration of IPI-145 (25 mg BID for 5 days), resulted in a predicted geometric mean AUC ratio of 4.85, which was in good

agreement with the observed value of 4.29. Application of the IPI-145 and IPI-656 models at doses of 25 and 75 mg BID IPI-145 to predict the likely outcomes of interaction with midazolam in oncology patients indicated increases in midazolam exposure of approximately 5.82- and 7.37-fold, respectively

CYP2C8 substrates

PBPK simulations were used to assess the effect of duvelisib on two CYP2C8 substrates, repaglinide and rosiglitazone. The predicted AUC ratios of rosiglitazone with coadministration of duvelisib 1, 5, and 25 mg BID in healthy subjects were 1.00, 1.00 and 1.02, respectively. Similarly, the predicted AUC ratios of repaglinide with coadministration of duvelisib 25 mg BID and 75 mg BID in subjects with hematologic malignancies were 1.62 and 1.72, respectively.

Impact of gastric pH on duvelisib absorption

Duvelisib is a weak base (pKa of 3.9) with pH-dependent solubility. Solubility is reduced with increased pH from 1.3 to 3.9 and a GastroPlus model with PBPK simulations was used to assess the impact on duvelisib absorption and thus exposure with increased pH. Increased gastric pH from 1.3 to 5 was predicted to reduce the absorption of duvelisib with up to ≈ 25%. In addition, *in vitro* data has demonstrated pH levels >3 to compromise duvelisib solubility. Based on scientific literature, proton pump inhibitor treatment is known to elicit an increase in gastric pH to > 4 for a substantial share (50-80%) of the day. However, popPK and efficacy data do not indicate an effect on AUC of duvelisib by PPIs and did not indicate any impact on the efficacy of duvelisib from coadministration of PPIs.

Contraceptives

No interaction studies with oral contraceptives have been conducted (see discussion on Clinical Pharmacology).

2.4.3. Pharmacodynamics

Mechanism of action

Duvelisib (IPI-145) is an oral, dual inhibitor of class I phosphoinositide-3-kinase (PI3K)-δ and PI3K-γ being developed for the treatment of patients with previously treated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), and follicular lymphoma (FL). PI3K-δ inhibition targets the survival and proliferation of malignant B cells, such as those derived from CLL patients. In contrast, PI3K-γ inhibition blocks the recruitment and differentiation of CD4+ T cells and macrophages, which in turn support the proliferation and survival of malignant B cells.

Primary and Secondary pharmacology

The exposure-response (ER) analysis was based on PK, biomarker, efficacy, and safety data collected from Studies IPI-145-01, IPI-145-02, IPI-145-06, and IPI-145-07. Population PK models were utilised to study exposure-response (ER) analyses and to perform simulations for exposure-pharmacodynamic biomarkers. The application of the PD biomarkers CD63 expression, phosphorylated AKT, and Ki67 for examination of the relationship between PK exposure and efficacy is considered reasonable.

Proof of inhibition of PI3K-δ by duvelisib came from reduction in the level of phosphorylated AKT (p-AKT), a direct downstream effect of PI3K inhibition, in the dose ascending study IPI-145-02. p-AKT inhibition was rapid and sustained up to 24h following single dose administration and was comparable between 25 and 75 mg BID dose levels. An Emax model was used to describe the relationship between p-AKT concentrations and plasma duvelisib concentrations. Maximal p-AKT inhibition at day 1 estimated was 85% (2.7% CV) and at cycle 2 day 1 66% (7.7% CV). The estimated plasma IPI-145 concentration that would result in 50% inhibitory effect (EC50) on p-AKT following a single dose was estimated to be 6.07 ng/mL (Cycle 1, Day 1) and was estimated to be 26.4 ng/mL following multiple doses (Cycle 2, Day 1).
Ex vivo inhibition of basophil PI3K-δ typically reached a maximum inhibition in blood samples obtained at 1 to 2 hours following single dose period (studies IPI-145-01 and 02). In healthy subject a dose response was up to 10 mg duvelisib but in patients' blood samples there was no difference between 25 mg and 75 mg duvelisib treatment apparent. The percent inhibition of blood PI3K-γ was highly variable following single and multiple dose administration and did not appear to be related to dose (study IPI-145-02).

Maximal p-AKT and Ki67 inhibition were observed at plasma concentrations achieved at the 25 mg BID dose, with no additional suppression of p-AKT at higher doses/plasma concentrations.
A simulation was applied for prediction of percentage coverage above the targeted threshold (IC50) for the biomarkers p-AKT, PI3K-δ and PI3K-γ. The duvelisib 25 mg BID regimen was estimated to ensure >99% coverage above the IC50 threshold for p-AKT and PI3K-δ, and ~80% for PI3K-γ. The 15 mg BID dosing elicited similar coverage compared to 25 mg BID in terms of p-AKT and PI3K-δ, whereas the 48% coverage above threshold for PI3K-γ was substantially reduced compared to the 25 mg dosing. The following table summarises the percentage of coverage above threshold at steady state for each biomarker.

Table 18 Percentages (%) Coverage for Biomarkers Threshold (IC_{50} orIC_{90}) at Steady-State

Biomarker	15 mg BID		25 mg BID	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}
p-AKT	99.8	78.6	99.9	92.8
PI3K-δ (CD63)	99.3	60.0	99.9	84.7
PI3K-γ (CD63)	48.3	0.0	79.5	0.0

BID = twice daily; C = cycle; D = day; IC_{50} = half-maximal inhibitory concentration; IC_{90} = 90% inhibitory concentration; p-AKT = phosphorylated AKT; PI3K = phosphoinositide-3-kinase
Source: Report VER_DUV_DEC2017_PPK

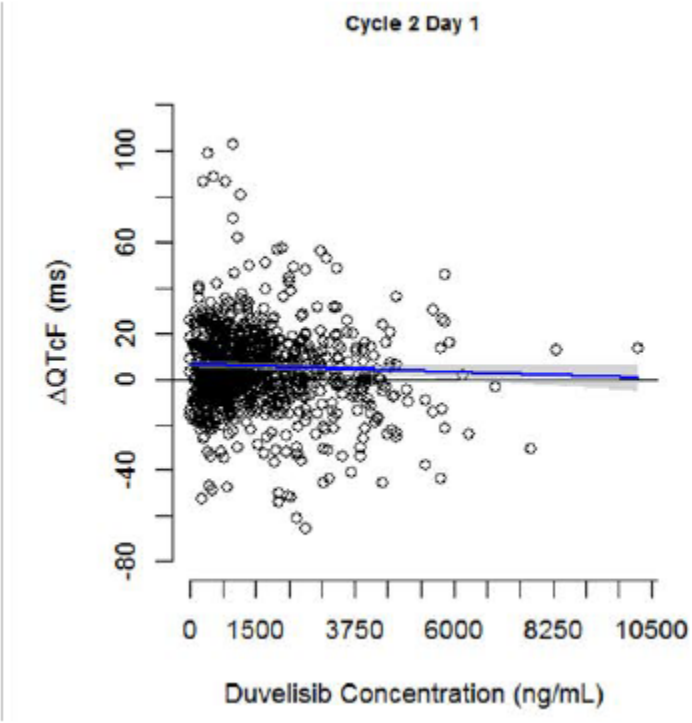
Secondary pharmacology

Cardiac repolarisation by QT interval evaluation

Duvelisib was anticipated to have a very low potential for QTc interval prolongation on the basis of the *in vitro* assessment of hERG potassium current inhibition as well as cardiovascular safety pharmacology study data in monkeys showing no adverse effects in the cardiovascular system with doses up to 150 mg/kg.
The clinical development programme for duvelisib included no thorough QT/QTc study and the potential for duvelisib to prolong the QTc interval was assessed based on triplicate ECG data collected from Studies IPI-145-01 (healthy subjects) and IPI-145-02 (patients with hematologic malignancies) collected pre-dose and following single/multiple dosing of duvelisib.

Based on the dataset from study IPI-145-02 including 2035 datapoints from 210 subjects with advanced hematologic malignancies, duvelisib exposure-QTc relationship was described by a linear drug-effect model with a negative slope (-0.000574 ms per ng/mL of duvelisib) and a positive intercept (3.76 ms). The lack of statistically significant slope (p = 0.1307) indicate a lack of relationship between duvelisib exposure and QTc prolongation (Report INFI-PCS-104 and Report VS27000006A).
Overall, it is considered justified that duvelisib holds a limited and clinically non-significant potential for QTc prolongation.

Figure 13. Model-Predicted C-QTc Relationship for Protocol IPI-145-02



Mean (solid line) and 90% confidence intervals (shaded area) predictions are shown overlaid with observed data (open circles). The mean prediction shown does not include the effect of nominal time after dose or study visit but represents the drug effect only. The shaded area represents model uncertainty and does not incorporate between subject or residual variability.

Pharmacodynamic interactions with other medicinal products or substances

No pharmacodynamic drug interaction studies were submitted. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or systemic steroids > 20 mg prednisone (or equivalent) QD was an exclusion criterion in study IPI-145-07.

Relationship between plasma concentration and effect

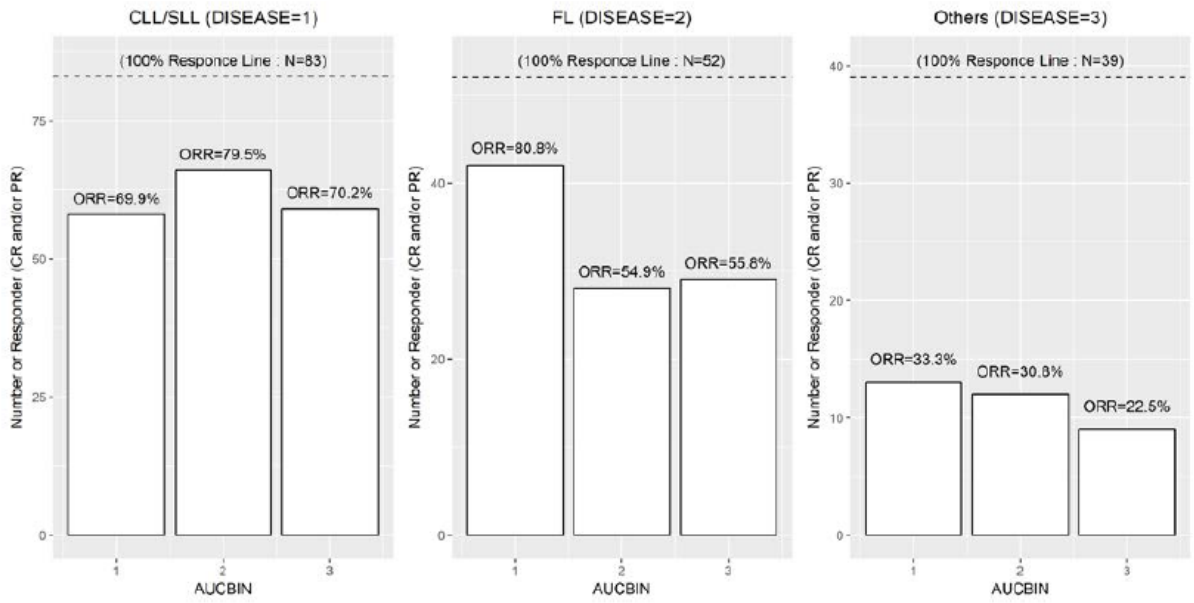
The exposure-response analysis utilised pooled data collected from 5 studies (1 Phase 1 study and 4 Phase 2/3 studies) including patients with advanced hematologic malignancies, and patients with relapsed or refractory leukaemia or lymphoma. The final ER database for analysis contained data from 552 subjects.

In terms of safety, it is considered justified that no clear correlation exists between duvelisib exposure and occurrence of the majority of AEs of special interest.

In terms of efficacy, the data do not support a higher dose than 25 mg BID.

Graphical evaluations of ER for ORR by DISEASE are shown in Figure 8 and these point to a lack of relationship between exposure and ORR.

Figure 14 ORR by AUC tertiles in CLL, FL and other studies



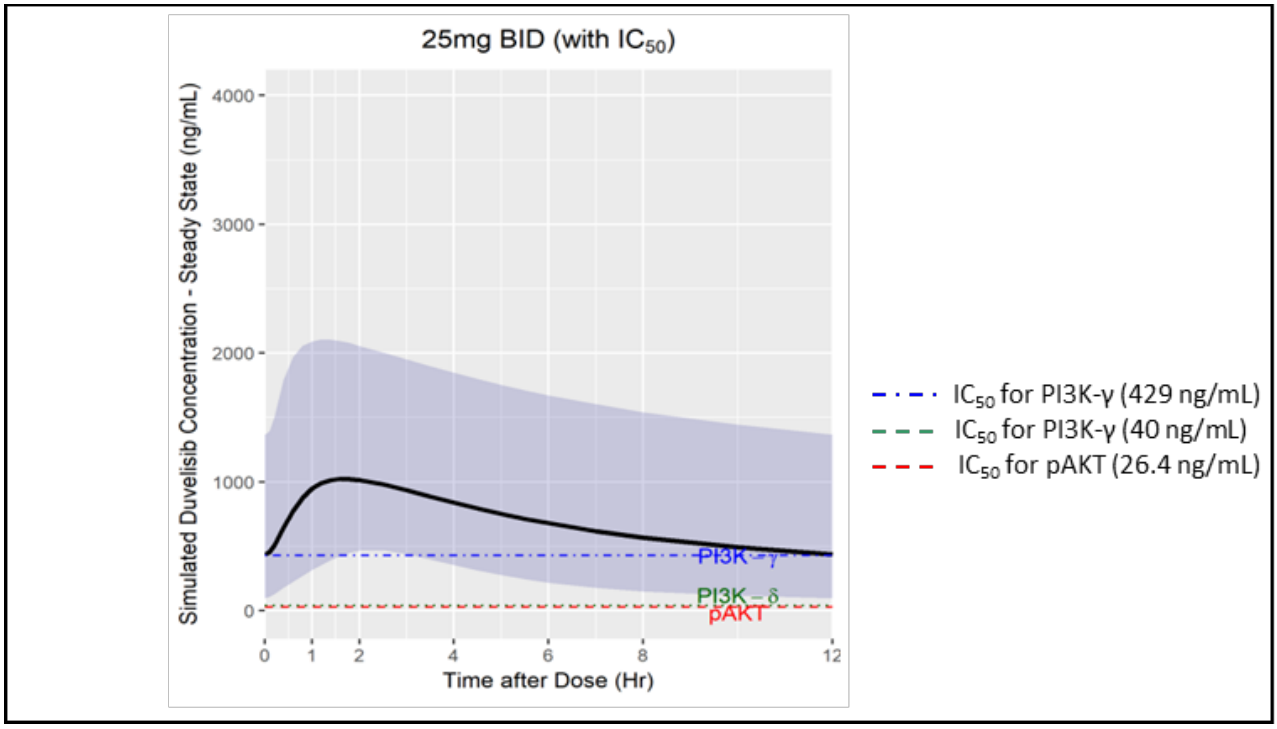
DISEASE – disease category (1=CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma, 2=FL, follicular lymphoma, 3=Others), ORR – Objective response rate, AUCBIN – time-averaged area under the concentration time curve with parent (duvelisib) by tertiles, CR – compelte response, PR – partial response, N - number.

Source: ORR_sub-analysis_byDISEASE.png, ORR_analysis_output.txt

Note: AUCP was binned into three equal number of subjects (tertiles), DISEASE=1: AUCBIN cut-off at [< 6709], [≥6709, < 9984], [≥9984], DISEASE=2: AUCBIN cut-off at [< 7125], [≥7125, < 9725], [≥9725], and DISEASE=3: AUCBIN cut-off at [< 11164], [≥11164, < 21658], [≥21658] (nanogram*hour/milliliter).

Duvelisib has a mean plasma t1/2 of 6.8 hours and BID administration maintains trough concentrations above the targeted IC50 for PI3K-δ and PI3K-γ inhibition. Pharmacodynamic analyses on biomarkers as well as pharmacokinetic analyses in terms of trough concentrations above the targeted IC_{50} for PI3K-δ and PI3K-γ inhibition are shown in Figure 15.

Figure 15 Simulated Duvelisib Steady-State Plasma Concentration at 25 mg BID and Inhibition of pAKT, PI3K-δ, and PI3K-γ



BID = twice daily; IC_{50} = half-maximal inhibitory concentration; p-AKT = phosphorylated AKT; PI3K = phosphoinositide-3-kinase

Note: The solid black line is the median of the simulated concentration, shared area is upper and lower 95th percentiles of simulated concentration.

Source: Report VER_DUV_DEC2017_PPK

2.4.4. Discussion on clinical pharmacology

The bioanalytical methods to determine duvelisib and IPI-656 concentrations in plasma and urine have been adequately validated. The time course of duvelisib PK was described by a 2-compartment model with first-order elimination and transit absorption model. The popPK model is used for exposure-effect relationships and it has been modified with a time-dependent clearance and using a first-order absorption (ka). The model showed successfully convergence. There remains a trend for dose dependency, but the model describes the elimination of the 25 mg adequately. The pharmacokinetics of the metabolite in healthy subjects is better described with the revised model.

PBPK modelling and simulations were aimed to support dosing recommendation for co-medication of duvelisib with strong CYP3A4 inhibitors.

In vivo DDI studies with ketoconazole, fluconazole, and midazolam were used to verify the model. Following extensive evaluation by means of sensitivity analyses the PBPK model with a fixed fraction absorbed was considered fit for predictions of the effect of moderate and strong CYP3A4 inhibitors on the exposure of duvelisib under steady-state conditions.

The PBPK model was also used to assess the inhibition potential of duvelisib and IPI-656 on CYP3A4 or CYP2C8 substrates. Although a qualification on CYP2C8 inhibition should preferably conducted with more substrates and inhibitors as indicated in the guideline on the reporting of PBPK modelling and simulation (EMA/CHMP/458101/2016, mechanistically the lack of CYP2C8 inhibition is in line with PBPK modelling on CYP3A4 inhibition (which was verified by DDI studies with midazolam and ketoconazole). The PBPK model is considered fit for predictions of the effect of duvelisib as perpetrator.

Absorption, distribution, metabolism, and excretion of duvelisib have overall been adequately described based on studies in healthy subjects. The pharmacokinetic characteristics include a tmax of ~1 hour, an absolute bioavailability of 42% with no clinically relevant effect of concomitant food, volume of distribution at steady state of 12.3 L, a whole blood to plasma duvelisib ratio of ~0.5 indicating a limited distribution to blood cells. Duvelisib plasma protein binding using an equilibrium dialysis method at 37°C was 95.9% at 1 µM (Report 346N-001). Using rapid equilibrium dialysis (RED) methodology and liquid chromatography-tandem mass spectrometry (LC-MS/MS) for detection, duvelisib plasma protein binding was 98.7% at 1 µM and 10 µM.

CYP3A4 is the primary cytochrome P450 in the metabolism of duvelisib with the major metabolite IPI-656 being pharmacologically inactive at relevant exposure levels, and thus, of limited clinical relevance. CYP3A4*22 is associated with low hepatic CYP3A4 expression and activity, however, the impact of the CYP3A4*22 allele to increase duvelisib exposure may be limited because duvelisib is a low extraction drug and multiple pathways contribute to the elimination of duvelisib. Duvelisib and its metabolites are primarily excreted in faeces with minimal renal excretion. In subjects with advanced hematologic malignancies, the volume of distribution was reported to be 28.5 L and the t½ 4.7 hours at steady-state.

In healthy subjects (study 01, M15-412), accumulation of duvelisib was ~1.5 comparing AUCtau (multiple dose) with AUC0-inf (single dose) in the dose range 1 to 5 mg bid. This indicates a change in pharmacokinetics with repeated dosing, which may be caused by time-dependent inhibition of CYP3A4 by duvelisib.

Duvelisib has one chiral centre and is administered as S-duvelisib. As no metabolic transformation occurs at or near the stereocentre of duvelisib, metabolism-dependent chiral conversion seems unlikely.

In vitro studies demonstrated CYP3A4 to be the primary CYP enzyme responsible for duvelisib metabolism with both duvelisib and IPI-656 being determined as direct inhibitors of CYP2C8 and CYP3A4 as well as metabolism-dependent inhibitors of CYP3A4. The results from *in vitro* studies indicate a low likelihood for DDIs between duvelisib and IPI-656 and substrates as well as inhibitors of intestinal, renal, or hepatic transporters.

Relevant human clinical DDI studies investigating the impact of ketoconazole (CYP3A4 inhibitor), rifampin and etravine (CYP3A4 inducers) on duvelisib PK as well as the impact of duvelisib on midazolam (CYP3A4 substrate) were conducted based on the findings from these non-clinical investigations; Study on the effect of a strong CYP3A4 inhibitor (ketoconazole) on single dose duvelisib; a study on the effect of a strong CYP3A4 inducer (rifampicin) on single dose duvelisib , a study on the effect of a moderate CYP3A4 inducer (etravirine) on single dose duvelisib and a study on the effect of duvelisib at steady-state on a CYP3A4 substrate (midazolam).

In addition, PBPK simulations were performed to evaluate the impact of CYP3A4 inhibitors and CYP3A4 inducers on duvelisib PK as well as the impact of duvelisib on CYP3A4 and CYP2C8 substrates under steady-

state conditions. The applicant has based on the PBPK model reported co-administration of duvelisib 20 mg BID with the moderate CYP3A inhibitor fluconazole to elicit similar IPI-145 exposures compared to 25 mg BID duvelisib monotherapy; hence, no dose adjustment of duvelisib is necessary in case of concomitant use of moderate CYP3A4 inhibitors. The above effects are reflected in the SmPC including dose recommendations for concomitant use with strong 3A4 inhibitors.

Co-administration with a strong CYP3A inducer decreases duvelisib area under the curve (AUC), which may reduce COPIKTRA efficacy. In the SmPC section 4.5 it is recommended to avoid co-administration of COPIKTRA with strong CYP3A4 inducers. In terms of CYP3A4 substrates the SmPC states that "Co-administration with COPIKTRA increases AUC of a sensitive CYP3A4 substrate, which may increase the risk of toxicities of these drugs. Consider reducing the dose of the sensitive CYP3A4 substrate and monitor for signs of toxicities of the co-administered sensitive CYP3A substrate". The recommendations in terms of reduced dosing of sensitive CYP3A4 substrates as well as monitoring for signs of toxicity when in case of concomitant treatment with duvelisib are considered reasonable.

In vitro data suggested that duvelisib and IPI-656 are direct inhibitors of CYP2C8 enzyme. No clinical study was conducted due to the limited number of narrow therapeutic drugs predominantly metabolised by CYP2C8. Instead, PBPK simulations were used to assess the effect of duvelisib on two CYP2C8 substrates, repaglinide and rosiglitazone. The predicted AUC ratios of rosiglitazone with coadministration of duvelisib 1, 5, and 25 mg BID in healthy subjects were 1.00, 1.00 and 1.02, respectively. Similarly, the predicted AUC ratios of repaglinide with coadministration of duvelisib 25 mg BID and 75 mg BID in subjects with hematologic malignancies were 1.62 and 1.72, respectively.

No information regarding CYP2C8 substrates is included in section 4.5 of the proposed SmPC. No interaction studies with oral contraceptives have been conducted. For the current indication no study will be requested as the mean age of the patient population was 64 years. As effectiveness of oral contraceptives is uncertain, it has been adequately described in section 4.6 of the SmPC that women using hormonal contraceptives should add a barrier method. This is acceptable, and the absence of an interaction study with oral contraceptives has been added in section 4.5 of the SmPC.

Based on the dataset from study IPI-145-02 including 2035 datapoints from 210 subjects with advanced hematologic malignancies, duvelisib exposure-QTc relationship was described by a linear drug-effect model with a negative slope (-0.000574 ms per ng/mL of duvelisib) and a positive intercept (3.76 ms). The lack of statistically significant slope ($p = 0.1307$) indicate a lack of relationship between duvelisib exposure and QTc prolongation. Overall, it is considered justified that duvelisib holds a limited and clinically non-significant potential for QTc prolongation.

A dedicated clinical study examined the pharmacokinetics of duvelisib in patients with impaired hepatic function, whereas the potential impact of various additional intrinsic factors, including age, gender, race and bodyweight as well as renal impairment have been examined by the use of population PK analyses. A similar exposure seems to exist in patients with hepatic impairment compared to healthy subjects.

No specific PK study has been performed in subjects with renal impairment, but less than 1% of an administered dose of duvelisib is excreted in urine as unchanged duvelisib. The results from the population PK analyses point to no clinically significant differences in PK parameters across subjects based on gender, bodyweight, race or age, which is considered reassuring. Based on the provided data, the statement in the SmPC regarding dose adjustment in renal impairment is considered acceptable.

The population data from the clinical studies including hematologic patients estimated similar duvelisib exposure in patients with mild or moderate renal impairment as compared to healthy subjects, which is considered reassuring. Duvelisib and metabolites are primarily excreted in faeces and < 15 % recovered in urine. No dose adjustment is recommended for subjects with mild and moderate impairment; however, caution should be taken in subjects with severe and end-stage renal impairment (with or without dialysis). The weight range in the clinical studies is wide and a fixed dose as proposed is considered acceptable.

The results from *in vitro* studies indicated a low likelihood for DDIs between duvelisib and IPI-656 and substrates as well as inhibitors of intestinal, renal, or hepatic transporters.

Relevant human clinical DDI studies as well as PBPK modelling were performed to investigate the impact of ketoconazole (CYP3A4 inhibitor), rifampin and etravine (CYP3A4 inducers) on duvelisib PK as well as the impact of duvelisib on midazolam (CYP3A4 substrate) and repaglinide and rosiglitazone (CYP2C8 substrates). The main route of elimination for duvelisib is metabolism followed by excretion in faeces. CYP3A4 is involved in formation of most metabolites including IPI-656, which is the major metabolite. The importance of CYP3A4 in the elimination of duvelisib was supported by the interactions with ketoconazole (strong CYP3A4 inhibitor), which increased duvelisib exposure approximately 4-fold. Due to time-dependent CYP3A4 auto-inhibition, duvelisib susceptibility to moderate and strong CYP3A4 inhibitors is decreased under steady-state conditions and it is recommended to reduce the dose of duvelisib to 15 mg BID when co-administration with strong CYP3A4 inhibitors is required. Co-administration of rifampicin (strong CYP3A4 inducer) decreased duvelisib exposure by 5-fold. Co-medication with strong CYP3A4 inducers is not recommended. These interactions have been adequately reflected in the SmPC. Due to the higher duvelisib and IPI-656 exposures in patients compared to healthy subjects, midazolam exposure is estimated to increase > 5-fold. Hence, duvelisib and its major metabolite, IPI-656, are considered strong CYP3A4 inhibitors and co-administration may lead to increased serum concentrations of the other. Concomitant treatment of duvelisib with sensitive CYP3A substrates should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.

PBPK modelling was used to justify absence of *in vivo* drug-drug interaction studies with CYP2C8 substrates. Simulations showed a low probability for a clinically meaningful DDI between duvelisib and CYP2C8 substrates, hence a DDI study with a CYP2C8 substrate can be waived.

The SmPC has been adequately updated concerning the used of co administration of duvelisib with moderate CYP3A inducers.

Duvelisib (IPI-145) is an oral, dual inhibitor of class I phosphoinositide-3-kinase (PI3K)-δ and PI3K-γ. The exposure-response (ER) analysis was based on PK, biomarkers (CD63 expression, phosphorylated AKT, and Ki67), efficacy, and safety data collected from studies IPI-145-01, IPI-145-02, IPI-145-06, and IPI-145-07. Population PK models were utilised to study exposure-response (ER) analyses and to perform simulations for exposure-pharmacodynamic biomarkers.

Maximal p-AKT as well as Ki67 inhibition were observed at plasma concentrations achieved at the 25 mg BID dose, with no additional suppression at higher doses/plasma concentrations. A simulation was applied for prediction of percentage coverage above the targeted threshold (IC50) for the biomarkers p-AKT, PI3K-δ and PI3K-γ. The duvelisib 25 mg BID regimen was estimated to ensure >99% coverage above the IC50 threshold for p-AKT and PI3K-δ, and ~80% for PI3K-γ. The 15 mg BID dosing elicited similar coverage compared to 25 mg BID in terms of p-AKT and PI3K-δ, whereas the 48% coverage above threshold for PI3K-γ was substantially reduced compared to the 25 mg dosing.

In terms of safety, it is considered justified that no clear correlation exists between duvelisib exposure and occurrence of the majority of AEs of special interest.

The clinical development programme for duvelisib included no thorough QT/QTc study, as it was argued by the applicant that the presented data provides sufficient evidence in terms of no duvelisib-mediated QTc prolongation at supratherapeutic doses. In study IPI-145-02 following multiple dosing with duvelisib up to 75 mg BID, there was no correlation between duvelisib or IPI-656 plasma concentrations and change in QTc interval. Overall, it is considered justified that duvelisib holds a limited and clinically non-significant potential for QTc prolongation.

Given the patient population likely to be taking this medicine will largely be elderly, the applicant was requested to investigate possibilities to administer the drug product to patients who have problems with swallowing the capsules. Based on the available clinical data (comparative plasma profiles for six healthy male subjects administered 25 mg duvelisib as capsules and 25 mg duvelisib as oral solution), the bioequivalence between the product administrated as whole capsule and the capsule content suspended in soft food cannot be concluded. In addition, as described in the Quality section, chemical stability studies of the drug substance in different types of soft food is missing. The potential for certain soft foods to be an effective means of oral delivery of the drug for patients with swallowing difficulties needs further investigation. Taking into account the *Reflection paper on the pharmaceutical development of medicines for use in the older population EMA/CHMP/QWP/292439/2017 (October 2020), and the draft guidance available from the US FDA, Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments (July 2018)*, the Sponsor expects that all the age levels in the geriatric population (as per ICH E7, people aged 65-74, 75-84 and 85+ years) would be included in any future proposed instructions on alternative methods of administration.

The selection of the BID dosing regimen was based on the PK properties of duvelisib observed in study IPI-145-02. Duvelisib has a mean plasma t1/2 of 6.8 hours and BID administration was chosen over QD administration to maintain trough concentrations above the targeted IC50 for PI3K-δ and PI3K-γ inhibition.

The selection of duvelisib 25 mg BID in CLL and FL was based on the efficacy, safety, and PD data obtained from Study IPI-145-02 (see also Clinical efficacy section); the 75 mg BID dose did not provide any additional clinical benefit compared to 25 mg BID. The selection of the 25 mg BID dose was further supported by the pharmacodynamic analyses on biomarkers as well as pharmacokinetic analyses in terms of trough concentrations above the targeted IC_{50} for PI3K-δ and PI3K-γ inhibition.

2.4.5. Conclusions on clinical pharmacology

Pharmacology of duvelisib and its major metabolite IPI-656 have been extensively characterised in both healthy subjects and subjects with advanced hematologic malignancies.

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

In order to explore alternative administration of duvelisib, the applicant will assess the potential for certain soft foods to be an effective means of oral delivery of the drug for patients with swallowing difficulties across all the age levels in the geriatric population (as per ICH E7, people aged 65-74, 75-84 and 85+ years) in order to improve future proposed instructions on alternative methods of administration. When supportive data have been obtained, a variation application will be submitted to revise the Product Information regarding additional advice on the method of administration.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The selection of the dose and regimen of duvelisib monotherapy for Phase 2 and 3 studies was based on available preclinical data and data obtained from two clinical studies, Study IPI-145-01 (a Phase 1 single and multiple ascending dose study in healthy subjects) and Study IPI-145-02 (a Phase 1 dose escalation and expansion study in subjects with advanced hematologic malignancies).

Selection of twice daily dosing

The selection of the twice daily dosing regimen was based on the pharmacokinetic properties of duvelisib observed in both IPI-145-01 and IPI-145-02. Duvelisib has a mean plasma half-life of 6.8 hours (Study IPI-145-01), and twice daily administration was chosen over once daily administration to maintain trough concentrations above the targeted IC50 for PI3K-δ and PI3K-γinhibition. The IC50 determinations were based on human whole blood assays, in which duvelisib was shown to inhibit PI3K-δ-specific degranulation of basophils with an average 50% inhibitory concentration (IC50) value of 96.1 nM, and PI3K-γ-specific degranulation of basophils with an average IC50 value of 1028 nM.

Selection of 25 mg BID

The selection of duvelisib 25 mg BID in CLL/SLL was based on the pharmacodynamic, efficacy, and safety data obtained from Study IPI-145-02 (n = 210). This study included a Dose Escalation Phase (3+3 design), in which duvelisib was administered from 8 mg to 100 mg BID, with 75 mg BID determined to be the maximum tolerated dose based on a 1-month observation period. This study also included several Expansion Cohorts in select hematologic malignancies where subjects received either 25 mg or 75 mg BID.

In this study, clinically meaningful activity was observed in subjects with relapsed/refractory CLL/SLL receiving 25 mg BID, with no demonstrable additional efficacy benefit attained with higher doses in either population.

Summary of Best Overall Response and Overall Response Rate (ATS) – Subjects with Relapsed/Refractory CLL/SLL:

	Duvelisib Dose BID				
	8 mg (N = 1)	15 mg (N = 2)	25 mg (N = 28)	75 mg (N = 24)	Total (N = 55)
Overall Response Rate (ORR) (CR + PR)					
ORR	1 (100)	1 (50.0)	16 (57.1)	13 (54.2)	31 (56.4)
95% Confidence Interval	(2.5, 100)	(1.3, 98.7)	(37.2, 75.5)	(32.8, 74.4)	(42.3, 69.7)
Best Overall Response					
Complete Response (CR)	0	0	1 (3.6)	0	1 (1.8)
Partial Response (PR)	1 (100)	1 (50.0)	15 (53.6)	13 (54.2)	30 (54.5)
Stable Disease (SD)	0	1 (50.0)	10 (35.7)	8 (33.3)	19 (34.5)
Progressive Disease (PD)	0	0	1 (3.6)	1 (4.2)	2 (3.6)
Unknown (UN)	0	0	1 (3.6)	2 (8.3)	3 (5.5)

2.5.2. Main studies

Main study in CLL - Study IPI-145-07 (DUO trial)

A Phase 3 Study of IPI-145 versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

Methods

Study Participants

The subject population included patients with relapsed or refractory CLL or SLL (as defined per IWCLL/IWG criteria). The key inclusion and exclusion criteria are presented below.

Key Inclusion Criteria

• Diagnosis of active CLL or SLL that meets at least one of the IWCLL 2008/IWG criteria for requiring treatment (Binet Stage ≥ B and/or Rai Stage ≥ I)

• Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy

• Not appropriate for treatment with a purine-based analogue regimen (per National Comprehensive Cancer Network or European Society for Medical Oncology guidelines), including relapse ≤ 36 month from a purine-based chemoimmunotherapy regimen or relapse ≤ 24 months from a purine-based monotherapy regimen

• Measurable disease with a lymph node or tumour mass > 1.5 cm in at least 1 dimension as assessed by computed tomography (CT)

• Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (corresponds to Karnofsky Performance Status ≥ 60%)

• Must have met the following laboratory parameters:

– Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3 × upper limit of normal (ULN)

– Total bilirubin ≤ 1.5 × ULN

– Serum creatinine ≤ 2.0 × ULN

– Haemoglobin ≥ 8.0 g/dL with or without transfusion support

– Platelet count ≥ 10,000 µL with or without transfusion support

Key Exclusion Criteria

• History of Richter's transformation or prolymphocytic leukaemia

• Autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) that is uncontrolled or requiring > 20 mg once daily (QD) of prednisone (or equivalent) to maintain haemoglobin > 8.0 g/dL or platelets > 10,000 µL without transfusion support

• Refractory to ofatumumab (defined as progression or relapse < 12 months of receiving ofatumumab monotherapy or < 24 months of receiving an ofatumumab containing regimen)

• Prior allogeneic transplant (prior autologous stem cell transplant > 6 months prior to study entry was permitted)

• Prior exposure to a PI3K inhibitor (eg, GS-1101, duvelisib) bcl-2-, or a Bruton's tyrosine kinase (BTK) inhibitor

• Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or systemic steroids > 20 mg prednisone (or equivalent) QD.

• Human immunodeficiency virus (HIV) infection

• Prior, current, or chronic hepatitis B or hepatitis C infection

• Unable to receive prophylactic treatment for pneumocystis or herpes simplex virus (HSV)

Treatments

Subjects were subsequently randomised returned to the clinic on Day 1 to receive their first dose of study drug (either duvelisib or ofatumumab). The first treatment cycle for each treatment arm was 3 weeks (21±2 days). Subsequent treatment cycles were 4 weeks (28±4 days).

Subjects randomised to duvelisib monotherapy self-administered duvelisib orally, 25 mg BID continuously in 28-day cycles with the exception of Cycle 1. The first dose of duvelisib monotherapy was in clinic on Day 1, initiating Cycle 1 of treatment. Subjects returned for a second clinical visit on Day 8±2. Cycle 1 was 21 days, with all subsequent cycles 28 days in length. Cycle 2 had clinic visits on Day 1 and on Day 15±2. Each subsequent cycle (Cycle 3-7) and then every odd cycle (Cycle 9 to 19) had only one clinic visit on Day 1. Subjects were instructed to take each dose of duvelisib at approximately the same times every day. Missed doses were not made up. At clinic visits where blood was drawn for PK, the morning dose of duvelisib was administered in-clinic.

Subjects received duvelisib continuously for 18 cycles or until disease progression or unacceptable toxicity, whichever came first. After completing approximately 18 cycles of treatment with duvelisib, subjects with stable disease or better may have received additional treatment with duvelisib based on the judgement of the Investigator.

Table 19 Dose interruption/ hold/ modifications for duvelisib-related toxicities

Duvelisib-related Toxicities [a, b]	**Dose Interruption/Hold/Modification/Recommendation for Duvelisib** [c]
Non-hematologic: ≥ Grade 2 pneumonitis/pneumonia Or ≥ Grade 3 all other nonhematologic	**First occurrence:** Withhold until return to ≤ Grade 1 or Baseline level; re-challenge therapy at original dose level. **Second occurrence of same AE:** Withhold until return to ≤ Grade 1 or Baseline level; re-initiate therapy at one dose level lower from current dose. **Third occurrence of same AE:** Withhold until return to ≤ Grade 1 or Baseline level; re-initiate therapy at one dose level lower from current dose. **Fourth occurrence of same AE:** Discontinue subject from study drug
Hematologic: ≥ Grade 3 febrile neutropenia Or ≥ Grade 3 thrombocytopenia with Grade ≥ 2 hemorrhage	
Recommendations for implementation of dose interruption Immediate hold for Grade 4 or higher nonhematologic toxicities and Grade 3 or higher febrile neutropenia For all other events, reduce from BID dosing to QD for 2 days, then hold	

Abbreviations: AE = adverse event; BID = twice daily.
a. Duvelisib-related toxicity = possible, probable, or definite relationship to duvelisib.
b. Toxicity grades are defined per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Note if parameter is not defined by CTCAE, then AE grading criteria should be utilized.
c. Refer to Table 7 for duvelisib dose levels.

Table 20 Dosing levels for duvelisib

Dose level	Dose (mg)
1	25 BID
-1	15 BID
-2	10 BID
-3	5 BID

Subjects randomised to ofatumumab received 8 weekly IV infusions, starting with an initial dose of ofatumumab of 300 mg followed by 7 weekly doses of 2000 mg. Thereafter, subjects received 2000 mg ofatumumab once every cycle for 4 cycles or until disease progression or unacceptable toxicity, whichever came first. Administration of ofatumumab was not to exceed the 12 doses (within 7 cycles) as described in the prescribing information. After dosing with ofatumumab was complete (ie, through Cycle 7 or ETT), subjects continued to have clinical assessments every odd cycle (Clinical Assessment Period) through Cycle 19 Day 1 or until disease progression, subject withdrawal, or initiation of additional anticancer treatment. After Cycle 19 Day 1, disease response assessments continued every 6 cycles from randomisation or until disease progression, subject withdrawal, or initiation of additional anticancer treatment.

Table 21 Dose interruption/ hold/ modifications for ofatumumab-related toxicities

Ofatumumab-related Toxicities [a, b]	Dose Interruption/Hold/Modification/Recommendation for Ofatumumab
Infusion Reactions	Infusion interruptions • For Grade 1, 2, or 3 infusion reaction, if the infusion reaction resolved or remained less than or equal to Grade 2, infusion was resumed with the following modifications according to the initial Grade of the infusion reaction – Grade 1 or 2: Infused at one-half of the previous infusion rate – Grade 3: Infused at a rate of 12 mL/hour • After resuming the infusion, the infusion rate could be increased according to the Principal Investigator, based on subject tolerance • For Grade 4 infusion reactions, the infusion was not to resume **Modifications:** • Grade 3 or 4 infusion reaction with previous infusion: – Next ofatumumab dose reduced to 300 mg • Increased subsequent dose(s) to 2000 mg if no Grade 3 or Grade 4 infusion reaction occurred
Nonhematologic: Grade 3 or higher	Withheld until returned to ≤ Grade 1 or Baseline level; re-challenged therapy at original dose level.
Hematologic: Grade 3 or higher febrile neutropenia	Withheld until returned to ≤ Grade 1 or Baseline level; re-challenged therapy at original dose level.
Grade 3 or higher thrombocytopenia associated with Grade 2 or higher hemorrhage	Withheld until return to ≤ Grade 1 or Baseline level; re-challenged therapy at original dose level.
a. Related = possible, probable, or definite relationship to ofatumumab b. Toxicity grades were defined per CTCAE Version 4.03. Note if parameter was not defined by CTCAE, then AE grading criteria were used.	

Objectives

This study was a randomised, open-label, parallel design to assess the potential **superiority** of duvelisib treatment over ofatumumab treatment on PFS in subjects with CLL or SLL.

Primary Objective

The primary objective of this study was to examine the efficacy of duvelisib monotherapy versus ofatumumab monotherapy in subjects with relapsed or refractory CLL or SLL.

Secondary Objectives

Secondary objectives of this study were:

• To determine the safety of duvelisib

• To evaluate the PK of duvelisib and, if applicable, its metabolite(s)

Exploratory Objectives

Exploratory objectives of this study were:

• To evaluate the health-related quality-of-life (QoL) of subjects

• To evaluate pharmacodynamic biomarkers of duvelisib

• To evaluate biomarkers that may predict duvelisib clinical activity and/or safety

• To evaluate mechanisms of resistance in subjects who exhibit disease progression while being treated with duvelisib or ofatumumab

• To evaluate genomic features of tumours predictive of response in subjects treated with duvelisib or ofatumumab

Outcomes/endpoints

PFS was defined as the time from randomisation to the first documentation of progressive disease as determined by independent review or death due to any cause. Disease response and progression status were determined via the modified IwCLL criteria for subjects with CLL.

Efficacy endpoints for Study IPI-145-07 were defined as follows:

Primary

- Progression-free survival (PFS), defined as the time from randomisation to the first documentation of PD or death due to any cause as assessed by the IRC

Secondary

- Overall response rate (ORR), defined as a best overall response (BOR) of complete response/remission (CR), CR with incomplete marrow recovery (CRi), partial response/remission (PR), or PR with lymphocytosis (PRwL), according to either IWCLL or IWG criteria with modification for treatment-related lymphocytosis
- Overall survival (OS), defined as the time from randomisation to death due to any cause
- Rate of lymph node response (LNR), defined as a ≥ 50% decrease in the sum of product diameters (SPD) of target lymph nodes
- Rate of haematologic improvement, defined as any of following maintained for ≥ 60 days without transfusion or exogenous growth factors:
  - Neutrophil count > 1,500/µL OR an increase of ≥ 50% from baseline
  - Haemoglobin > 11 g/dL OR an increase of ≥ 50% from Baseline
  - Platelet count > 100 000/µL OR an increase of ≥ 50% from Baseline
- Duration of response (DOR), defined as time from the first documentation of response to the first documentation of PD or death due to any cause

Both disease response and progression status were determined by an independent blinded panel of radiologists and oncologists (ie, IRC). Responses were also assessed by the study Investigator. Disease response was per modified IWCLL/IWG criteria, with the following modifications: (1) an additional category was added to allow for PR with lymphocytosis (PRwL); and (2) the criteria for PD did not include PD based only on worsening lymphocytosis or isolated increase in target lesion(s) in the absence of other objective evidence of disease progression.

Confirmatory imaging review by the central reader was required prior to discontinuing a subject from the study due to PD. All disease response assessment data, including peripheral blood, physical examination, disease-related constitutional symptom, and CT scan data, were used in determining an individual subject's disease response and/or progression status.

Randomisation and blinding (masking)

Eligible patients were randomised in a 1:1 ratio to either ofatumumab or duvelisib. The randomisation was stratified by the presence of 17p deletion, prior progression within 12 months after previous purine analogue-based therapy, and the presence of Grade 4 cytopenia at Baseline.

Sample size

Approximately 300 eligible patients were planned to be randomised 1:1 to duvelisib or ofatumumab arms to achieve ≈ 90 % power to detect a HR of 0.6. The sample size calculation was based on the one-sided log-rank test at an alpha level of 0.025. One interim analysis was planned using the Lan-DeMets spending function for O'Brien-Fleming boundary for the alpha spending function.

Statistical methods

The primary efficacy analysis was based on ITT population, including all randomised subjects who were designated to treatment group according to randomisation. The PP analysis set included all patients in the ITT analysis set without violating the protocol in a way that could affect the study outcome. The PP analysis was used for secondary analysis for selected efficacy analyses. The definition of the analysis sets and how they were applied is agreed.

For assessing the difference in IRC-PFS between the two arms, a log-rank test stratified by the randomisation factors was used. A Cox proportional hazards model stratified by the randomisation factors was used to calculate the HR. Patients with no adequate baseline, patients with no adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment, and patients without documented progression or death before data cut-off were censored. Patients who started a new anticancer treatment before documented PD were also censored, as well as patients with documented progression or death following a long gap between adequate disease status assessments. To assess the impact of the censoring rules, a sensitivity analysis mimicking a worst-case scenario where subjects alive without documented progression by data cut-off and who are "lost to follow-up" are censored if they are on the control arm and treated as having a PFS event if they are on the experimental arm. In order to assess the robustness of the results, additional analyses were planned: INV-PFS, unstratified analysis, the same analysis performed using the AT and PP analysis set and event free survival.

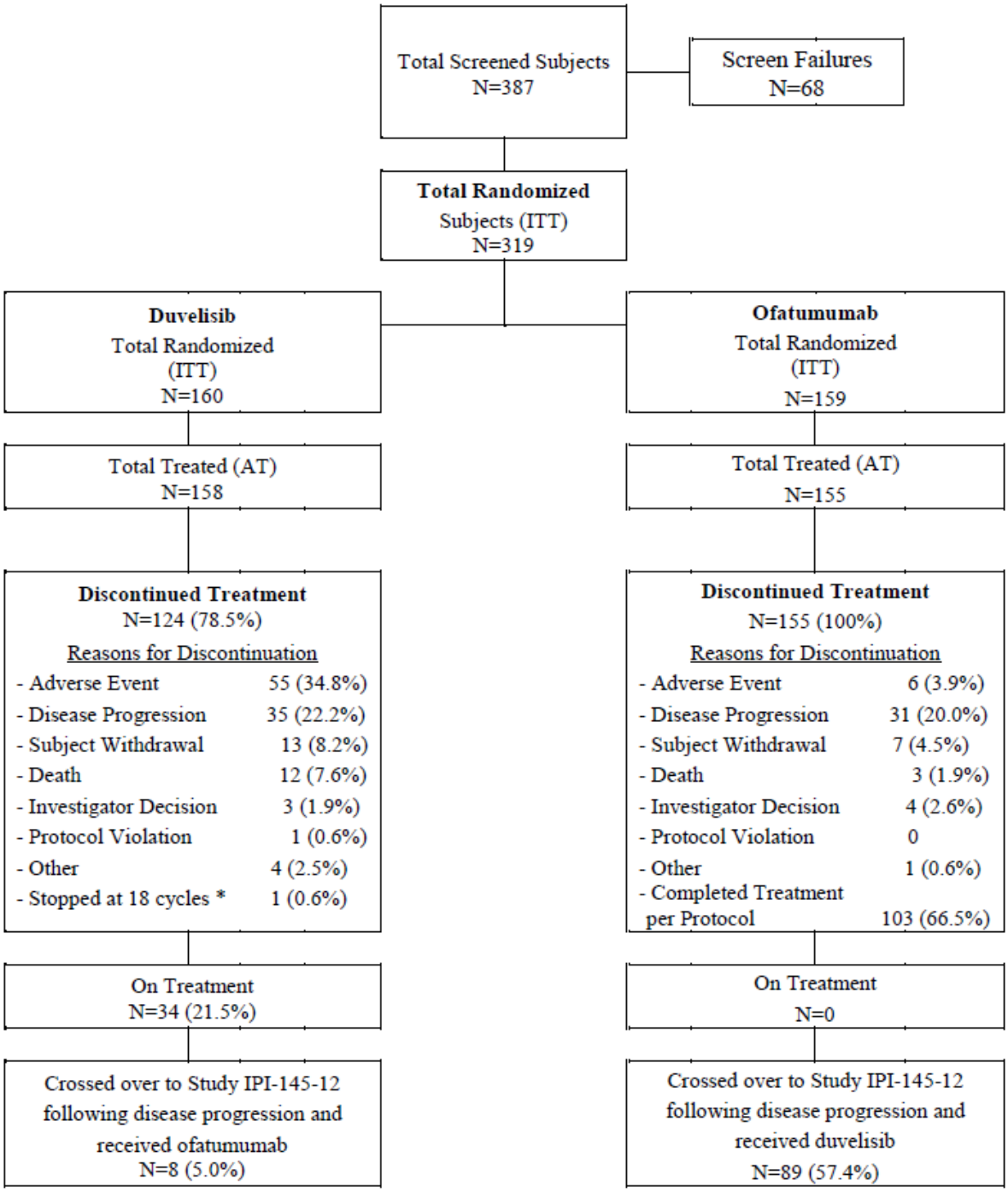
The applicant performed several additional analyses to assess the robustness of the results and the effect of the censoring. The primary endpoint PFS will be tested at an overall one-sided alpha of 0.025. One interim analysis for early stopping due to efficacy was planned for PFS when 50% of the target PFS events were observed. This IA also included the option of stopping the trial due to futility. If PFS was significant, then the

key secondary endpoints ORR and OS would be sequentially tested in a hierarchical approach. For OS, two interim analyses were planned after approximately 24, 58 and 166 OS events. A Lan-DeMets alpha spending function with an O'Brien-Fleming stopping boundary was implemented to consider the interim analyses.

Results

Participant flow

Figure 16 Subjects' disposition



*the protocol allowed for subjects who had achieved a sustained response (> 3 months) (CR or PR) at 18 months to discontinue treatment; subjects may have received duvelisib beyond 18 months at the discretion of the Investigator.

Two patients in the duvelisib arm and four patients in the ofatumumab were randomised but not treated. One patient in the duvelisib arm was diagnosed with metastatic melanoma before initiating treatment.

Table 22 Disposition of Subjects, Summary of Discontinuation from Treatment (All Treated Analysis Set, 22 March 2019 data cut-off date)

Category	Duvelisib 25 mg BID (N=158) n (%)	Ofatumumab (N=155) n (%)	Total (N=313) n (%)
All Treated Analysis Set	158	155	313
Ongoing on Treatment	10 (6.3)	0	10 (3.2)
Discontinued Treatment [a]	148 (93.7)	155 (100)	303 (96.8)
Reason Treatment Discontinued			
Adverse Event that Requires Permanent Discontinuation of Study Treatment	62 (39.2)	6 (3.9)	68 (21.7)
Protocol-Specified Disease Progression	43 (27.2)	31 (20.0)	74 (23.6)
Death	15 (9.5)	3 (1.9)	18 (5.8)
Lost to Follow-up	0	0	0
Noncompliance to Protocol	0	0	0
Investigator Decision	6 (3.8)	4 (2.6)	10 (3.2)
Termination of Study by Sponsor	0	0	0
Voluntary Withdrawal by Subject	14 (8.9)	7 (4.5)	21 (6.7)
Completed Treatment Period per Protocol	1 (0.6)	103 (66.5)	104 (33.2)
Protocol Deviation	2 (1.3)	0	2 (0.6)
Other	5 (3.2)	1 (0.6)	6 (1.9)

[a]: Discontinued treatment and reason treatment discontinued are based on the treatment termination page of the eCRF.
Source: MAA CLL/SLL Efficacy TLFs Study IPI-145-07 Updated Survival Analysis Table 14.1.1.2 (22 March 2019 data cutoff)

Recruitment

Of the 319 randomised patients 51 (16%) came from the US, 33 (10%) from Australia and New Zealand and the remaining 235 patients (74%) from eight European countries.

Table 23 Randomisation Stratification Criteria (Intent-to-Treat Analysis Set) per IRT

Randomization Stratification Factors, As Randomized	Duvelisib (N=160) n (%)	Ofatumumab (N=159) n (%)
High Risk Cytogenetics (17p deletion)		
Present	38 (23.8)	37 (23.3)
Absent	122 (76.3)	122 (76.7)
Refractory/Early Relapse to Purine Analog-based Treatment (progression < 12 months after fludarabine/pentostatin)		
Yes	50 (31.3)	48 (30.2)
No	110 (68.8)	111 (69.8)
Grade 4 Cytopenia at Baseline		
Presence	17 (10.6)	18 (11.3)
Absence	143 (89.4)	141 (88.7)

Abbreviations: ITT = intent-to-treat; IRT = interactive response technology.
Note: Percentages are based on the number of intent-to-treat subjects in each treatment group.
Reference Table 14.1.1.5

Conduct of the study

Main protocol amendments included: Exclusion criterion 15 stating that: "Baseline QTcF >480 ms (average of triplicate readings) was amended as in *Amendment 1:* Baseline QTcF exclusion criterion has been changed from >480 ms to >500 ms: "This change is based on updated safety data from ongoing clinical trials with IPI-145; based on new QTc data, there was no justification for the lower threshold." However in a*mendment 2:* The QTcF exclusion criteria has changed from QTcF > 500 ms to > 480 ms: Changed the baseline QTcF to 480 ms per FDA request.

Protocol amendment no.3 related to the number of duvelisib cycles:

- The maximum number of duvelisib treatment cycles (39 cycles) has been removed to permit subjects experiencing clinical benefit after 39 cycles to continue duvelisib treatment until disease progression or unacceptable toxicity
- The criteria for receiving additional duvelisib beyond Cycle 19 have been modified to reflect potential clinical benefit of a stable disease (SD) response. Previously, subjects with SD were also required to have persistent lymphadenopathy > 50% of baseline (with at least 1 target lesion ≥ 1.5 cm in diameter) but with a peripheral blood ALC ≤ 50% of baseline (or < 4,000/µL). These additional requirements have been removed such that subjects with an SD response at Cycle 19 day 1 may continue duvelisib treatment until disease progression or unacceptable toxicity

Table 24 Subjects Censored Due to No Evidence of Progression or Death for PFS by IRC Assessment – Study IPI-145-07

	Subjects Receiving 2 or More Prior Therapies	
	Duvelisib 25 mg BID N=95	**Ofatumumab N=101**
Subjects censored due to no evidence of progression or death	30	8
Subjects remaining in study follow-up, n (%)	**23 (77)**	**2 (25)**
Subjects remaining on treatment	17	0
Subjects discontinued from treatment	6	2[a]
Subjects discontinued from study follow-up, n (%)	**7 (23)**	**6 (75)**
Subject withdrew	6	5
Lost to follow-up	1	1

Abbreviations: BID = twice daily; IRC = Independent Review Committee; PFS = progression-free survival.
[a]All subjects completed protocol-specified ofatumumab regimen
Source: Data on file.

Baseline data

Table 25 Demographic and Baseline Characteristics, Study IPI-145-07 (ITT Analysis Set)

Category	Duvelisib N=160	Ofatumumab N=159
Age (yrs)		
Median (Min, Max)	69.0 (39, 90)	69.0 (39, 89)
Age Category (yrs), n (%)		
< 65 years	48 (30.0)	54 (34.0)
≥ 65 years	112 (70.0)	105 (66.0)
Sex, n (%)		
Male	96 (60.0)	95 (59.7)
Female	64 (40.0)	64 (40.3)
Race, n (%)		
White	150 (93.8)	142 (89.3)
Black/African American	1 (0.6)	1 (0.6)
Other	1 (0.6)	3 (1.9)
Unknown	2 (1.3)	4 (2.5)
Not Reported	6 (3.8)	9 (5.7)
Ethnicity, n (%)		
Hispanic or Latino	8 (5.0)	7 (4.4)
Not Hispanic/Latino	130 (81.3)	133 (83.6)
Unknown	2 (1.3)	2 (1.3)
Not Reported	20 (12.5)	17 (10.7)
BMI (kg/m^2) [a]		
Median (Min, Max)	25.476 (17.27, 41.02)	26.175 (17.26, 80.91)

a. Body Mass Index = weight (kg) / height (m)2. Subject with BMI of 80.91 has a height of 90 cm due to amputation.
Source: Study IPI-145-07 CSR Table 14.1.3.1; Listing 16.2.4.1

Table 26 Disease History, Study IPI-145-07 (Intent-to-Treat Analysis Set)

Category	Duvelisib (N=160)	Ofatumumab (N=159)
Diagnosis, n (%)		
CLL	155 (96.9)	157 (98.7)
SLL	5 (3.1)	2 (1.3)
Years from Initial Diagnosis [a]		
Median (Min, Max)	7.45 (0.4, 29.7)	6.70 (0.3, 34.7)
Months from most recent relapse/refractory Diagnosis [b]		
Median (Min, Max)	2.55 (0.2, 80.2)	2.40 (0.2, 58.2)
Current Stage – Rai, n (%)		
I	15 (14.4)	12 (13.5)
II	31 (29.8)	27 (30.3)
III	19 (18.3)	12 (13.5)
IV	39 (37.5)	38 (42.7)
Total	*104 (100)*	*89 (100)*
Current Stage – Binet, n (%)		
A	1 (1.8)	0
B	32 (57.1)	46 (65.7)
C	23 (41.1)	24 (34.3)
Total	*56 (100)*	*70 (100)*
Subjects with Bulky Disease (Baseline Lesion ≥ 5 cm) [c]	74 (46.3)	72 (45.3)
Subjects with Abnormal Liver Assessment at Screening	29 (18.1)	29 (18.2)
Subjects with Abnormal Spleen Assessment at Screening	60 (37.5)	51 (32.1)
Baseline Lymphocytes ($x10^9$/L)		
Median (Min, Max)	37.65 (0.0, 382.3)	34.90 (0.0, 407.4)

Note: Percentages are based on the number of intent-to-treat subjects in each treatment group. For Initial and Current Stage, percentages are based on the number of subjects in each treatment group with a response.

[a] Years from initial diagnosis date to date of randomization.

[b] Months from most recent relapse/refractory diagnosis date to date of randomization.

[c] Bulky disease is defined as yes if the longest diameter of any target lesion at screening ≥ 50 mm based on imaging or clinical examination per Investigator assessment.

Source: Study IPI-145-07 CSR Table 14.1.5.1

Table 27 Baseline Prognostic Features, Study IPI-145-07 (Intent-to-Treat Analysis Set)

Category	Duvelisib N=160	Ofatumumab N=159
17p deletion [a]		
Present	33 (20.6)	44 (27.7)
Absent	111 (69.4)	102 (64.2)
Indeterminate	16 (10.0)	13 (8.2)
IGHV Status		
Mutated	29 (18.1)	25 (15.7)
Unmutated	110 (68.8)	116 (73.0)
Indeterminate	21 (13.1)	18 (11.3)
CD38		
Positive (≥ 30%)	69 (43.1)	70 (44.0)
Negative (< 30%)	79 (49.4)	74 (46.5)
Indeterminate	12 (7.5)	15 (9.4)
ZAP70		
Positive (> 19%)	86 (53.8)	83 (52.2)
Negative (≤ 19%)	62 (38.8)	61 (38.4)
Indeterminate	12 (7.5)	15 (9.4)
17p deletion [a]		
***TP53* mutation**		
Present	32 (20.0)	29 (18.2)
Absent	108 (67.5)	112 (70.4)
Indeterminate	20 (12.5)	18 (11.3)
17p deletion or *TP53* mutation [a, b]		
Either or Both Present	49[c] (30.6)	52 (32.7)
Neither Present	83 (51.9)	84 (52.8)
Indeterminate	28 (17.5)	23 (14.5)

Note: Percentages are based on the number of intent-to-treat subjects in each treatment group.
[a] As determined by central laboratory assessment.
[b] Missing results are reported as indeterminate.
[c] Includes one subject with a *TP53* mutation determined 8 days after initiation of study treatment.
Source: Study IPI-145-07 CSR Table 14.1.3.1

Table 28 Prior therapies at baseline, ITT population

Category	Statistic	Duvelisib 25 mg BID (N=160)	Ofatumumab (N=159)	Total (N=319)
Number of Prior Systemic Therapy Regimens	n	159	159	318
	Mean	2.2	2.3	2.3
	Std Dev	1.51	1.53	1.52
	Median	2.0	2.0	2.0
	Q1, Q3	1.0, 3.0	1.0, 3.0	1.0, 3.0
	Min, Max	1, 10	1, 8	1, 10
Number of Prior Systemic Therapy Regimens				
1	n (%)	64 (40.0)	58 (36.5)	122 (38.2)
2	n (%)	45 (28.1)	46 (28.9)	91 (28.5)
3 or More	n (%)	50 (31.3)	55 (34.6)	105 (32.9)
Months from Most Recent Systemic Therapy [a]	n	159	159	318
	Mean	28.03	23.86	25.94
	Std Dev	27.167	22.273	24.889
	Median	21.70	17.60	19.50
	Q1, Q3	9.00, 37.80	7.10, 35.10	7.80, 35.80
	Min, Max	0.8, 148.8	0.5, 105.8	0.5, 148.8
Subjects with < 12 months from Most Recent Systemic Therapy	n (%)	52 (32.5)	63 (39.6)	115 (36.1)
Subjects with Prior Radiotherapy	n (%)	1 (0.6)	5 (3.1)	6 (1.9)
Subjects with Prior Surgery Related to Primary Diagnosis	n (%)	4 (2.5)	1 (0.6)	5 (1.6)
Months from Most Recent Therapy [b]	n	159	159	318
	Mean	28.03	23.86	25.94
	Std Dev	27.167	22.273	24.889
	Median	21.70	17.60	19.50
	Q1, Q3	9.00, 37.80	7.10, 35.10	7.80, 35.80
	Min, Max	0.8, 148.8	0.5, 105.8	0.5, 148.8
Subjects with < 12 months from Most Recent Therapy	n (%)	52 (32.5)	63 (39.6)	115 (36.1)

Note: Percentages are based on the number of intent-to-treat subjects in each treatment group.
[a] Months from stop date of most recent prior systemic therapy to date of randomization.
[b] Months from stop date of most recent therapy, which may include prior systemic therapy, prior radiotherapy, or prior surgery, to date of randomization.
Program Name: t-14-01-06-01.sas Data Cut-off: 19MAY2017 Table Generation: 30OCT2017 11:23

Numbers analysed

Table 29 Analysis sets

Category	Duvelisib 25 mg BID n (%)	Ofatumumab n (%)	Total n (%)
Randomized (Intent-to-Treat Analysis Set [a])	160	159	319
Randomized and Not Dosed	2 (1.3)	4 (2.5)	6 (1.9)
Dosed (All Treated Analysis Set [b])	158 (98.8)	155 (97.5)	313 (98.1)
Per Protocol Analysis Set [c]	158 (98.8)	158 (99.4)	316 (99.1)

Note: Percentages are based on the number of randomized subjects in each treatment group.
[a] The Intent-to-Treat (ITT) Analysis Set includes all subjects who were randomized.
[b] The All Treated Analysis Set includes all subjects who received any amount of duvelisib 25 mg BID or ofatumumab.
[c] The Per Protocol Analysis Set includes all subjects in the ITT Analysis Set who do not violate the terms of the protocol in a way that would significantly affect the outcome of the study.
Program Name: t-14-01-01-01.sas Data Cut-off: 19MAY2017 Table Generation: 30OCT2017 11:17

Source: CSR-07

Outcomes and estimation

Primary endpoint: PFS

Table 30 Progression-Free Survival, Blinded IRC (Intent-to-Treat Analysis Set)

Category	**Duvelisib (N=160)**	**Ofatumumab (N=159)**
Subjects with Event (Progression or Death), n (%)	93 (58.1)	110 (69.2)
Progression	*74 (46.3)*	*101 (63.5)*
Death before progression	*19 (11.9)*	*9 (5.7)*
Subjects Censored, n (%)	67 (41.9)	49 (30.8)
No evidence of progression or death	*51 (31.9)*	*12 (7.5)*
No adequate Baseline disease assessment	*2 (1.3)*	*4 (2.5)*
No adequate post-Baseline disease assessment	*4 (2.5)*	*6 (3.8)*
Documented progression or death following a long gap between adequate disease assessments	*0*	*0*
New anticancer treatment or procedure started before documented progression	*10 (6.3)*	*27 (17.0)*
Percentiles, Estimate in Months (95% Confidence Interval)		
25th Percentile	8.6 (5.4, 9.1)	5.5 (4.4, 8.7)
Median (50th Percentile)	13.3 (12.1, 16.8)	9.9 (9.2, 11.3)
75th Percentile	24.8 (22.1, NE)	13.0 (12.7,14.1)
Kaplan-Meier Event-Free Estimate (95% Confidence Interval)		
Month 6	0.78 (0.71, 0.84)	0.72 (0.64, 0.79)
Month 12	0.60 (0.51, 0.67)	0.39 (0.31, 0.48)
Hazard Ratio for Duvelisib/Ofatumumab (95% Confidence Interval) [a]	0.52 (0.39, 0.69)	-
P-value [b]	< 0.0001	-

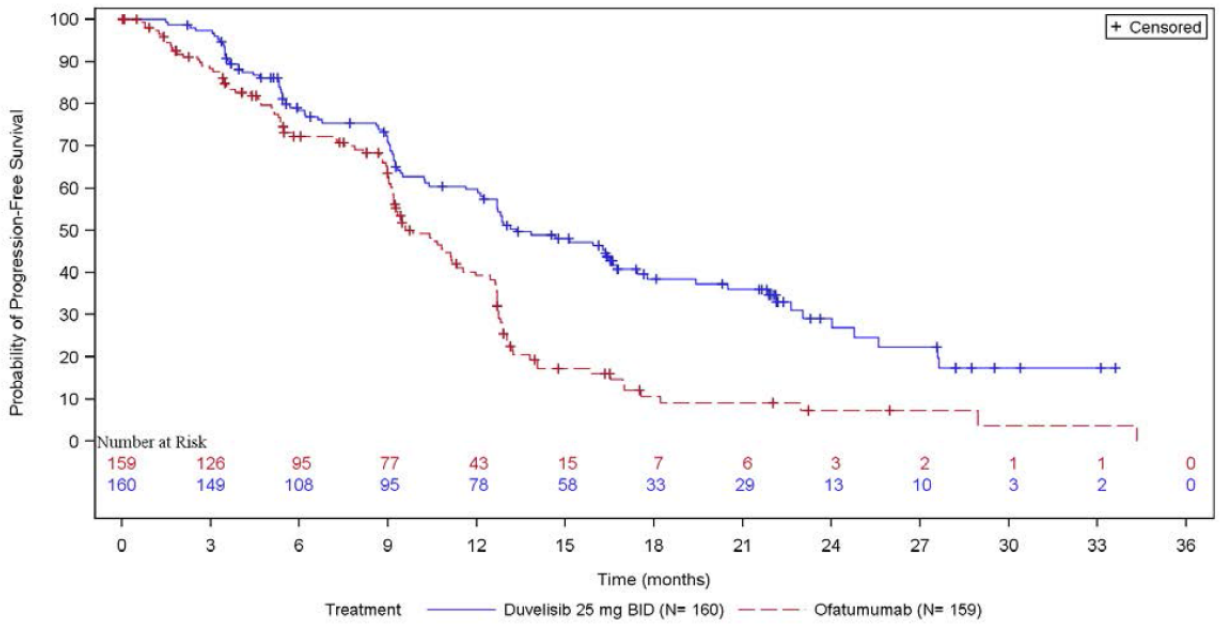
Abbreviations: NE = Not Estimable

Note: Percentages are based on the number of intent-to-treat subjects in each treatment group.

a. Stratified Cox proportional hazards model using randomization strata as used for randomization.

b. One-sided stratified log-rank test to compare duvelisib 25 mg BID versus ofatumumab using randomization strata as used for randomization

Figure 17 Progression – free survival (ITT)



Abbreviations: BID = twice a day; IRC = independent review committee; ITT = intent-to-treat.
Source: Figure 14.2.1.1; Listing 16.2.6.1

PFS per IRC Sensitivity Analysis 1

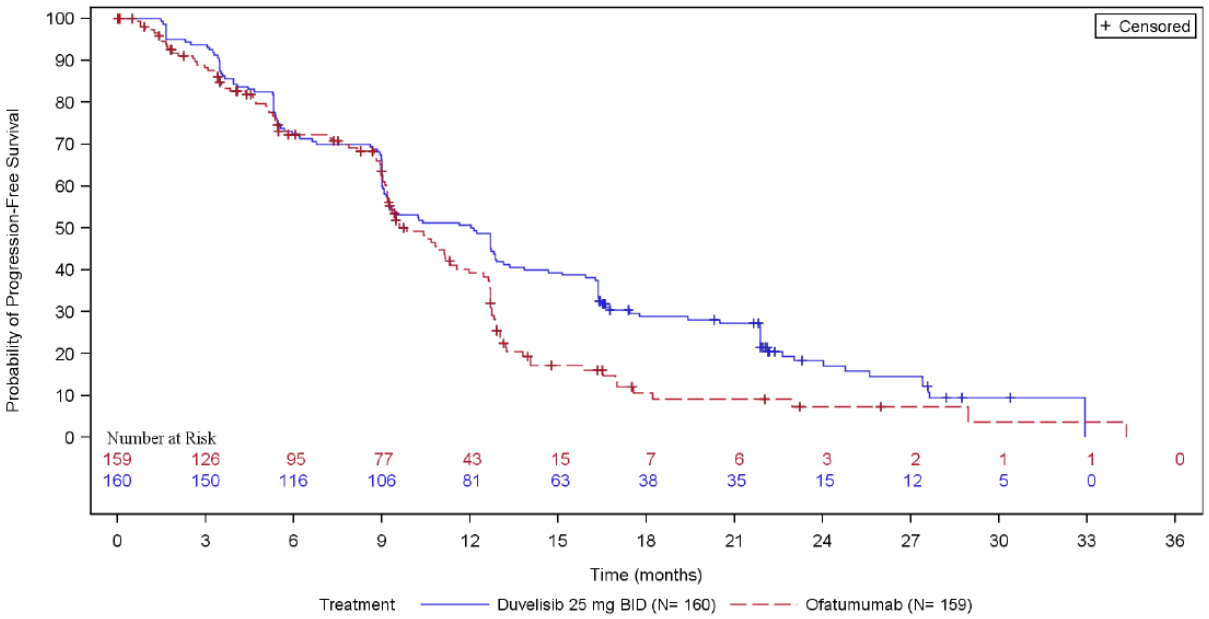
In this sensitivity analysis of PFS, subjects who discontinued treatment and did not have a documented PFS event were re-classified as an event at the time of last adequate disease assessment. The results of this sensitivity analysis showed a median PFS for duvelisib of 10.6 months (95% CI: 9.1, 12.8) and for ofatumumab of 9.0 months (95% CI: 7.3, 9.2), with a hazard ratio of 0.52 (95% CI: 0.41, 0.66; p<0.0001).

PFS per IRC Sensitivity Analysis 2

The results of this sensitivity analysis showed a median PFS for duvelisib of 12.1 months (95% CI: 9.1, 12.8) and for ofatumumab of 9.0 months (95% CI:8.8, 9.5), with a hazard ratio of 0.55 (95% CI: 0.43, 0.70; p<0.0001).

For the event free survival analysis, where new anticancer therapy initiated prior to documented disease progression or death was considered an event and not censored, which seems like a clinically plausible situation, the results were similar to the primary analysis. Median PFS for duvelisib was 12.8 months (95% CI: 10.3, 16.4) and for ofatumumab 9.3 months (95% CI: 9.0, 10.4) (p < 0.0001). The hazard ratio for duvelisib vs ofatumumab was 0.47 (95% CI: 0.36, 0.61).

Figure 18 K-M curves on PFS blinded independent central review worst case sensitivity analysis, ITT



ote: Subjects alive without documented progression and missing at least one disease assessment right before data cut-
ff are treated as censored at the last adequate disease assessment for Ofatumumab and as having PFS event at the time
f the next scheduled assessment following the last adequate disease assessment for Duvelisib.
rogram Name: f-14-02-01-01.sas Data Cut-off: 19MAY2017 Figure Generation: 31OCT2017 12:49

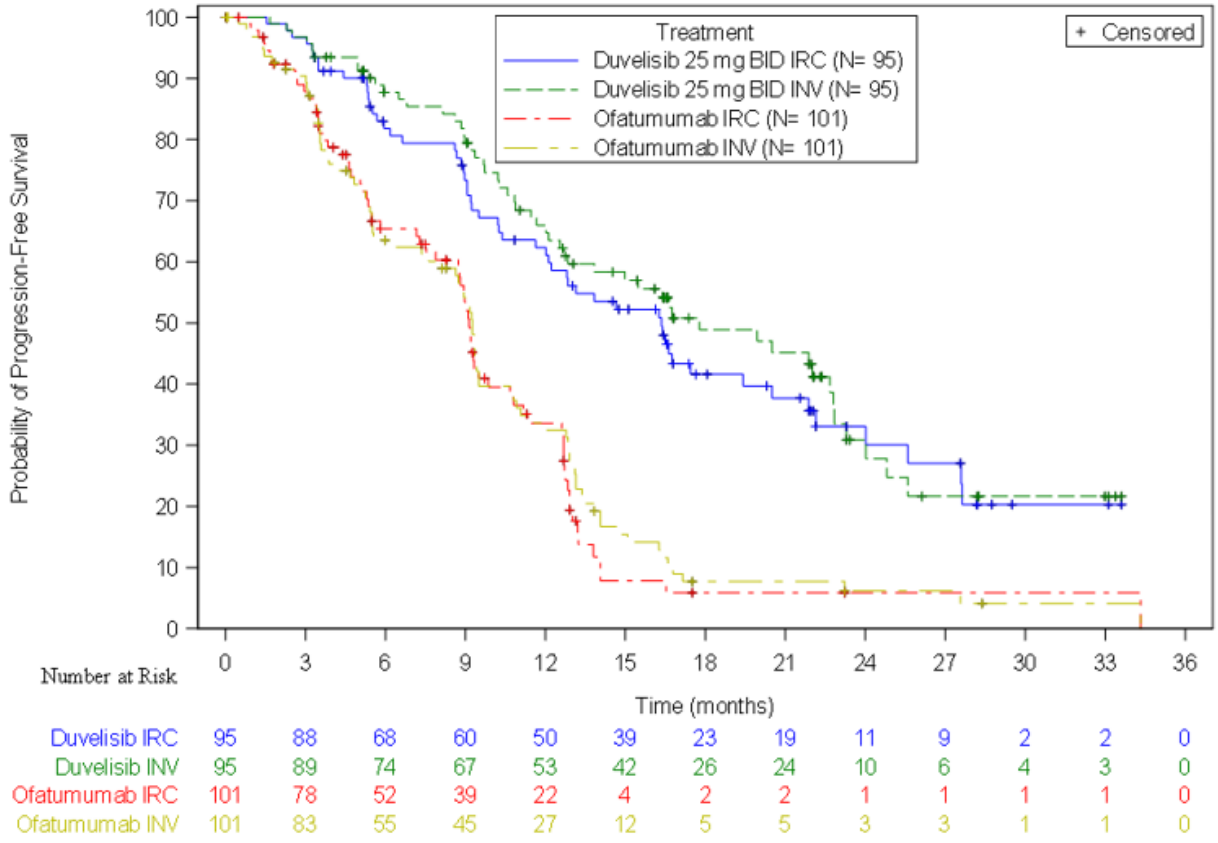
For subjects having received at least two prior therapies the median PFS was 16.4 months (95% CI: 12.0, 20.5) for duvelisib versus 9.1 months for ofatumumab (95% CI: 7.9, 10.7), with a hazard ratio of 0.4 (95% CI: 0.27, 0.59). For patients with only 1 prior therapy the median PFS was 12.7 months (95% CI: 9.1, 17.8) for duvelisib versus 12.0 months for ofatumumab (95% CI: 9.6, 12.8) with a hazard ratio of 0.8 (95% CI: 0.5, 1.28).

Table 31 PFS by IRC and INV Assessment, Subjects with at Least Two Prior Therapies – Study IPI-145-07

	IRC Assessment		Investigator Assessment	
Category	**Duvelisib 25 mg BID (N=95)**	**Ofatumumab (N=101)**	**Duvelisib 25 mg BID (N=95)**	**Ofatumumab (N=101)**
Subjects with event (progression or death), n (%)	55 (57.9)	70 (69.3)	52 (54.7)	82 (81.2)
Progression	44 (46.3)	62 (61.4)	38 (40.0)	71 (70.3)
Death before progression	11 (11.6)	8 (7.9)	14 (14.7)	11 (10.9)
Subjects censored, n (%)	40 (42.1)	31 (30.7)	43 (45.3)	19 (18.8)
No evidence of progression or death	30 (31.6)	8 (7.9)	34 (35.8)	8 (7.9)
No adequate baseline disease assessment	2 (2.1)	3 (3.0)	2 (2.1)	3 (3.0)
No adequate post-baseline disease assessment	2 (2.1)	5 (5.0)	1 (1.1)	4 (4.0)
New anticancer treatment or procedure started before documented progression	6 (6.3)	15 (14.9)	6 (6.3)	4 (4.0)
Median PFS, months (95% confidence interval)	16.4 (12.0, 20.5)	9.1 (7.9, 10.7)	17.8 (12.7, 22.8)	9.3 (7.6, 9.5)
Kaplan-Meier event-free estimate (95% confidence interval)				
Month 6	0.82 (0.72, 0.89)	0.65 (0.54, 0.74)	0.88 (0.79, 0.93)	0.64 (0.53, 0.73)
Month 12	0.62 (0.51, 0.72)	0.34 (0.23, 0.44)	0.66 (0.55, 0.75)	0.32 (0.23, 0.42)
Hazard ratio for duvelisib/ofatumumab (95% confidence interval) [a]	0.40 (0.27, 0.59)		0.35 (0.24, 0.51)	

Source: t-ah14-02-01-81-01, t-02-01-pfs-inv-nptx-ge2 (data on file)
Abbreviations: BID = twice daily; IRC = Independent Review Committee; INV = Investigator; PFS = progression-free survival
[a] Stratified Cox proportional hazards model using randomisation strata as used for randomisation

Figure 19 Kaplan-Meier Estimate of PFS by IRC and INV Assessment, Subjects with at Least Two Prior Therapies – Study IPI-145-07



Abbreviations: BID = twice daily; IRC = Independent Review Committee; INV = Investigator; PFS = progression-free survival

Table 32 PFS Sensitivity Analysis i: Subjects Who Received New Anticancer Therapy Before Confirmed Progression are Censored at Date of New Anticancer Therapy, Subjects with at Least Two Prior Therapies – Study IPI-145-07

	IRC Assessment		**Investigator Assessment**	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
Subjects with events, n (%)	55 (57.9)	70 (69.3)	52 (54.7)	82 (81.2)
Progression	44 (46.3)	62 (61.4)	38 (40.0)	71 (70.3)
Death without progression	11 (11.6)	8 (7.9)	14 (14.7)	11 (10.9)
Subjects censored, n (%)	40 (42.1)	31 (30.7)	43 (45.3)	19 (18.8)
No evidence of progression or death	30 (31.6)	8 (7.9)	34 (35.8)	8 (7.9)
No adequate baseline disease assessment	2 (2.1)	3 (3.0)	2 (2.1)	3 (3.0)
No adequate post-baseline disease assessment	2 (2.1)	5 (5.0)	1 (1.1)	4 (4.0)

	IRC Assessment		Investigator Assessment	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
New anticancer treatment or procedure started before documented progression	6 (6.3)	15 (14.9)	6 (6.3)	4 (4.0)
Percentiles, estimate in months (95% CI)				
25th percentile	8.9 (5.5, 10.3)	4.7 (3.5, 5.8)	9.7 (8.2, 12.0)	4.7 (3.5, 5.5)
Median (50th percentile)	16.4 (12.1, 20.5)	9.2 (7.9, 10.7)	17.8 (12.9, 22.8)	9.3 (7.6, 10.7)
75th percentile	27.6 (22.1, NE)	12.9 (11.3, 13.2)	25.6 (22.8, NE)	13.1 (11.6, 14.7)
Hazard ratio for duvelisib/ofatumumab	0.41		0.35	
(95% confidence interval) [b]	0.28, 0.61		0.24, 0.51	
p-value [a]	<.0001		<.0001	

Abbreviations: BID = twice daily; CI = confidence interval; IRC = Independent Review Committee; NE = not evaluable; PFS = progression-free survival

[a] One-sided stratified log-rank test to compare duvelisib 25 mg BID versus ofatumumab using randomisation strata as used for randomisation.

[b] Stratified Cox proportional hazards model using randomisation strata as used for randomisation.

Table 33 PFS Sensitivity Analysis ii: Subjects who Received New Anticancer Therapy in the Ofatumumab Arm are Followed Until Death or Data Cut-off Date, Subjects with at Least Two Prior Therapies – Study IPI-145-07

	IRC Assessment		Investigator Assessment	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
Subjects with events, n (%)	55 (57.9)	74 (73.3)	52 (54.7)	84 (83.2)
Progression	44 (46.3)	62 (61.4)	38 (40.0)	71 (70.3)
Death without progression	11 (11.6)	12 (11.9)	14 (14.7)	13 (12.9)
Subjects censored, n (%)	40 (42.1)	27 (26.7)	43 (45.3)	17 (16.8)
No evidence of progression or death	30 (31.6)	8 (7.9)	34 (35.8)	8 (7.9)
No adequate baseline disease assessment	2 (2.1)	3 (3.0)	2 (2.1)	3 (3.0)
No adequate post-baseline disease assessment	2 (2.1)	5 (5.0)	1 (1.1)	4 (4.0)
New anticancer treatment or procedure started before documented progression	6 (6.3)	0	6 (6.3)	0
Data cutoff	0	11 (10.9)	0	2 (2.0)
Percentiles, estimate in months (95% CI)				
25th percentile	8.9 (5.5, 10.3)	4.7 (3.4, 5.8)	9.7 (8.2, 11.7)	4.7 (3.5, 5.5)

	IRC Assessment		Investigator Assessment	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
Median (50th percentile)	16.4 (12.0, 20.5)	9.2 (8.7, 12.6)	17.8 (12.7, 22.8)	9.3 (7.9, 10.8)
75th percentile	27.6 (21.9, NE)	13.8 (12.7, 26.5)	24.8 (22.8, NE)	13.4 (12.8, 16.5)
Hazard ratio for duvelisib/ofatumumab	0.58		0.40	
(95% confidence interval) [b]	0.41, 0.83		0.28, 0.58	
p-value [a]	0.0029		<.0001	

Abbreviations: BID = twice daily; CI = confidence interval; IRC = Independent Review Committee; NE = not evaluable; PFS = progression-free survival

[a] One-sided stratified log-rank test to compare duvelisib 25 mg BID versus ofatumumab using randomisation strata as used for randomisation.

[b] Stratified Cox proportional hazards model using randomisation strata as used for randomisation.

Table 34 PFS Sensitivity Analysis iii: PFS Times for Subjects who Received New Anticancer Therapy are Imputed Based on Subject in the Same Treatment Arm, Subjects with at Least Two Prior Therapies – Study IPI-145-07

	IRC Assessment		Investigator Assessment	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
Subjects with events, n (%)	61 (64.2)	85 (84.2)	58 (61.1)	86 (85.1)
Progression	50 (52.6)	77 (76.2)	44 (46.3)	75 (74.3)
Death without progression	11 (11.6)	8 (7.9)	14 (14.7)	11 (10.9)
Subjects censored, n (%)	34 (35.8)	16 (15.8)	37 (38.9)	15 (14.9)
No evidence of progression or death	30 (31.6)	8 (7.9)	34 (35.8)	8 (7.9)
No adequate baseline disease assessment	2 (2.1)	3 (3.0)	2 (2.1)	3 (3.0)
No adequate post-baseline disease assessment	2 (2.1)	5 (5.0)	1 (1.1)	4 (4.0)
Delta=1				
Median estimate in months (95% prediction interval)	16.36 (14.65, 16.39)	9.13 (8.97, 9.20)	17.38 (16.66, 19.94)	9.26 (9.17, 9.26)
Hazard ratio for duvelisib/ofatumumab	0.374		0.357	
(95% prediction interval)	(0.348, 0.424)		(0.338, 0.392)	
Delta=1.5				
Median estimate in months (95% prediction interval)	16.26 (14.65, 16.39)	9.13 (8.97, 9.20)	16.76 (16.66, 17.77)	9.26 (9.17, 9.26)
Hazard ratio for duvelisib/ofatumumab	0.376		0.360	

	IRC Assessment		Investigator Assessment	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
(95% prediction interval)	(0.349, 0.425)		(0.339, 0.394)	
Delta=2				
Median estimate in months (95% prediction interval)	16.26 (14.65, 16.39)	9.13 (8.97, 9.20)	16.76 (16.66, 17.77)	9.26 (9.17, 9.26)
Hazard ratio for duvelisib/ofatumumab	0.377		0.363	
(95% prediction interval)	(0.350, 0.426)		(0.340, 0.397)	
Delta=3				
Median estimate in months (95% prediction interval)	16.26 (14.65, 16.36)	9.13 (8.97, 9.20)	16.76 (16.66, 17.77)	9.26 (9.17, 9.26)
Hazard ratio for duvelisib/ofatumumab	0.379		0.367	
(95% prediction interval)	(0.352, 0.428)		(0.343, 0.398)	

Source: MI_IRC_primary, MI_INV_primary (data on file)

Abbreviations: BID = twice daily; IRC = Independent Review Committee; PFS = progression-free survival

Table 35 PFS Sensitivity Analysis iv: Subjects who Received New Anticancer Therapy Before Documented PFS are Imputed as PFS Events at Date of Switch, Subjects with at Least Two Prior Therapies – Study IPI-145-07

	IRC Assessment		Investigator Assessment	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
Subjects with events, n (%)	61 (64.2)	85 (84.2)	58 (61.1)	86 (85.1)
Progression	50 (52.6)	77 (76.2)	44 (46.3)	75 (74.3)
Death without progression	11 (11.6)	8 (7.9)	14 (14.7)	11 (10.9)
Subjects censored, n (%)	34 (35.8)	16 (15.8)	37 (38.9)	15 (14.9)
No evidence of progression or death	30 (31.6)	8 (7.9)	34 (35.8)	8 (7.9)
No adequate baseline disease assessment	2 (2.1)	3 (3.0)	2 (2.1)	3 (3.0)
No adequate post-baseline disease assessment	2 (2.1)	5 (5.0)	1 (1.1)	4 (4.0)
Percentiles, estimate in months (95% CI)				
25th percentile	8.8 (5.5, 10.2)	4.0 (3.1, 5.1)	9.7 (8.2, 11.5)	3.9 (3.4, 5.4)

	IRC Assessment		Investigator Assessment	
	Duvelisib 25 mg BID (N=95) n (%)	**Ofatumumab (N=101) n (%)**	**Duvelisib 25 mg BID (N=95) n (%)**	**Ofatumumab (N=101) n (%)**
Median (50th percentile)	14.7 (11.6, 19.3)	8.8 (5.5, 9.2)	16.8 (12.6, 21.9)	9.1 (6.1, 9.4)
75th percentile	25.6 (19.5, NE)	12.6 (9.9, 12.9)	24.8 (22. 7, NE)	12.9 (10.9, 14.1)
Hazard ratio for duvelisib/ofatumumab	0.34		0.36	
(95% confidence interval) [b]	0.24, 0.50		0.25, 0.52	
p-value [a]	<.0001		<.0001	

Abbreviations: BID = twice daily; CI = confidence interval; IRC = Independent Review Committee; PFS = progression-free survival

[a] One-sided stratified log-rank test to compare duvelisib 25 mg BID versus ofatumumab using randomisation strata as used for randomisation.

[b] Stratified Cox proportional hazards model using randomisation strata as used for randomisation.

Key secondary endpoints: ORR and OS

Table 36 ORR, blinded IRC (ITT)

Best Overall Response	Duvelisib (N=160) n (%)	Ofatumumab (N=159) n (%)	P-value [a]
Overall Response Rate (ORR) (CR, CRi, PR, or PRwL)	**118 (73.8)**	**72 (45.3)**	**< 0.0001**
95% Confidence Interval	*(66.9, 80.6)*	*(37.5, 53.0)*	
Odds Ratio (95% Confidence Interval)	*3.50 (2.16, 5.65)*		
ORR without PRwL (CR, CRi, or PR)	117 (73.1)	72 (45.3)	< 0.0001
95% Confidence Interval	*(66.3, 80.0)*	*(37.5, 53.0)*	
Odds Ratio (95% Confidence Interval)	*3.37 (2.09, 5.43)*		
CR	1 (0.6)	1 (0.6)	
CRi [b]	0	0	
PR	116 (72.5)	71 (44.7)	
PRwL	1 (0.6)	0	
SD	34 (21.3)	63 (39.6)	
PD	2 (1.3)	10 (6.3)	
Other [c]	6 (3.8)	14 (8.8)	

Abbreviations: CR = complete response; CRi = complete response with incomplete marrow recovery; ITT = intent-to-treat; ORR = overall response rate; PD = progressive disease; PR = partial response; PRwL = partial response with lymphocytosis; SD = stable disease.

Note: Percentages are based on the number of intent-to-treat subjects in each treatment group. The overall response is determined using the best overall response from the blinded IRC.

a. One-sided stratified Cochran-Mantel-Haenszel test to compare duvelisib 25 mg BID versus ofatumumab using randomization strata, as randomized.
b. CRi applies to subjects with a diagnosis of CLL only.
c. Other includes responses of Unknown due to missing, incomplete, or inadequate data; No Evidence of Disease if radiological and clinical data indicate no disease involvement; and Not Evaluable if no target lesions were identified at Baseline and the radiological and clinical data at post-Baseline does not support the disease response of PD or Unknown.

Source: Table 14.2.2.1

Source: CSR-07

Table 37 Efficacy in CLL or SLL After at Least Two Prior Therapies (IPI-145-07)

Outcome per IRC	COPIKTRA N = 95	Ofatumumab N = 101
PFS		
Median PFS (95% CI), months [a]	16.4 (12.0, 20.5)	9.1 (7.9, 10.7)
Hazard Ratio (95% CI), [b] COPIKTRA/ofatumumab	0.4 (0.27, 0.59)	
p-value	≤0.0001	
Response rate		
ORR, n (%)[c] (95% CI)	75 (78.9) (70.7, 87.1)	39 (38.6) (29.1, 48.1)
p-value	≤0.0001	
LNRR[d], n (%)[c] (95% CI)	84 (88.4) (82.0, 94.9)	14 (13.9) (7.1, 20.6)

Outcome per IRC	COPIKTRA N = 95	Ofatumumab N = 101
OS[e]		
Median OS (95% CI), months [a]	NE	NE
Hazard Ratio (95% CI), [b] COPIKTRA/ofatumumab	0.82 (0.49, 1.37)	
p-value	0.4397	

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; PFS = progression-free survival; PR = partial response; SE = standard error

[a] Kaplan-Meier estimate

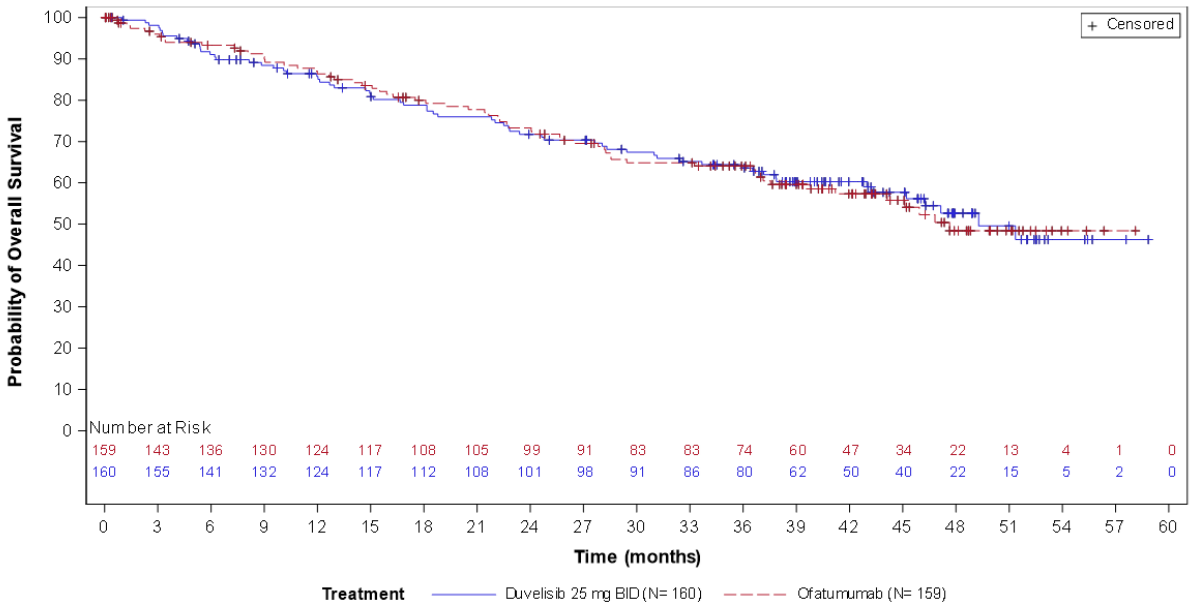
[b] Stratified Cox proportional hazards model using randomisation strata as used for randomisation

[c] IWCLL or revised IWG response criteria, with modification for treatment-related lymphocytosis

[d] Lymph node response rate, with lymph node response defined as ≥ 50% decrease in the sum of the products (SPD) of target lymph nodes

[e] Overall survival (OS) analysis includes data from subjects who received ofatumumab on Study and subsequently received duvelisib in an extension study, based on intent-to-treat analysis. Subjects in both arms continued to be followed for OS after discontinuation of randomised treatment, regardless of subsequent therapies received.

Figure 20 updated OS results for all subjects in the ITT analysis set



Source: MAA CLL/SLL Efficacy TLFs Study IPI-145-07 Updated Survival Analysis Figure 14.2.3.1

The OS analysis for all subjects in the ITT analysis set and for subjects with 2 or more prior systemic therapies in the ITT analysis set, comparing the results for the primary endpoint analysis and the OS update – presented below

Table 38 OS results comparison: primary endpoint analysis and the OS update (ITT)

	Primary Endpoint Analysis (19 May 2017 data cutoff)		OS update (22 March 2019 data cutoff)	
	Duvelisib 25 mg BID (N=160)	Ofatumumab (N=159)	Duvelisib 25 mg BID (N=160)	Ofatumumab (N=159)
Death, n (%)	46 (28.8)	45 (28.3)	64 (40.0)	62 (39.0)
Censored, n (%)	114 (71.3)	114 (71.7)	96 (60.0)	97 (61.0)
Median OS in months (95% CI)	NE (31.1, NE)	NE (28.6, NE)	49.3 (43.2, NE)	47.6 (39.8, NE)
Hazard Ratio for Duvelisib/Ofatumumab (95% Confidence Interval)	0.99 (0.65, 1.50)		0.99 (0.70, 1.40)	
p-value	0.4807		0.4753	

Source: MAA CLL/SLL Efficacy TLFs Study IPI-145-07 Updated Survival Analysis Table 14.2.4.1 (22 March 2019 data cutoff)

Table 39 OS results comparison: primary endpoint analysis and the OS update- patients with 2 or more prior systemic therapies

	Original NDA Submission (19 May 2017 data cutoff)		Interim OS update (22 March 2019 data cutoff)	
	Duvelisib 25 mg BID (N=95)	Ofatumumab (N=101)	Duvelisib 25 mg BID (N=95)	Ofatumumab (N=101)
Death, n (%)	28 (29.5)	34 (33.7)	42 (44.2)	44 (43.6)
Censored, n (%)	67 (70.5)	67 (66.3)	53 (55.8)	57 (56.4)
Median OS in months (95% CI)	NE (27.6, NE)	NE (24.1, NE)	46.3 (32.4, NE)	41.2 (28.6, NE)
Hazard Ratio for Duvelisib/Ofatumumab (95% CI)	0.82 (0.49, 1.37)		0.89 (0.58, 1.38)	

Abbreviations: BID = twice daily; CI = confidence interval; NDA = new drug application; NE = Not Estimated; OS = overall survival.

Source: MAA CLL/SLL Efficacy TLFs Study IPI-145-07 Updated Survival Analysis Table 14.2.4.1.1 (22 March 2019 data cutoff)

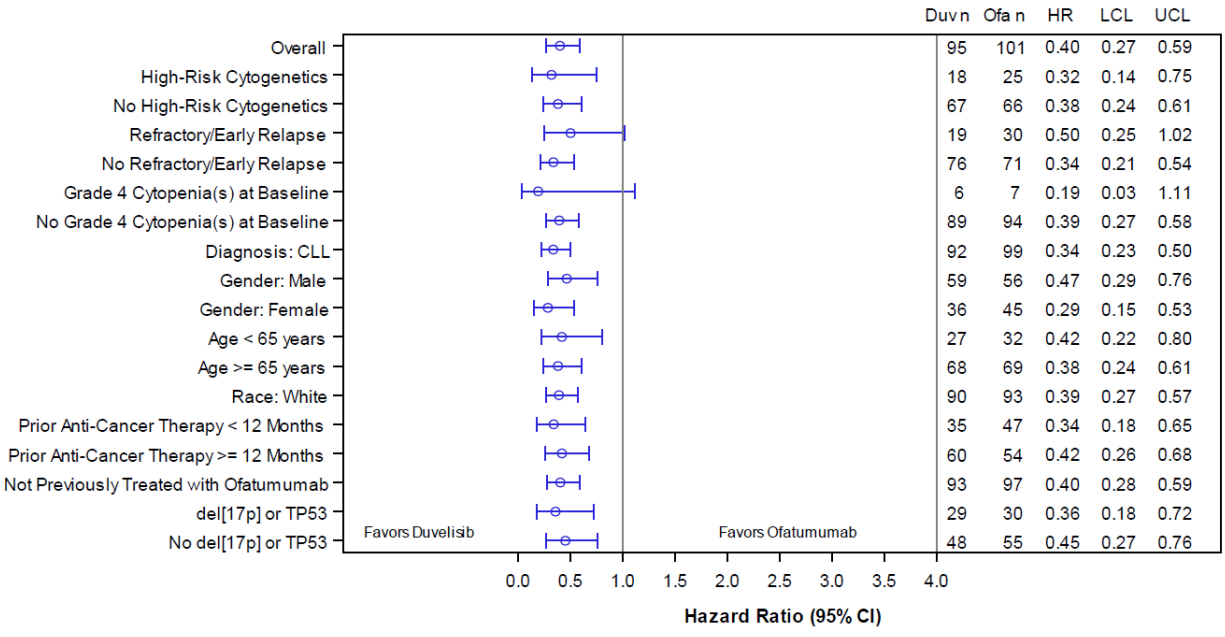
Ancillary analyses

Ten predefined subgroup analyses were performed for PFS per IRC, including the 3 stratification variables at randomisation. The subgroup analysis demonstrated consistent results of PFS improvement with duvelisib with HR below 1.

Table 40 Summary of PFS and response rates in subgroups therapy in Patients with at Least 2 Prior Therapies – (IPI-145-07)

Outcome per IRC	**COPIKTRA**	**Ofatumumab**
17p deletion/*TP53* mutation	**N=29**	**N=30**
Median PFS (95% CI), months [a]	12.8 (8.9, 22.1)	8.7 (5.3, 12.6)
Hazard Ratio (95% CI), [b] COPIKTRA/ofatumumab	0.36 (0.18, 0.72)	
ORR, (95% CI)[c]	72.4 (56.1, 88.7)	36.7 (19.4, 53.9)
Age ≥65	**N=68**	**N=69**
Median PFS (95% CI), months [a]	16.4 (10.4, 24.0)	9.2 (8.7, 10.8)
Hazard Ratio (95% CI), [b] COPIKTRA/ofatumumab	0.38 (0.24, 0.61)	
ORR, (95% CI)[c]	77.9 (68.1, 87.8)	39.1 (27.6, 50.6)
Unmutated IGHV	**N=65**	**N=70**
Median PFS (95% CI), months [a]	17.4 (12.0, 24.0)	9.0 (7.3, 10.7)
Hazard Ratio (95% CI), [b] COPIKTRA/ofatumumab	0.27 (0.17, 0.45)	
ORR, (95% CI)[c]	86.2 (77.8, 94.6)	40 (28.5, 51.5)

Figure 21 Hazard ratios (duvelisib/ofatumumab) for patients having received ≥ 2 prior treatments



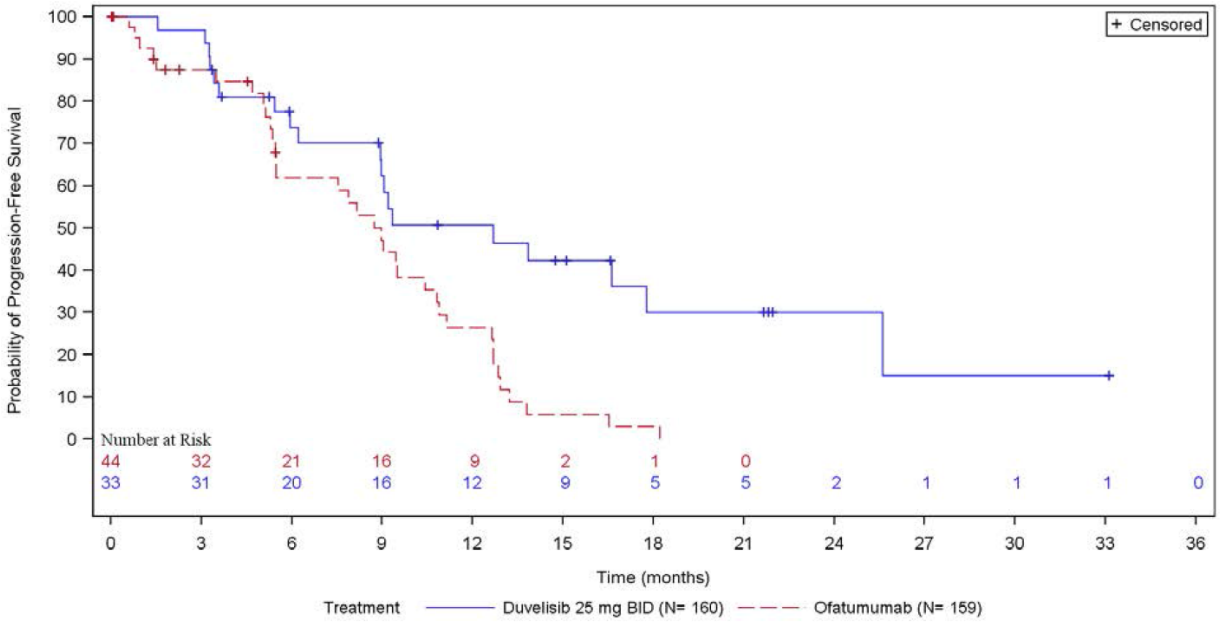
Abbreviations: CI = confidence interval; DUV = duvelisib; HR = hazard ratio; IRC = Independent Review Committee; LCL = lower confidence level; OFA = ofatumumab; PFS = progression-free survival; UCL = upper confidence level.
Source: MAA Efficacy TLFs Study IPI-145-07 Study Figure 14.2.1.6.1

Table 41 PFS in Subjects with 17p Deletion ITT population

Category	Duvelisib (N=33)	Ofatumumab (N=44)
Subjects with Event (Progression or Death), n (%)	19 (57.6)	35 (79.5)
Disease Progression	*14 (42.4)*	*33 (75.0)*
Death before progression	*5 (15.2)*	*2 (4.5)*
Subjects Censored, n (%)	14 (42.4)	9 (20.5)
No evidence of progression or death	*9 (27.3)*	*2 (4.5)*
No adequate Baseline disease assessment	*1 (3.0)*	*2 (4.5)*
No adequate post-Baseline disease assessment	*0*	*2 (4.5)*
Documented progression or death following a long gap between adequate disease assessments	*0*	*0*
New anticancer treatment or procedure started before documented progression	*4 (12.1)*	*3 (6.8)*
Percentiles, Estimate in Months (95% Confidence Interval)		
25th Percentile	5.9 (3.3, 9.1)	5.3 (1.5, 7.5)
Median (50th Percentile)	12.7 (8.9, 17.8)	9.0 (5.5, 10.8)
75th Percentile	25.6 (13.8, NE)	12.6 (9.5, 12.9)
Kaplan-Meier Event-Free Estimate (95% Confidence Interval)		
Month 6	0.74 (0.54, 0.86)	0.62 (0.44, 0.75)
Month 12	0.51 (0.31, 0.67)	0.27 (0.13, 0.42)
Hazard Ratio for Duvelisib/Ofatumumab (95% Confidence Interval) [a]	0.41 (0.23, 0.74)	
P-value [b]	0.0011	

Abbreviations: NE = Not Estimable
Note: Percentages are based on the number of intent-to-treat subjects in each treatment group.
a. Stratified Cox proportional hazards model using randomization strata as used for randomization.
b. One-sided stratified log-rank test to compare duvelisib vs ofatumumab using randomization strata as used for randomization.
Source: Table 14.2.1.10

Figure 22 PFS in subjects with 17p deletion (ITT)



Abbreviations: BID = twice a day; IRC = independent review committee; ITT = intent-to-treat.
Source: Figure 14.2.1.7; Listing 16.2.6.1

Subjects Refractory/Early Relapse to Purine Analogue-Based Therapy

Patients refractory to or with an early relapse after purine analogue-based therapy (stratification factor at randomisation) have a dismal prognosis. In study IPI-145-07 the median PFS for these patients for duvelisib was 10.4 months (95% CI: 9.0, 16.6) and for ofatumumab 8.1 months (95% CI: 3.4, 10.4)). The hazard ratio for duvelisib vs ofatumumab was 0.51 (95% CI: 0.27, 0.96). In patients not refractory/early relapse to prior purine analogue-based therapy the median PFS for duvelisib was 15.1 months (95% CI: 12.7, 17.8) and for ofatumumab 10.8 months (95% CI: 9.3, 12.6). The hazard ratio for duvelisib vs ofatumumab was 0.53 (95% CI: 0.38, 0.73).

Subjects with unmutated IGHV

An analysis of PFS in subjects with unmutated IGHV was also performed.

Table 42 PFS per IRC Assessment (ITT Analysis Set) in Subjects with Unmutated IGHV – Study IPI-145-07

Endpoint	Duvelisib (N =110)	Ofatumumab (N =116)
PFS		
Median (95% CI) (months)	13.8 (12.7, 19.4)	9.5 (9.0, 11.1)
Hazard Ratio for Duvelisib/ Ofatumumab (95% CI)	0.39 (0.27, 0.55)	
p-value[a]	<0.0001	

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; ITT = Intent-to-Treat; PFS = progression-free survival;
[a] One-sided log-rank test to compare duvelisib 25 mg BID vs ofatumumab.
Source: MAA CLL/SLL Efficacy TLFs Study IPI-145-07 Table Table 3l_ighv

Summary of main efficacy results

Table 43 Summary of efficacy for trial IPI-145-07: A Phase 3 Study of Duvelisib vs Ofatumumab

Title: A Phase 3 Study of Duvelisib (IPI-145) vs Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma		
Study identifier	Protocol number: IPI-145-07 EudraCT number: 2013-003639-31	
Design	Randomised, Controlled, Parallel Arm, Open-label, Active Comparison, Multi-centre	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	40 months Not applicable 32.5 months (Study IPI-145-12)
Hypothesis	Superiority	
Treatments groups	Duvelisib 25 mg BID (DUV)	Duvelisib 25 mg BID administered orally (as capsules) twice daily in 28-day cycles throughout the study (with the exception of Cycle 1 which was 21 days). The median duration of exposure for the duvelisib arm was 50 weeks (range: 1-160) 160 subjects were randomised to receive duvelisib

	Ofatumumab (OFA)		8 weekly infusions, starting with an initial dose of ofatumumab 300 mg IV on Day 1, followed by 7 weekly doses of 2000 mg IV; thereafter, subjects received ofatumumab 2000 mg IV once every month for 4 months. Administration of ofatumumab was not to exceed 12 doses (within 7 cycles), as described in the prescribing information. The median duration of exposure for the ofatumumab arm was 23 weeks (range: 1-26). 159 subjects were randomised to receive ofatumumab
Endpoints and definitions	Primary endpoint	Progression -free survival (PFS)	Time from randomisation to the first documentation of progressive disease (PD) as determined by independent review or death due to any cause. PFS will be estimated using Kaplan-Meier method.
	Key secondary endpoint	Overall response rate (ORR)	Overall response (based on independent review) is defined as the best response of complete response/remission (CR), CR with incomplete marrow recovery (CRi), partial response/remission (PR), or PR with lymphocytosis (PRwL), according to the IWCLL or revised IWG Response Criteria, with modification for treatment-related Lymphocytosis
	Secondary endpoint	Lymph node response rate (LNRR)	Lymph node response is defined as ≥ 50% decrease in the sum of the products (SPD) of target lymph nodes (*not shown)*
	Key secondary endpoint	Overall survival (OS)	Time from randomisation to death. OS will be estimated using Kaplan-Meier method (*not shown; no difference shown or expected)*
	Secondary endpoint	Duration of response (DOR)	Time from the first documentation of response to first documentation of PD or death due to any cause. DOR will be estimated using Kaplan-Meier method (*not shown)*
Database cut-off	19 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: all randomized subjects who receive any amount of study drug with treatment group designated according to randomisation The primary analysis was to be performed after approximately 185 PFS events were observed		

Descriptive statistics and estimate variability	Treatment group	DUV *{as per above terminology}*	OFA *{as per above terminology}*
	Number of subjects	160	159
	PFS Median (months)	13.3	9.9
	95% Confidence Interval	(12.1,16.8)	(9.2,11.3)
Effect estimate per comparison	Primary endpoint (PFS by independent review)	Comparison groups	DUV, OFA
		Hazard ratio (Stratified Cox proportional hazards model using randomisation strata as used for randomisation)	0.52
		95% confidence interval	(0.39, 0.69)
		P-value (One-sided stratified log-rank test to compare DUV versus OFA using randomisation strata as used for randomisation)	< 0.0001
Notes	Among the 160 subjects randomised to receive DUV, there were 93 PFS events (74 subjects with progression, 19 subjects who died). Among the 159 subjects randomised to receive OFA, there were 110 PFS events (101 subjects with progression, 9 subjects who died)		
Analysis description	**Secondary Analysis (pre-specified)**		
Analysis population and time point description	Intent to treat: all randomised subjects who received any amount of study drug with treatment group designated according to randomisation The secondary analysis was performed at the same time the primary analysis was performed		

Descriptive statistics and estimate variability	Treatment group	DUV	OFA
	Number of subjects	160	159
	ORR (percentage of subjects achieving CR, CRi, PR, or PRwL)	73.8	45.3
	95% Confidence Interval	(66.9, 80.6)	(37.5, 53.0)
Effect estimate per comparison	Secondary endpoint (ORR by independent review)	Comparison groups	DUV, OFA
		Odds Ratio	3.37
		95% confidence interval	(2.09, 5.43)

		P-value (One-sided stratified Cochran-Mantel-Haenszel test to compare DUV versus OFA using randomization strata, as randomised)	< 0.0001
Analysis description	**Secondary Analysis (post-hoc)**		
Analysis population and time point description	Intent to treat: all randomised subjects who received any amount of study drug with the treatment group with ≥ 2 prior therapies The secondary analysis was performed at the same time the primary analysis was performed		
Descriptive statistics and estimate variability	Treatment group	DUV	OFA
	Number of subjects	95	101
	PFS Median (months)	16.4	9.1
	95% Confidence Interval	(12.0, 20.5)	(7.9, 10.7)
Effect estimate per comparison	Primary endpoint (PFS by independent review)	Comparison groups	DUV, OFA
		Hazard ratio	0.4
		95% confidence interval	(0.27, 0.59)
		P-value (One-sided stratified log-rank test to compare DUV versus OFA using randomisation strata as used for randomisation)	< 0.0001
Descriptive statistics and estimate variability	ORR (percentage of subjects achieving CR, CRi, PR, or PRwL)	78.9	38.6
	95% Confidence Interval	(70.7, 87.1)	(29.1, 48.1)
	Secondary endpoint (ORR by independent review)	Comparison groups	DUV, OFA
		Odds Ratio	6.74
		95% confidence interval	(3.38, 13.43)

Effect estimate per comparison		P-value (One-sided stratified Cochran-Mantel-Haenszel test to compare DUV versus OFA using randomisation strata, as randomised)	< 0.0001

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

Not applicable

Clinical studies in special populations

Table 44 Age groups in trials IPI-145-02, IPI-145-06, IPI-145-07, IPI-145-12

	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 (N=158)	64/158	44/158	3/158
Non-controlled trials (N=145)	53/145	28/145	2/145

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia

Main study in FL - Study IPI-145-06

A Phase 2 Study of IPI-145 in Subjects with Refractory indolent non-Hodgkin lymphoma

Methods

Study Participants

Inclusion Criteria

For inclusion into the study, subjects were required to fulfil all of the following criteria:

- Age 18 years or older.
- Subjects who have been diagnosed with indolent NHL (defined as FL, MZL [splenic, nodal and extranodal], or SLL) that has progressed.
    - For subjects for whom the most recent biopsy was performed > 36 months before the first dose of duvelisib, a repeat biopsy to confirm histology was to be performed, unless medically contraindicated.

- For subjects who progressed within 2 months of initiating last prior chemotherapy, a repeat biopsy to confirm histology was to be performed, unless medically contraindicated.

- Subjects must have disease that is refractory to a chemotherapy regimen or RIT. The chemotherapy regimen (with or without rituximab) must have contained at least 1 alkylating agent or purine nucleoside antagonist. Refractory is defined as either:
  - Lack of a CR or PR while receiving the chemotherapy regimen or RIT or:
  - Progressive disease (PD) within 6 months of the last dose of the chemotherapy regimen or RIT documented by computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI) obtained within 6 months after the last dose

    Subjects exhibiting clinical progression within 6 months after the last dose of a chemotherapy regimen or RIT who were unable to undergo CT, PET/CT, or MRI within the 6-month timeframe were allowed up to an additional 30 days to confirm radiologic progression.
- Subjects must have disease that is refractory to rituximab. (see table 23 below)
- Lack of a CR or PR during treatment with a full course of single-agent rituximab (≥ 4 doses of 375 mg/m2, weekly) or ≥ 2 doses of ≥ 375 mg/m2 of rituximab in combination with chemotherapy
- PD within 6 months of the last dose of a full course of single-agent rituximab or rituximab in combination with chemotherapy
- PD during, or within 6 months of the last dose of, a rituximab maintenance therapy
- Measurable disease with a lymph node or tumour mass ≥ 1.5 cm in at least 1 dimension by CT, PET/CT, or MRI.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (corresponds to Karnofsky Performance Status [KPS] ≥ 60%).
- Adequate renal function, defined as serum creatinine ≤ 2 x upper limit of normal (ULN).
- Adequate hepatic function, defined as total bilirubin ≤ 1.5 x ULN (unless elevated due to Gilbert's syndrome) and AST and ALT levels ≤ 3x ULN.
- Negative serum or urine β human chorionic gonadotropin (βhCG) pregnancy test within 1 week before first dose of study drug if the subject is a woman of childbearing potential (WCBP) (defined as a sexually mature woman who has not undergone surgical sterilisation or who has not been naturally post-menopausal for at least 24 consecutive months for women ≤ 55 years or 12 consecutive months for women > 55 years).
- Willingness of male and female subjects who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study, including 30 days after the last dose of duvelisib. Sexually active men, and women using oral contraceptive pills, were also to use barrier contraception.
- Ability to adhere to the study visit schedule and all protocol requirements.
- Signed and dated IRB-/IEC-approved informed consent form before any study-specific Screening procedures were performed.

Table 45 Refractoriness to prior therapy as eligibility requirement for study IPI-145-06

Prior Therapy	Requirement
Chemotherapy regimen or RIT *The chemotherapy regimen must have contained at least 1 alkylating agent or purine nucleoside antagonist*	– No response (CR/PR) while receiving treatment OR – PD within 6 months of the last dose of therapy as documented by computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI) obtained within 6 months after the last dose
Rituximab	– No response (CR/PR) during treatment with a full course of single-agent rituximab (≥ 4 doses of 375 mg/m^2, weekly), or ≥ 2 doses of ≥ 375 mg/m2 of rituximab in combination with chemotherapy OR – PD during or within 6 months of the last dose of a full course of single-agent rituximab/rituximab-chemotherapy/rituximab maintenance therapy
Abbreviations: CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PR = partial response; RIT = radioimmunotherapy. Source: Study IPI-145-06 CSR.	

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the study:

- Candidate for potentially curative therapies at the time of informed consent, in the opinion of the Investigator.
- Prior treatment with any PI3K inhibitor or Bruton's tyrosine kinase (BTK) inhibitor.
- Prior history of allogeneic hematopoietic stem cell transplant.
- Major surgery within 28 days before the first dose of study drug.
- Prior chemotherapy, cancer immunosuppressive therapy, or other investigational agents within 4 weeks before first dose of study drug.
- Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or systemic steroids > 20 mg prednisone (or equivalent) once daily (QD).
- Grade 3B FL and/or clinical evidence of transformation to a more aggressive subtype of lymphoma.
- Symptomatic central nervous system (CNS) NHL; a lumbar puncture was not required unless CNS involvement with NHL was clinically suspected.
- Ongoing systemic bacterial, fungal, or viral infections at the time of initiation of study treatment (defined as requiring therapeutic dosing of an antimicrobial, antifungal, or antiviral agent). Note: Subjects on antimicrobial, antifungal, or antiviral prophylaxis were not specifically excluded if all other inclusion/exclusion criteria were met and there was no presence of active infection.
- Human immunodeficiency virus (HIV) infection.

- Baseline QTc measurements using the Fridericia's correction method (QTcF) > 500 ms (average of triplicate readings). Note: This criterion did not apply to subjects with a right or left bundle branch block.
- Prior, current, or chronic hepatitis B or hepatitis C infection or positive result for anti-hepatitis C antibody (HCVAb), hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb).
- Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster virus (HZV) at time of initiation of study treatment.
- History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause, or suspected alcohol abuse (iNHL in the liver was not an exclusion criterion).
- Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition); any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the subject's risk to participating in this study.
- Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix, bladder cancer, or prostate cancer not requiring treatment. Subjects with previous malignancies were eligible provided that they had been disease-free for 2 years or more.
- History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to first dose of study drug.
- Prior surgery or gastrointestinal dysfunction that may affect absorption of study drug (eg, gastric bypass, gastrectomy).
- Use of live or live attenuated vaccines within 30 days prior to signing informed consent form.
- Administration of medications or foods that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A within 2 weeks prior to the first dose of study drug treatment.
- Female subjects who are pregnant or breastfeeding.

FL patients refractory to rituximab + chemotherapy or RIT have a dismal prognosis: The applicant has stated that PFS decreases with additional lines of therapy and is estimated to be 1.5 years, 1.1 years, and <1 year, among second-, third-, and fourth-line FL patients, respectively.

Patients with prior treatment with any PI3K inhibitor or Bruton's tyrosine kinase (BTK) inhibitor were excluded, which may have implications for the indication. This is discussed later.

Treatments

Dose modifications and dosing levels after various AEs were as in the pivotal CLL study (07). Duvelisib was administered orally (as capsules) twice daily in 28-day cycles throughout the study until disease progression or unacceptable toxicity. The starting dose was 25 mg BID, although doses may have been modified (reduced or held) for individual subjects experiencing toxicities assessed as at least possibly related to duvelisib or at the discretion of the Investigator.

Table 46 Dose modifications based on the occurrence of duvelisib-related toxicities

Duvelisib-related Toxicities [a, b]	Dose Interruption/Hold/Modification/Recommendation for Duvelisib [c]
Non-hematologic: Grade 2 or higher Pneumonitis/Pneumonia Or Grade 3 or higher all other Nonhematologic	**First occurrence:** Withhold until return to ≤ Grade 1 or baseline level; re-challenge therapy at original dose level. **Second occurrence of same AE:** Withhold until return to ≤ Grade 1 or baseline level; re-initiate therapy at one dose level lower from current dose. **Third occurrence of same AE:** Withhold until return to ≤ Grade 1 or baseline level; re-initiate therapy at one dose level lower from current dose. **Fourth occurrence of same AE:** Discontinue subject from study drug.
Hematologic: Grade 3 or higher febrile neutropenia Or New Grade 4 neutropenia > 7 days duration Or Grade 3 or higher thrombocytopenia with Grade ≥ 2 hemorrhage Or New Grade 4 thrombocytopenia of any duration requiring transfusion support	

Recommendations for implementation of dose interruption

Immediate hold for Grade 4 or higher nonhematologic toxicities and Grade 3 or higher febrile neutropenia.

For all other events, reduce from BID dosing to QD for two days, then hold.

ABBREVIATIONS: AE = adverse event; BID = twice daily.

a. Duvelisib-Related=possible, probable, or definite relationship to duvelisib determined by Investigator.
b. Toxicity grades are defined per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Note: If parameter is not defined by CTCAE, then AE grading criteria according to the study protocol were to be utilized.

Table 47 Duvelisib dose levels

Dose Level	Dose (mg)
1	25 BID
-1	15 BID
-2	10 BID
-3	5 BID

ABBREVIATION: BID = twice daily.

Objectives

Primary Objective

The primary objective of this study was to evaluate the antitumour activity of duvelisib administered to subjects diagnosed with iNHL (defined as FL, SLL, or MZL [splenic, nodal and extranodal]) whose disease is refractory to rituximab and to either chemotherapy or RIT.

Secondary Objectives

- To evaluate the safety of duvelisib in all subjects
- To evaluate additional efficacy parameters in all subjects
- To evaluate the PK of duvelisib and, if applicable, its metabolite(s)

Outcomes/endpoints

Primary endpoint

ORR

ORR, with overall response defined as best response of a complete response/remission (CR) or partial response/remission (PR) according to the International Working Group (IWG) Criteria. The independent review committee assessment was used for the primary analysis.

Key secondary endpoints

Duration of response (**DOR**) is defined as the time from the first documentation of response to the first documentation of progressive disease (PD) or death due to any cause.

Progression-free survival (**PFS**) is defined as the time from the first dose of study treatment to the first documentation of PD or death due to any cause.

Overall survival (**OS**) is defined as the time from the first dose of study treatment to the date of death.

Time to response (**TTR**) defined as the time from the first dose of study treatment to the first documentation of response (complete or partial).

The primary endpoint of IRC-ORR was defined as best response of CR or PR according to the revised IWG Criteria (Cheson et al., 2007). The applicant formulated several key secondary endpoints: DOR, PFS, OS, TTR as well as several exploratory endpoints. The choice of ORR as primary endpoint is considered appropriate for a phase 2 study, and the secondary endpoints are meaningful although difficult to interpret given the single-arm design.

This study aims to demonstrate the null hypothesis that the primary endpoint ORR is ≤30% against the alternative that ORR is ≥45%. Approximately 120 patients are planned to be enrolled to achieve 90 % power at alpha level of 0.025. Of those 120 subjects, 80 will be FL. One interim futility analysis (non-binding) will be performed 4 months after at least 30 subjects (25% of total) have initiated treatment.

The applicant defined as the null hypothesis an ORR equal or below 30 % responders. However, the alternative hypothesis is ORR equal or larger than 45 %. It could be understood that the applicant would aim to ORR around 45 % but any response rate larger than 30 % would be considered successful. Furthermore, the applicant did not specify whether the 30 % limit should be crossed by the estimate or the lower bound of the confidence interval. The applicant clarified that the study was to be considered successful if the p-value for a 1-sided exact binomial test was significant at the 0.025 level, which would be generally consistent with a lower bound of a two-sided 95% CI that exceeds 30%.

Initially the ORR was expected to be ≥ 55%: "A sample size of approximately 120 iNHL subjects with at least 100 FL subjects with an expected ORR of 55% will have 2-sided, 95% confidence bounds of 45.7%-64.1% when the exact binomial method is employed. These bounds about the ORR are thought to adequately characterise the clinical activity of IPI-145 in this patient population" (Initial protocol April 2, 2013 page 21/80). The applicant clarified that there were no assumptions specified regarding the ORR for the FL population.

In the protocol v3 (3 Nov 2015), the null hypothesis was changed to ORR ≤30% against the alternative ORR ≥45% and the number of FL patients to be included changed from 100 to 80. The applicant explained that the sample size was changed based on the accrual pattern.

Randomisation and blinding (masking)

This is a single arm study.

Statistical methods

Analysis sets:

The primary efficacy analysis was based on a modified ITT population, including all subjects who had received at least one dose of duvelisib regardless of diagnosis. The Evaluable Analysis Set included only patients who did not have major protocol deviations, received treatment for at least 8 weeks and have adequate baseline and at least one post-baseline tumour assessment. The EAS was used as a secondary analysis set for selected efficacy analyses.

The use of a complete ITT population as the primary analysis population would have been preferred in order to preserve the ITT principle. All patients who successfully completed the screening phase were treated. Therefore, it is understood that a complete ITT population and the m-ITT would have been identical in this case. The use of the EAS in supplementary analysis is agreed.

Interim analysis (futility) for ORR:

This study has one primary endpoint and several secondary endpoints. Multiplicity correction due to several secondary endpoints was not planned. One interim futility analysis was planned for ORR. The IA was scheduled around 4 months after at least 30 subjects had received duvelisib. The interim analysis was conducted based on the Investigator's assessment and a recommendation on futility of the study was provided by an Independent Data Monitoring Committee.

It is agreed that the IA for futility does not affect the type I error. Since no strategy was planned to control for multiplicity across several secondary endpoints, those are considered exploratory.

Primary endpoint/ORR:

A one-sided exact binomial test at 0.025 was used to test ORR against the null hypothesis (% CR + PR ≤30%). The test will be performed in the overall population (FL+MZL+ SLL). The proportion of responders will be presented for the individual diseases although they will not be tested. Patients with missing or non-evaluable response rate were set to non-responders. No sensitivity analyses were planned for the FL population.

The use of the binomial test to compare the proportion of responders is acceptable. In the result section, the percentage of responders for each subgroup is presented together with the 95 % CI. The applicant explained that the Clopper-Pearson method was used, which is agreed. The imputation of missing data as non-responders is agreed since it is a conservative approach in a single arm trial.

Key secondary endpoints:

PFS, DOR and OS were analysed using the Kaplan-Meier method. The censoring rules for PFS and DOR included censoring of patients without adequate baseline assessment. Patients without adequate postbaseline assessment were also censored unless death occurred before their first scheduled assessment. Patients without documented progression or death before the data cut-off were also censored. If an event was documented before a long gap between assessment, those events were considered in the analysis, otherwise the patient was censored at the last date of assessment before the gap. Patients were also censored if they started a new anticancer therapy before documented progression. The censoring rules for OS included censoring of patients without documented death at the date of last contact.

The use of Kaplan-Meier method for DOR, PFS and OS is endorsed. The censoring rules for PFS are not agreed. The applicant assumed that patients who were censored due to other reasons than still being in the study without experiencing an event (e.g. treatment switch, lost to follow-up) have similar risk for progression/ death than the patients who remained in the study. This assumption has not been justified and it is in general not considered plausible. For example, study discontinuation could be related to lack of efficacy or tolerability, and therefore those patients are not similar to those who continued in the study. According to the IRC-assessment for PFS, 61 patients were censored in the overall population, of those 40 were censored with no evidence of progression or death and 14 were censored due to switch to new treatment.

Results

Participant flow

Figure 23 Participant flow

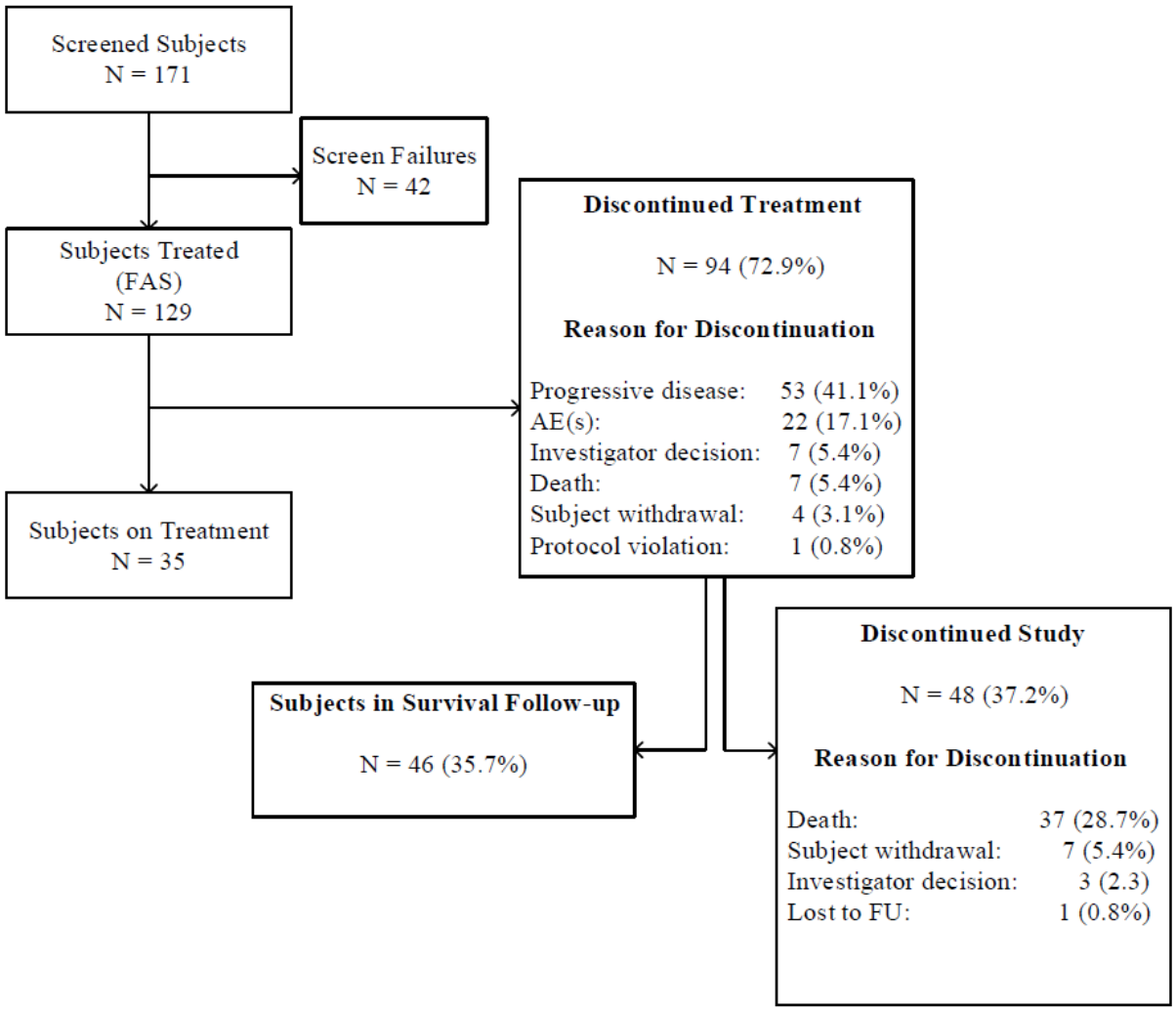


Table 48 Subject disposition Study IPI-145-06 (FAS)

Characteristic	FL (N=83)	SLL (N=28)	MZL (N=18)	Overall (N=129)
Subjects Still on Treatment, n (%)	3 (3.6)	1 (3.6)	1 (5.6)	5 (3.9)
Subjects off Treatment, n (%)	80 (96.4)	27 (96.4)	17 (94.4)	124 (96.1)
Reason for Treatment Discontinuation, n (%)				
AE	17 (20.5)	8 (28.6)	6 (33.3)	31 (24.0)
Death	5 (6.0)	2 (7.1)	0	7 (5.4)
Noncompliance with Protocol	1 (1.2)	0	0	1 (< 1)
Physician Decision	7 (8.4)	4 (14.3)	1 (5.6)	12 (9.3)
PD	46 (55.4)	12 (42.9)	8 (44.4)	66 (51.2)
Subject Withdrawal	4 (4.8)	1 (3.6)	1 (5.6)	6 (4.7)
Other	0	0	1 (5.6)	1 (< 1)
Subjects in Survival Follow-up, n (%)	24 (28.9)	3 (10.7)	6 (33.3)	33 (25.6)
Median Duration of Duvelisib Exposure [a] (Months), (Min, Max)	4.9 (0.4, 45.5)	11.6 (0.7, 32.1)	8.4 (0.9, 31.3)	6.7 (0.4, 45.5)

Abbreviations: AE = adverse events; FL = follicular lymphoma; SLL = small lymphocytic lymphoma; N = number; MZL = marginal zone lymphoma

max = maximum; min = minimum; PD = progressive disease.

Note: Percentages are based on the number of subjects in each dose group for the All-Treated Analysis Set.

a. Duration of exposure (weeks) = (date of last dose – date of first dose + 1)/7, rounded to one decimal.

Source: MAA FL Efficacy TLFs Table 14.1.1.3, Table 14.1.8.1.

Table 49 Major protocol deviations in study IPI-145-06

Deviation Category/Deviation Term	Overall N = 129 n (%)
Subjects with any major deviation	**49 (38.0)**
Concomitant Medications	**13 (10.1)**
Prophylaxis not administered per protocol	13 (10.1)
Dosing	**12 (9.3)**
Continued treatment after documented disease progression	6 (4.7)
Dose administration and/or modification guidelines not followed	4 (3.1)
Investigational product handling/accountability procedures not followed	2 (1.6)
Exclusion Criteria	**12 (9.3)**

Deviation Category/Deviation Term	Overall N = 129 n (%)
Anticancer therapy administered within 4 weeks before first dose of study drug	2 (1.6)
Prior hepatitis B/hepatitis C infection	2 (1.6)
Screening hepatitis serology test(s) not performed	8 (6.2)
Subject had prior treatment with Bruton's tyrosine kinase inhibitor	1 (0.8)
ICF	**1 (0.8)**
Subject not re-consented to ICF amendment	1 (0.8)
Inclusion Criteria	**13 (10.1)**
Adequate hepatic function not confirmed	2 (1.6)
Subject did not have disease that is refractory to a chemotherapy induction regimen or RIT	9 (7.0)
Subject did not have disease that is refractory to rituximab	2 (1.6)
Informed Consent	**4 (3.1)**
Collection of optional sample without proper consent	4 (3.1)
Other	**2 (1.6)**
Study procedures performed by untrained staff	2 (1.6)
SAE	**5 (3.9)**
SAE/MEOI not reported within the timelines specified in the protocol.	5 (3.9)
Visit Procedure/Requirement	**3 (2.3)**
Subject provided with study materials not approved by IRB/EC	3 (2.3)

ABBREVIATIONS: EC = Ethics Committee; ICF = informed consent form; IRB = Institutional Review Board; MEOI = medical event of interest; RIT = radioimmunotherapy; SAE = serious adverse event.
Source: Table 14.1.2.1, Listing 16.2.2.1

Table 50 Summary of Subjects Censored for IRC-Assessed PFS With No Evidence of Disease Progression or Death – Study IPI-146-06

	FL (N=83)	SLL (N=28)	MZL (N=18)	Overall (N=129)
Subjects censored for IRC-assessment of PFS, n (%)	32 (38.6)	6 (21.4)	10 (55.6)	48 (37.2)
No documented progression or death, n (%)	10 (12.0)	1 (3.6)	5 (27.8)	16 (12.4)
Subjects remaining on treatment	**2**	**0**	**1**	**3**
Subjects discontinued from treatment	**8**	**1**	**4**	**13**
Adverse event	4	0	2	6
Physician decision	2	1	0	3
Disease progression	1	0	1	2
Withdrawal by subject	1	0	0	1
Other	0	0	1	1

Abbreviations: FL = follicular lymphoma; IRC = Independent Review Committee; PFS = progression-free survival; SLL = small lymphocytic lymphoma; MZL = marginal zone B cell lymphoma.
Source: MAA FL Efficacy TLFs Table 14.2.1.1 (Data on file)

SAP Amendment history:

The changes made in the final version of SAP were in line with the changes made in the 4 versions of the protocol and were implemented before the data cut-off date. The changes made in the protocol are of importance and they are discussed in the section Changes in the protocol and sample size. Minor changes regarding descriptive analyses/tables were made. These changes made are not considered to affect the interpretation of the results.

Table 51 Changes in planned analyses in the SAP

SAP Version	Section	Summary of Change	Reason for Change
2.0	3.2	Change the number of FL subjects	Update per Protocol Amendment 2
2.0	3.4	Change internal DMC to external IDMC	Update per Protocol Amendment 2
2.0	5.3	Remove CR as an exploratory endpoint	Update per Protocol Amendment 3
2.0	6.5	Definition of refractory	Be consistent with entry criteria
2.0	6.5	Add additional subgroup analysis for the primary endpoint	Better understand the performance of Duvelisib
2.0	7.1.4	Add analysis of specific prior therapies	Better characterise patient population
2.0	7.2.2.3	Add analysis of OS rate at 12 months	Needed as the median may not be available at the time of primary analysis
2.0	7.2.2.4	Change the analysis method for TTR	TTR can be summarized descriptively as no censoring is involved
2.0	7.3.2	Change the presentation of some lab data	Better present lab data

Baseline data

The median age was 65 years (range: 30-90) and the majority of subjects had an ECOG Performance Status of 0 (46.5%) or 1 (48.1%) at baseline, so quite fit compared to the general relapsed iNHL population. At baseline, the majority of subjects had elevated LDH (66.7%), 40% had bulky disease, and 84.5% had NHL stage III or IV, which are all poor prognostic features as reflected in the prognostic system FLIPI for FL.

The median number of prior systemic regimens was three with 88% having received at least two prior regimens. 94% of FL patients were refractory to their most recent prior anticancer therapy, and 81% were refractory to ≥ 2 prior therapies.

Table 52 Subject Demographics for FAS Overall and by Lymphoma Subtype

Category	FL N = 83	SLL N = 28	MZL N = 18	Overall N = 129
Age (years)				
n	83	28	18	129
Mean	62.0	64.6	69.3	63.6
SD	11.89	9.38	12.61	11.69
Median	64.0	63.0	67.0	65.0
Q1, Q3	55.0, 71.0	57.0, 71.0	61.0, 77.0	57.0, 72.0
Min, Max	30, 82	48, 83	41, 90	30, 90
Age (years), n (%)				
< 65	43 (51.8)	15 (53.6)	6 (33.3)	64 (49.6)
≥ 65	40 (48.2)	13 (46.4)	12 (66.7)	65 (50.4)
Sex, n (%)				
Male	56 (67.5)	19 (67.9)	13 (72.2)	88 (68.2)
Female	27 (32.5)	9 (32.1)	5 (27.8)	41 (31.8)
Race, n (%)				
American Indian or Alaskan Native	1 (1.2)	0	0	1 (0.8)
Asian	1 (1.2)	0	0	1 (0.8)
Black or African American	3 (3.6)	1 (3.6)	2 (11.1)	6 (4.7)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	74 (89.2)	27 (96.4)	15 (83.3)	116 (89.9)
Other	1 (1.2)	0	0	1 (0.8)
Unknown	1 (1.2)	0	1 (5.6)	2 (1.6)
Missing	2 (2.4)	0	0	2 (1.6)
Ethnicity, n (%)				
Hispanic or Latino	3 (3.6)	0	0	3 (2.3)
Not Hispanic or Latino	74 (89.2)	27 (96.4)	17 (94.4)	118 (91.5)
Missing	6 (7.2)	1 (3.6)	1 (5.6)	8 (6.2)
ECOG Performance Status at Screening, n (%)				
0	42 (50.6)	12 (42.9)	6 (33.3)	60 (46.5)
1	35 (42.2)	15 (53.6)	12 (66.7)	62 (48.1)
2	6 (7.2)	1 (3.6)	0	7 (5.4)

Source: CSR-06 (first part of Table 12)

Table 53 Baseline Disease Characteristics – Study IPI-146-06 in Subjects Treated with Duvelisib 25 mg BID Monotherapy

Characteristic	FL (N=83)	SLL (N=28)	MZL (N=18)	Overall (N=129)
Years from Initial Diagnosis[a]				
Median (Min, Max)	4.3 (0.3, 27.0)	6.3 (0.9, 16.5)	2.4 (0.8, 9.7)	4.5 (0.3, 27.0)
No. Prior Systemic Anticancer Therapies (%)				
1	10 (12.0)	4 (14.3)	3 (16.7)	17 (13.2)
2	19 (22.9)	4 (14.3)	8 (44.4)	31 (24.0)
≥ 3	48 (57.8)	20 (71.4)	7 (38.9)	81 (62.8)
Median (range)	3.0 (1, 10)	3.0 (1,18)	2.0 (1, 8)	3.0 (1, 18)
Current Disease Stage by Method, n (%)				
I	3 (3.6)	1 (3.6)	2 (11.1)	6 (4.7)
II	10 (12.0)	2 (7.1)	1 (5.6)	13 (10.1)
III	38 (45.8)	7 (25.0)	6 (33.3)	51 (39.5)
IV	32 (38.6)	17 (60.7)	9 (50.0)	58 (45.0)
Subjects with Bulky Disease [b]	31 (37.3)	13 (46.4)	7 (38.9)	51 (39.5)
FLIPI Score, n (%)				
Low risk (0-1 adverse factor)	11 (13.3)	N/A	N/A	N/A
Intermediate risk (2 factors)	17 (20.5)	N/A	N/A	N/A
Poor risk (≥ 3 adverse factors)	54 (65.1)	N/A	N/A	N/A
Elevated LDH [c]				
Yes	62 (74.7)	16 (57.1)	8 (44.4)	86 (66.7)
No	20 (24.1)	12 (42.9)	10 (55.6)	42 (32.6)
Missing	1 (1.2)	0	0	1 (0.8)

Abbreviations: BID = twice daily; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; iNHL = indolent non-Hodgkin lymphoma; LDH = lactate dehydrogenase; N/A = not applicable; max = maximum; min = minimum; n = number.

a. Years from initial diagnosis date to date of first dose of duvelisib.

b. Bulky disease is defined as any tumour with at least a 5-cm diameter by CT scan.

c. Higher than upper limit of normal; derived from laboratory data at Baseline.

Source: IPI-145-06 CSR Table 14.1.5.1, 14.1.6.2

Table 54 Subjects Refractory to Select Prior Systemic Anticancer Therapies - Study IPI-145-06

Refractory to Therapy	FL (N=83) n (%)
Rituximab [a]	82 (98.8)
Alkylating Agent/Purine Analogue	75 (90.4)
Alkylating Agent	74 (89.2)
Combination of Rituximab and Alkylating Agent	74 (89.2)
Bendamustine [b]	43 (51.8)
Bendamustine-Rituximab [a,b]	36 (43.4)
Anthracycline	35 (42.2)
R-CHOP	26 (31.3)
R-CVP	20 (24.1)
Purine Analogue	12 (14.5)
Radioimmunotherapy	4 (4.8)
Disease Refractory to Most Recent Regimen	78 (94.0)
Disease Refractory to ≥ 2 Regimens	67 (80.7)

Abbreviations: FL = follicular lymphoma; N= total number; n = criteria number; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone.

a. Exposure to Rituximab must be at least 22 days (4 doses as single agent or 2 doses in combination) to be considered as refractory.

b. Exposure to bendamustine must be at least 22 days (2 Cycles) to be considered as refractory.

Source: IPI-145-06 CSR Table 14.1.6.4

Numbers analysed

Table 14.1.1.1
Subject Accountability, Analysis Sets
Full Analysis Set

Category	FL (N=83) n (%)	SLL (N=28) n (%)	MZL (N=18) n (%)	Overall (N=129) n (%)
Subjects in Full Analysis Set	83 (100)	28 (100)	18 (100)	129 (100)
Subjects in Evaluable Analysis Set	64 (77.1)	25 (89.3)	12 (66.7)	101 (78.3)

Outcomes and estimation

Primary and secondary endpoints

Table 55 Key Efficacy Results (Full Analysis Set) – Study IPI-145-06 (Subjects with FL) per IRC

Endpoint	Subjects with FL (N=83)
ORR	
n (%)	35 (42.2)
95% CI	(31.4, 53.5)
BOR, n (%)	
CR	1 (1.2)
PR	34 (41.0)
SD	29 (34.9)
PD	14 (16.9)
Unknown	5 (6.0) *
DOR (Months)	
Median (95% CI)	10.0 (4.5, 21.9)
PFS	
Number of Events, n (%)	51 (61.4)
Progression	41 (49.4)
Death without Progression	10 (12.0)
Median PFS (Months) (95% CI)	8.3 (5.3, 11.6)
OS	
Median OS (Months) (95% CI)	28.0 (20.8, NE)
TTR (Months)	
Median (range)	1.91 (1.6, 11.7)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; FL = follicular lymphoma; NE = not estimable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; TTR = time to response.

Note: Full Analysis Set = all subjects who received duvelisib.

* 1 subject with no evaluable disease; 4 subjects with no post-Baseline response assessment

Source: MAA FL Efficacy TLFs Table 14.2.1.1, Table 14.2.3.1, Table 14.2.2.1, Table 14.2.4.1, Table 14.2.5.1.

Table 14.2.1.1
Overall Response Rate per IRC
Full Analysis Set

	FL (N=83)	SLL (N=28)	MZL (N=18)	Overall (N=129)
Overall Response Rate (ORR) (CR + PR)				
ORR	35 (42.2)	19 (67.9)	7 (38.9)	61 (47.3)
95% Exact Binomial CI [a]	(31.4, 53.5)	(47.6, 84.1)	(17.3, 64.3)	(38.4, 56.3)
p-value [b]				<0.0001
Best Overall Response				
Complete Response (CR)	1 (1.2)	0	1 (5.6)	2 (1.6)
Partial Response (PR)	34 (41.0)	19 (67.9)	6 (33.3)	59 (45.7)
Stable Disease (SD)	29 (34.9)	4 (14.3)	9 (50.0)	42 (32.6)
Progressive Disease (PD)	14 (16.9)	3 (10.7)	1 (5.6)	18 (14.0)
Unknown (UN)	5 (6.0)	1 (3.6)	1 (5.6)	7 (5.4)
No Evidence of Disease (NED) [c]	0	1 (3.6)	0	1 (0.8)

Source: Updated data from data cut 18 May 2018

Median duration of response (DOR) in the FL population was 10 months (95% CI: 4.5, 21.9) and 9.9 months (95% CI: 4.5, 10.3) for the FAS as assessed by the IRC.

The applicant has presented the KM for DOR per investigator for both the ITT as well as the subgroup of patients with 2 prior lines of treatment. Results are in line with those reported for the IRC-based analysis as this was app. 10 months for both the ITT and patients with more than 2 prior regimens. Results are thus largely concordant.

Ancillary analyses

Generally, the numbers are too small to conclude anything from the subgroup analyses. Future studies may elucidate if there is a difference between efficacy in patients having received prior therapy with bendamustine or not, which is the subgroup with the largest difference between ORRs.

Table 56 Select Subgroup Analysis of Overall Response Rate per IRC in Subjects with FL (Study IPI-145-06)

Subgroup	N	ORR n (%)	95% CI
Number of Prior Therapies			
1-2	29	14 (48.3)	29, 68
1[a]	10	6 (60.0)	26, 88
3 or more	54	21 (38.9)	26, 53
2 or more	73	29 (39.7)	29, 52
Prior treatment with Bendamustine			
Yes	54	17 (31.5)	20, 46
No	29	18 (62.1)	42, 79
Refractory to Last Therapy			
Yes	78	33 (42.3)	31, 54
No	5	2 (40.0)	5, 85
Bulky Status (Baseline lesion ≥ 5 cm)			
Yes	31	12 (38.7)	22, 58
No	45	20 (44.4)	30, 60
Gender			
Male	56	25 (44.6)	31, 59
Female	27	10 (37.0)	19, 58
Age (years)			
< 65	43	21 (48.8)	33, 65
≥ 65	40	14 (35.0)	21, 52
Region			
US	25	14 (56.0)	35, 76
Non-US	58	21 (36.2)	24, 50

Abbreviations: CI = confidence interval; cm = centimetre; FL = follicular lymphoma; IRC = Independent Review Committee; N = total number; n= criteria number; ORR = overall response rate; US = United States.

a. All subjects who received one prior therapy had rituximab + chemotherapy.

Source: MAA FL Efficacy TLFs Figure 14.2.1.8.

In the subset of 30 FL subjects who were refractory to frontline R-CHOP or equivalent therapy, which represents a population with known poor prognostic features, an ORR of 33.3% was observed, with a median DOR of 12.6 months.

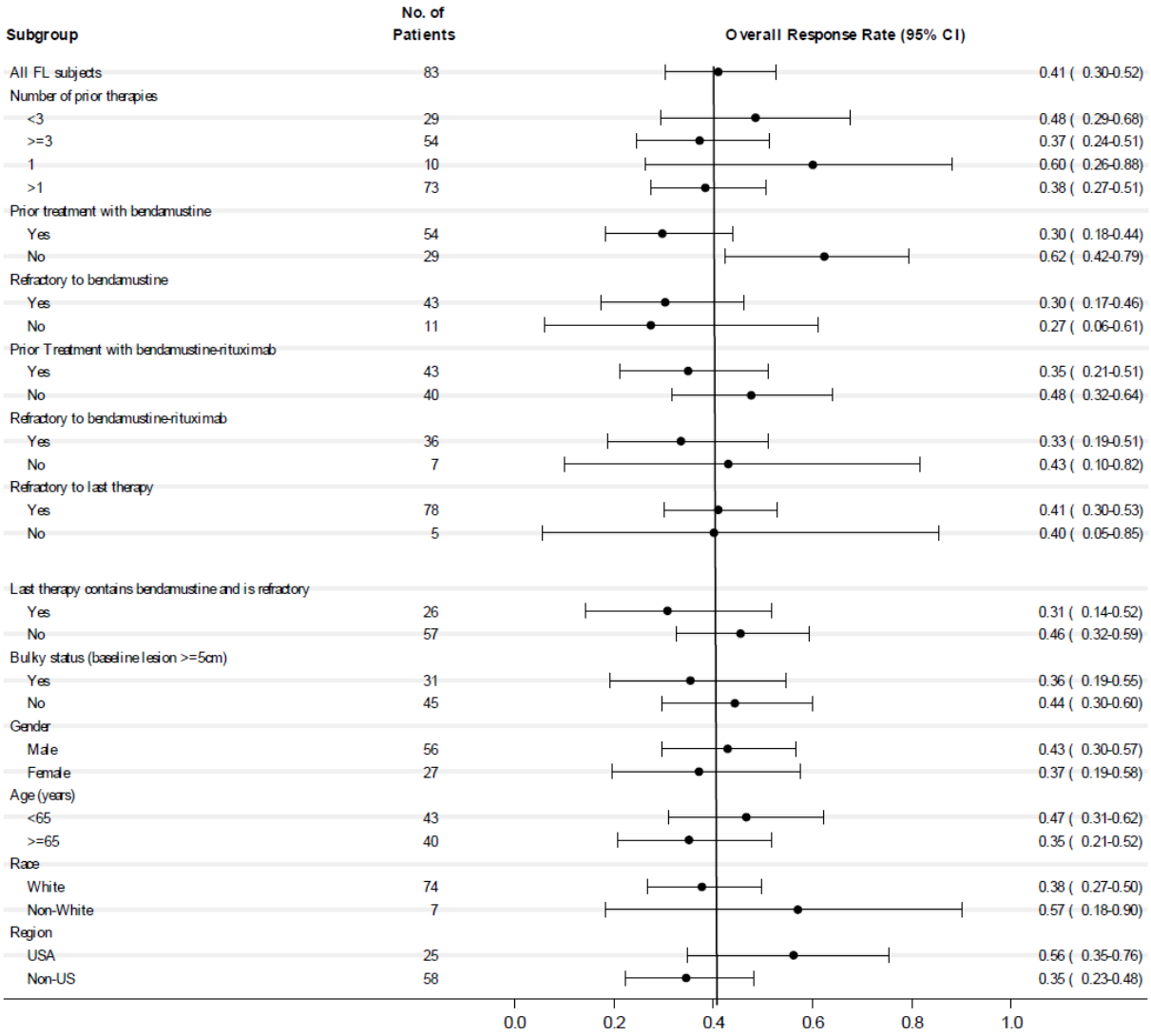
Table 57 Efficacy Results in Subjects Refractory to Frontline R-CHOP – Study IPI-145-06 (Subjects with FL) per IRC

Endpoint	FL Subjects Refractory to Frontline R-CHOP (N=30)
ORR	
n (%)	10 (33.3)
95% CI	(17.3, 52.8)
DOR (Months)	
Median (95% CI)	12.6 (1.8, NE)
PFS	
Number of Events, n (%)	21 (70.0)
Progression	13 (43.3)
Death without Progression	8 (26.7)
Median PFS (Months) (95% CI)	8.2 (2.2, 12.0)

Abbreviations: CI = confidence interval; DOR = duration of response; FL = follicular lymphoma; IRC = independent review committee; NE = not estimable; ORR = overall response rate; PFS = progression-free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Source: MAA FL Efficacy TLFs Table 14.2.1.1.2, Table 14.2.2.1,1 Table 14.2.3.1.

Figure 24 Subgroup Analysis of Overall Responses Rate for FL Subjects per IRC (FAS)



Source: Figure 14.2.1.8, Listing 16.2.6.1

Summary of main efficacy results

Table 58 Summary of efficacy for trial IPI-145-06

Title: A Phase 2 Study Of IPI-145 In Subjects with Refractory Indolent Non-Hodgkin Lymphoma			
Study identifier	Protocol number: IPI-145-06 EudraCT number: 2013-004008-20		
Design	Single Arm, Open-label, Multi-centre		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		59 months Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Duvelisib 25 mg BID (DUV)		Duvelisib 25 mg BID administered orally (as capsules) twice daily in 28-day cycles throughout the study (with the exception of Cycle 1 which was 21 days). The median duration of exposure for all subjects with indolent Non-Hodgkin lymphoma was 6.7 months (range: 0.4-45,5). The median duration of exposure for subjects with follicular lymphoma was 4.9 months (range: 2.7-9.3). 129 subjects with indolent Non-Hodgkin lymphoma received duvelisib. 83 subjects with follicular lymphoma received duvelisib.
Endpoints and definitions	Primary endpoint	Overall response rate (ORR)	Overall response (based on independent review) is defined as best response of complete response/remission (CR) or partial response/remission (PR) according to the revised International Working Group (IWG) Criteria
	Secondary endpoint	Duration of response (DOR)	Time from the first documentation of response to the first documentation of progressive disease (PD) or death due to any cause. DOR will be estimated using Kaplan-Meier method.
	Secondary endpoint	Progression-free survival (PFS)	Time from the first dose of study treatment to the first documentation of PD or death due to any cause. PFS will be estimated using Kaplan-Meier method.
	Secondary endpoint	Overall survival (OS)	Time from randomisation to death

	Secondary endpoint	Time to response (TTR)	Time from the first dose of study treatment to the first documentation of response (complete or partial)
	Exploratory endpoint	Lymph node response rate (LNRR)	Lymph node response (based on independent review) is defined as ≥ 50% decrease in the Sum of the Products of the Perpendicular Diameters (SPD) of nodal target lesions
Database lock	18 May 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set: all subjects who have been treated with at least one dose of DUV.		
Descriptive statistics and estimate variability	Treatment group	DUV	
	Number of subjects (*all subjects/ subjects with follicular lymphoma*)	129 / 83	
	ORR by independent review Percentage of subjects achieving CR or PR	47.3 / 42.2	
	95% Confidence Interval	(38.4, 56.3) / (31.4, 53.5)	
Effect estimate per comparison	Primary endpoint (ORR by independent review)	Comparison groups	N/A
Notes	This study was designed test the null hypothesis that the ORR in the overall population (FL+SLL+MZL) is ≤30% against the alternative that ORR is ≥45%.		

Analysis description	**Secondary Analysis (pre-specified)**	
Analysis population and time point description	Full analysis set: all subjects who have been treated with at least one dose of duvelisib. The secondary analysis results will be presented for subjects with follicular lymphoma only to focus on the intended indication. The secondary analysis was performed at the same time the primary analysis was performed	
Descriptive statistics and estimate variability	Treatment group	DUV
	Number of subjects	35
	DOR by independent review Median (months)	10.0
	95% Confidence Interval	(4.5, 21.9)

Effect estimate per comparison	Secondary endpoint (DOR by independent review)	Comparison groups	N/A
Descriptive statistics and estimate variability	Treatment group	DUV	
	Number of subjects	83	
	PFS by independent review Median (months)	8.3	
	95% Confidence Interval	(5.3, 11.6)	
Effect estimate per comparison	Secondary endpoint (PFS by independent review)	Comparison groups	N/A
Descriptive statistics and estimate variability	Treatment group	DUV	
	Number of subjects	83	
	OS Median (months)	28.0	
	95% Confidence Interval	(20.8, NE)	
Effect estimate per comparison	Secondary endpoint (OS)	Comparison groups	N/A
Descriptive statistics and estimate variability	Treatment group	DUV	
	Number of subjects	35	
	TTR Median (months)	1.91	
	Range (min. max)	(1.6, 11.7)	
Effect estimate per comparison	Secondary endpoint (TTR)	Comparison groups	N/A

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

Not applicable

Clinical studies in special populations

Table 59 Age Groups for Subjects with FL Treated with Duvelisib 25 mg BID – Study IPI – 145-02, Study IPI-145-06

	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 (N=0)	0	0	0
Non-controlled trials (N=96)	33/96	13/96	0

Abbreviations: BID = twice daily; FL = follicular lymphoma

Supportive studies

Study **IPI-145-06** (Study IPI-145-06 CSR) was a global, Phase 2, open-label, single-arm efficacy and safety study of duvelisib administered as monotherapy in subjects with iNHL. A total of 129 subjects were enrolled in the study, including 28 with SLL. All subjects received duvelisib 25 mg BID until PD or unacceptable toxicity. ORR was the primary endpoint and DOR and PFS among the secondary endpoints.

Study **IPI-145-12** CSR is a Phase 3, 2-arm, open-label, optional crossover extension study conducted in subjects with CLL/SLL who experienced radiologically-confirmed PD while receiving either duvelisib or ofatumumab monotherapy in Study IPI-145-07. Data presented include efficacy results from 89 subjects who received duvelisib monotherapy after experiencing PD while on ofatumumab monotherapy in Study IPI-145-07. The final CSR was based on a clinical data cut-off date of 19 July 2017, at which time 29 subjects remained on duvelisib. ORR was the primary endpoint and DOR and PFS secondary.

Study **IPI-145-02** was a Phase 1, open-label, dose-escalation study to determine the safety and maximum tolerated dose (MTD) of duvelisib monotherapy. The study was conducted in 2 parts: (1) a dose-escalation (DE) phase, utilising a 3+3 design, that enrolled subjects with any advanced haematologic malignancy and examined duvelisib doses from 8 mg BID to 100 mg BID, and (2) several expansion cohorts (ECs) that enrolled subjects with specific diseases, including iNHL, CLL/SLL, and T-cell lymphoma, and examined 2 doses of duvelisib (25 mg and 75 mg BID). In both parts of the study, duvelisib was administered until PD or unacceptable toxicity. A total of 210 subjects with advanced haematologic malignancies were enrolled, including 55 subjects with R/R CLL/SLL, 28 of whom received duvelisib monotherapy at a dose of 25 mg BID. Data from these 28 subjects were included in the SCE. Efficacy analyses were descriptive, with all response/progression endpoints based on Investigator assessments.

The median number of prior treatments was 3 in all three supportive studies as opposed to 2 in the pivotal phase 3 trial.

Median PFS was higher in the extension study (IPI-145-12) compared to the pivotal study (15.0 vs 13.3 months) where all patients had previously been treated with ofatumumab and thus gained an additional treatment thus supporting the larger efficacy in patients with a higher number of previous treatments. This was not the case for study 06 were all patients had SLL (N=28) and the median PFS was 11.7 months. Only the pivotal study had PFS as the primary endpoint.

No clear difference based on the number of prior therapies, as seen in study 07, is seen in study 012, which may in part be due to the low number of patients.

In study IPI-145-12 the ORR in patients with 17p- was 16/20 (80%) confirming the efficacy of duvelisib in this poor-prognosis population.

Table 60 ORR in the pivotal and supportive studies

	Pivotal Study IPI-145-07 N = 160		Supportive IPI-145-06 N = 28		Supportive IPI-145-12 N = 89	Supportive IPI-145-02 N = 28
	Per IRC	Per Investigator	Per IRC	Per Investigator	Per Investigator	Per Investigator
ORR, n (%)	118 (73.8)	99 (61.9)	19 (67.9)	24 (85.7)	65 (73.0)	16 (57.1)
95% Confidence Interval	66.9, 80.6	54.3, 69.4	47.6, 84.1	67.3, 96.0	63.8, 82.3	37.2, 75.5
CR	1 (0.6)	4 (2.5)	0	1 (3.6)	0	1 (3.6)
CRi	0	3 (1.9)	NP	NP	4 (4.5)	NP
PR	116 (72.5)	89 (55.6)	19 (67.9)	23 (82.1)	51 (57.3)	15 (53.6)
PRwL	1 (0.6)	3 (1.9)	NP	NP	10 (11.2)	NP
SD	34 (21.3)	53 (33.1)	4 (14.3)	3 (10.7)	13 (14.6)	10 (35.7)
PD	2 (1.3)	1 (0.6)	3 (10.7)	0	1 (1.1)	1 (3.6)
Other[a]	6 (3.8)	7 (4.4)	1 (3.6)	1 (3.6)	10 (11.2)	1 (3.6)
No Evidence of disease	0	0	1 (3.6)	0	0	0

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukaemia; CR = complete response; CRi = complete response with incomplete marrow recovery; IRC = Independent Review Committee; NP = not performed; ORR = overall response rate; PD = progressive disease; PR = partial response; PRwL = partial response with lymphocytosis; SD = stable disease.

[a] Includes not evaluable or missing responses

Source: Study IPI-145-07 CSR Table 14.2.2.1, Table 14.2.2.2; MAA CLL/SLL Efficacy TLFs Study IPI-145-06 Table 14.2.1.1, Table 14.2.1.2; Study IPI-145-12 CSR Table 14.2.1.1; Study IPI-145-02 CSR Table 14.2.1.1.2.

2.5.3. Discussion on clinical efficacy

The pivotal study to support the CLL indication is IPI-145-07; pivotal data for the FL indication is collected from IPI-145-06 with supportive data from IPI-145-02.

The selection of the dose and regimen of duvelisib monotherapy for Phase 2 and 3 studies was based on available preclinical data and data obtained from two clinical studies, Study IPI-145-01 (a Phase 1 single and multiple ascending dose study in healthy subjects) and Study IPI-145-02 (a Phase 1 dose escalation and expansion study in subjects with advanced hematologic malignancies). The selection of duvelisib 25 mg BID in CLL/SLL was based on the pharmacodynamic, efficacy, and safety data obtained from Study IPI-145-02 (n = 210). No demonstrable additional efficacy in terms of ORR was observed with higher doses, but a higher

number of deaths was observed in the 75 mg BID cohort. The dose finding studies did not include lower dose levels in the expansion cohorts (<25 mg BID).

CLL

Design and conduct of clinical studies

Study IPI-145-07 (DUO trial) is an open-label, multicentre, randomised (1:1) phase 3 study comparing the efficacy of duvelisib to ofatumumab in relapsed or refractory CLL/SLL patients who had previously received ≥ 1 therapy. The open-label design is endorsed given the different administration routes (IV and orally) of the treatments. To reduce bias, a blinded independent central review of disease status was conducted for the primary endpoint. Cross-over was allowed: Subjects who experienced radiographically confirmed disease progression on Study IPI-145-07 had the option to enrol in Study IPI-145-12.

The comparator ofatumumab is now obsolete as it has been deregistered in Europe for the treatment of CLL (although still available on a compassionate-use basis). At the time of the design of the study (21 Aug 2013) ofatumumab was approved by the EMA as monotherapy for CLL refractory to fludarabine and alemtuzumab. CHMP and COMP accepted this comparator.

Both 17p deletion and purine-analogue refractoriness are important adverse prognostic factors, and stratification according to these factors in phase 3 trials is in line with the updated IwCLL guideline (Hallek et al., 2018). This guideline also recommends stratification according to stage and IGHV mutational status, which has not been performed in this study.

Duvelisib was administered orally (as capsules) twice daily in 28-day cycles until disease progression or unacceptable toxicity. Subjects randomised to ofatumumab received 8 weekly IV infusions, starting with an initial dose of ofatumumab of 300 mg followed by 7 weekly doses of 2000 mg. Thereafter, subjects received 2000 mg ofatumumab once every cycle for 4 cycles or until disease progression or unacceptable toxicity, whichever came first. Administration of ofatumumab was not to exceed the 12 doses (within 7 cycles) as described in the prescribing information.

The selection of the 25 mg BID dose was further supported by pharmacodynamic analyses performed in Study IPI-145-02. As the serine/threonine kinase AKT is directly phosphorylated by PI3Ks, the reduction in phosphorylated AKT (p-AKT) was used as a pharmacodynamic marker for tumour cell PI3K inhibition in subjects with CLL. PK/pharmacodynamic analyses revealed a correlation between duvelisib plasma concentrations and percent p-AKT inhibition. Maximal p-AKT reductions were observed at plasma concentrations achieved at both the 25 mg BID and the 75 mg BID doses. In addition, the percentage of Ki67-positive CLL cells, an indicator of tumour cell proliferation, was measured in whole blood by flow cytometry predose on Cycle 1 Day 1 and following duvelisib dosing on Day 1 of Cycle 2, Cycle 3, and Cycle 4. The level of inhibition of Ki67 measured at Cycle 2 Day 1 was similar between the 25 mg BID and 75 mg BID doses.

Eligible patients were randomised in a 1:1 ratio to either ofatumumab or duvelisib. The randomisation was stratified by the presence of 17p deletion, prior progression within 12 months after previous purine analog-based therapy, and the presence of Grade 4 cytopenia at Baseline.

Blinding is not applicable since this study is designed as open-label which is endorsed given the different administration routes (IV and orally) of the treatments.

Study IPI-145-07 did not allow for the collection of disease assessments after initiation of subsequent anticancer therapy, due to the difficulty of obtaining consistent data on disease progression after a subject has withdrawn from study therapy. Due to this protocol design element as well as the proportion of subjects who withdrew from treatment and no longer remain in disease follow up, sensitivity analyses were performed to assess the impact of censoring on the results of the PFS analysis.

Blinding is not applicable since this study is designed as open-label. To reduce bias, a blinded independent central review of disease status was conducted for the primary endpoint.

Both 17p deletion and purine-analogue refractoriness are important adverse prognostic factors, and stratification according to these factors in phase 3 trials is in line with the updated IwCLL guideline (Hallek et al., 2018). This guideline also recommends stratification according to stage and IGHV mutational status, which has not been performed in this study.

Recognising that the different treatment schedules for duvelisib (treatment until progression or unacceptable toxicity for up to 18 cycles, with the potential to continue receive further cycles) and ofatumumab (fixed dosing for a total of 7 cycles) could impact the interpretation of sensitivity analysis 1, a subsequent sensitivity analysis was conducted. In this second sensitivity analysis of PFS, subjects alive without documented progression who were missing at least one disease assessment right before data cut-off were treated as having PFS event at the time of the next scheduled assessment following the last adequate disease assessment.

The sample size determination seems adequate. The primary and secondary endpoints are considered relevant and clinically meaningful in the proposed patient population.

As noted by the CHMP in their scientific advice the inclusion criterium of ≥ 1 prior therapy allows for a rather large/imprecise population. Furthermore, the CHMP advised: "In line with the exclusion of prior use of PI3K inhibitors, prior ofatumumab therapy should also be excluded or at least proposed as stratification factor." However, there were 4/159 patients in the ofatumumab arm having received prior ofatumumab treatment.

Efficacy data and additional analyses

The selection of duvelisib 25 mg BID in CLL/SLL was based on the pharmacodynamic, efficacy, and safety data obtained from Study IPI-145-02 (n = 210). In the event of toxicity the recommendation was to modify the duvelisib dose to 15 mg BID. The applicant has presented efficacy data from 43 patients (27%) in study 07 having received 15 mg duvelisib BID showing that the efficacy was not lower in these patients. This also seem to be the case in study 06 but here the number of patients in this category is even lower (13/83=16%), and no comparison to the population receiving 25 mg BID was made. Additionally, a PopPK analysis showed that at both 15 and 25 mg BID, the IC50s of both p-AKT and PI3K-d are exceeded at all times. Thus, dose-reduction to 15 mg BID duvelisib dose in the event of AEs is considered justified (see also discussion on Clinical Pharmacology).

The median PFS (ITT population) for duvelisib was 13.3 months (95% CI: 12.1, 16.8) and for ofatumumab 9.9 months (95% CI: 9.2, 11.3) with a hazard ratio of 0.52 (95% CI: 0.39, 0.70; p < 0.0001) and thus the study met its primary endpoint demonstrating statistically significant superiority of duvelisib over ofatumumab for PFS per IRC.

The PFS analysis relies on the assumption that patients who switched to another anticancer therapy before PD/death or who discontinued the study without a PFS event are comparable to those remaining in the study. This is not agreed since those patients could have discontinued treatment due to lack of efficacy or tolerability.

Moreover, the most common reason for censoring in the ofatumumab arm was reported as 'new anticancer treatment or procedure started prior to documented progression' in 27 (17.0%) subjects. Times for patients in this category were censored at the date of the last adequate disease status assessment, which means the progression-free survival times for these patients when receiving ofatumumab are unknown. The applicant has restricted the CLL indication to the post hoc-defined subgroup of patients who have received at least 2 lines of treatment.

The applicant presented the requested sensitivity analyses using the population corresponding to the new pursued indication: patients with at least 2 prior therapies. Patients who discontinued treatment before a PFS were considered in different ways: censored, imputed using the information from the patients observed in the same arm, followed up despite switching to a new anti-cancer therapy, and finally PFS events.

The results of the sensitivity analyses are concordant with those reported in the primary analysis. The median PFS per IRC vs Investigator assessment for duvelisib for the ITT population was 13.3 vs 17.6 months and for ofatumumab 9.9 vs 9.7 months. The difference between the IRC's and investigator's assessment of PFS was quite marked in the duvelisib arm demonstrating the need for IRCs to ensure consistent evaluation of study results. The concordance between Investigator and blinded IRC assessment of PFS events (progression, death, and censored) was 83.1% for the duvelisib arm and 79.9% for the ofatumumab arm.

Key secondary endpoint of ORR per modified IWCLL/IWG criteria for duvelisib vs ofatumumab was 73.8% for duvelisib vs 45.3% for ofatumumab ($p < 0.0001$). Lymph node response (LNR) rate was higher in duvelisib (85%) vs ofatumumab (16%). In subjects with a response, the median DOR was longer with duvelisib compared to ofatumumab (median DOR = 11.1 months duvelisib vs 9.3 months ofatumumab). The median OS of IPI-145-07 was not estimable in either treatment arm and results are difficult to assess due to use of further anticancer therapy in both arms. OS was similar between the two treatment arms at both the primary endpoint analysis and the additional 22 months follow up with no difference between the treatment arms. Updated OS is needed for evaluation as well as information on time to new anti-cancer therapy. The applicant has accepted a CHMP recommendation to provide the final OS results for both the ITT and finally approved subgroup at post-approval.

Although the subgroup analyses generally are consistent with the overall outcome, some analyses are of special interest, particularly regarding del 17p/TP53 mutation, as they represent a high-risk group of CLL. At the time of study initiation, the ESMO guideline listed no standard treatment for these patients. In study IPI-145-07, the applicant has stratified and performed a prespecified subgroup analysis on patients with the 17p deletion or TP53 mutation at baseline (48 randomised to duvelisib, 52 randomised to ofatumumab). In the subjects with 17p deletion or TP53 mutation duvelisib demonstrated statistically significant and clinically meaningful improvement over ofatumumab for PFS (HR=0.4, p=0.0002). Even though subjects with 17p del/TP53 mutation represent a high-risk group of CLL, the median PFS for duvelisib was only slightly lower (12.7 months subjects with mutation versus 14.7 months for subjects without mutation), also reflected in the ORR.

Approximately 60% of subjects received at least two prior therapies. The applicant provided a subgroup analysis (not planned in the study protocol) on the number of prior therapies (≥ 2 prior therapies versus 1 prior therapy). Median PFS was 16.4 months (95% CI: 12.0, 20.5) for duvelisib versus 9.1 months for

ofatumumab (95% CI: 7.9, 10.7), with a hazard ratio of 0.4 (95% CI: 0.27, 0.59) for patients with ≥ 2 prior therapies. For patients with only 1 prior therapy the median PFS was 12.7 months (95% CI: 9.1, 17.8) for duvelisib versus 12.0 months for ofatumumab (95% CI: 9.6, 12.8) with a hazard ratio of 0.8 (95% CI: 0.5, 1.28). Thus, the overall efficacy seems to be driven by the 60% of patients having received ≥ 2 prior therapies. Thus, duvelisib seems to work better in heavily pre-treated CLL patients contrary to what is generally seen with regards to efficacy, and thus fulfils an unmet need in this population. The applicant has amended the indication to include patients after two or more prior therapies. The inclusion and exclusion criteria of the pivotal trial (IPI-145-07) were extensive with respect to prior treatments, e.g. refractory to rituximab and chemotherapy and not eligible for SCT. Further, patients previously treated with a PI3 kinase inhibitors or BTK inhibitors were excluded from the CLL study and patients previously treated with a BCL-2 inhibitor were not enrolled. While treatment with duvelisib after progression on idelalisib treatment would be considered irrational, it is unknown whether prior exposure to BTK inhibitors or BCL-2 inhibitors might impact response to duvelisib. A reference from the indication towards section 5.1. has been added to guide the prescriber towards the lack of data in patients previously treated with BCL-2 or BTK inhibitors as these have a different MoA and thus efficacy could be expected. However, the efficacy of duvelisib after idelalisib has not been addressed and because of the similar MoA for idelalisib and duvelisib, efficacy of duvelisib after idelalisib treatment is questionable and since treatment with duvelisib comes with a severe toxicity, the applicant has added previous use of idelalisib as a warning in 4.4. with a cross reference from the indication towards 4.4 and 5.1.

Based on the results from the performed sensitivity analyses it seems that the censoring due to new anticancer medication in the ofatumumab arm did not substantially affect the results for the subgroup of patients who received 2 or more prior therapies.

The results of the adjusted PFS analysis were consistent with the primary analysis for the 2+ prior therapy subgroup. This suggests that the imbalance in prognostic factors (in particular, months since most recent therapy) did not have an overt influence on the results. It is therefore reasonable to conclude that there is a true subgroup effect, given that there is an overall positive ITT effect.

The applicant accepted a recommendation from the CHMP to provide the final OS results for Study IPI-145-07 for both the ITT and finally approved subgroup as soon as available.

FL - Design and conduct of clinical studies

The primary data for the FL indication is collected from a single arm Phase 2 Study IPI-145-06, with supportive data from a single arm Phase I study IPI-145-02. A single arm trial (SAT) carries important intrinsic limitations, which may be overcome in specific circumstances only. These include a predictable course of the disease, a well-described patient population, and compelling results indicative of clinical benefit, for which a well understood MoA is deemed helpful. A randomised controlled trial, RCT, would have been the preferred approach, although it is acknowledged that at study initiation a suitable effective comparator was not readily available.

Study IPI-145-06 is a Phase 2, open-label, single arm efficacy and safety study of duvelisib monotherapy administered orally to subjects with relapsed/refractory iNHL, including the subtypes of FL (n = 83), small lymphocytic lymphoma (SLL) (n = 28), and MZL (n = 18) for a total of 129 subjects. This study was designed to evaluate the effect of duvelisib 25 mg BID monotherapy in subjects with iNHL refractory to rituximab and

to either chemotherapy or radioimmunotherapy (RIT). FL patients refractory to rituximab + chemotherapy or RIT have a dismal prognosis.

The median age was 65 years (range: 30-90) and the majority of subjects had an ECOG Performance Status (PS) of 0 (46.5%) or 1 (48.1%) at baseline, so quite fit compared to the general relapsed iNHL population. At baseline, the majority of subjects had elevated LDH (66.7%), 40% had bulky disease, and 84.5% had NHL stage III or IV, thus a poor prognosis population.

The applicant has defined *refractory* FL as lack of a CR or PR while receiving chemotherapy regimen or RIT (radioimmunotherapy) and/or rituximab or PD within 6 months of the last dose. Thus, early relapse and refractory are not identical with the latter population expected to have the poorest prognosis.

The median number of prior systemic regimens was three with 88% having received at least two prior regimens. 94% of FL patients were refractory to their most recent prior anticancer therapy, and 81% were refractory to ≥ 2 prior therapies. At time of study initiation idelalisib and obinutuzumab were not yet approved in the EU. The efficacy of duvelisib in patients previously treated with idelalisib or obinutuzumab is unknown. Specific prior anticancer therapies were: (1) 100% received prior anti-CD20 rituximab; 95% in combination; (2) 69% received prior doxorubicin; (3) 65% received prior bendamustine, with 52% in combination with rituximab. The sought indication is for patients with previously treated FL who have received at least one prior therapy, the majority of the FL subjects had more than 2 prior anticancer regimens, only 10 (12%) of the included subjects had 1 prior treatment. The sample size is thus small to reliably conclude on efficacy between one prior or more than 2 prior treatments. The applicant has amended the indication to include FL patients after at least two prior systemic therapies.

The final efficacy analysis is based on a data cut-off of 18 May 2018. At that time, 5 subjects (3 with FL, 1 with SLL, and 1 with MZL) remained on treatment. The median duration of exposure was 4.9 months.

Patients with prior treatment with any PI3K inhibitor or Bruton's tyrosine kinase (BTK) inhibitor were excluded.

The primary objective of study IPI-145-06 was to evaluate the antitumour activity of duvelisib monotherapy administered to subjects diagnosed with iNHL (FL, SLL, and MZL) whose disease was refractory to rituximab and to either chemotherapy or RIT, whereas the indication is in the subgroup of refractory FL patients only.

The primary endpoint IRC-ORR was defined as best response of CR or PR according to the revised IWG Criteria (Cheson et al., 2007). The applicant formulated several key secondary endpoints: DOR, PFS, OS, TTR as well as several exploratory endpoints. The choice of ORR as primary endpoint is considered appropriate for a phase 2 study, and the secondary endpoints are meaningful although difficult to interpret given the single-arm design.

One interim futility analysis was planned for ORR. The IA was scheduled around 4 months after at least 30 subjects had received duvelisib. The interim analysis was conducted based on the Investigator's assessment and a recommendation on futility of the study was provided by an Independent Data Monitoring Committee. Since no strategy was planned to control for multiplicity across several secondary endpoints, those are considered exploratory.

The applicant defined as the null hypothesis an ORR equal or below 30 % responders. In the first version of the protocol, the ORR was expected to be ≥ 55% for the overall iNHL population but was revised so that the alternative hypothesis is ORR equal or larger than 45 %. The applicant clarified that there were no assumptions specified regarding the ORR for the FL population. In the protocol v3 the number of FL patients to be included changed from 100 to 80 due to recruitment problems. It could be understood that the

applicant would aim to ORR around 45 % but any response rate larger than 30 % would be considered successful. Furthermore, the applicant did not specify whether the 30 % limit should be crossed by the estimate or the lower bound of the confidence interval; the study was to be considered successful if the p-value for a 1-sided exact binomial test was significant at the 0.025 level, which would be generally consistent with a lower bound of a two-sided 95% CI that exceeds 30%.

Efficacy data and additional analyses

Initially the ORR for the entire iNHL population of at least 120 patients was expected to be ≥ 55% but was later amended in the protocol to ≥ 45% and turned out to be 45.7% (59/129; 95% CI: 36.9, 54.7) per IRC assessment. Two responses were CRs and 59 were PRs. The subgroup analysis in the FL population did not meet the expected ORR for the FAS as this was 42.2% ((35/83; 95% CI: 31.4, 53.5) with 1 CR and 34 PRs. The median DOR for the responders was 10.0 months. Due to heavy censoring (54.3%), the estimated median DOR was not reliable. Moreover, 28.6% was censored due to new anticancer treatment before documented progression in the FL population. The applicant has presented the KM for DOR per investigator for both the ITT as well as the subgroup of patients with 2 prior lines of treatment. Results are in line with those reported for the IRC-based analysis as this was approximately 10 months for both the ITT and patients with more than 2 prior regimens. Results are thus largely concordant.

The median PFS was 8.3 months (95% CI: 4.2, 10.0) for FL subjects and 8.4 months (95% CI: 5.8, 11.3) for the FAS. Ten patients experienced Death without Progression. However, due to the single-arm study design, the clinical significance of PFS, OS, TTR cannot be adequately interpreted.

Given the censoring for new anticancer therapy, it is considered that the combination of investigator and IRC progression events for FL in the single-arm study produces a more conservative estimate than that based on IRC alone. For the 2+ prior therapy subgroup, the median PFS was estimated to be 8.3 months. This is slightly lower than for the IRC results alone, and still considered to be clinically meaningful. In a comparable study (101-09; IRC assessed) of the PI3K inhibitor idelalisib the ORR was 57.6% in the iNHL cohort and 55.6% (40/72) in the FL subset with 16.7% (12/72) obtaining a CR (see Zydelig SmPC). Idelalisib received the indication as monotherapy for FL refractory (but not relapsed) to two prior therapies. Only refractory FL patients defined as in the IPI-145-06 study were included.

The ORR for the subgroup of ≥ 2 prior therapies was 29/73 (39.7%; 95% CI: 29,52). The applicant has revised the requested indication from the second line treatment of FL towards the third line (e.g. Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies with a reference to 5.1.). The newly proposed indication better reflects the studied population with 88% having received at least two prior regimens and 94% of FL patients were refractory to their most recent prior anticancer therapy, and 81% were refractory to ≥ 2 prior therapies. The addition of relapsed FL in the indication is not agreed as only refractory FL patients were included in study IPI-145-06 and the B/R in relapsed FL patients is not considered justified given the potentially long remission in these patients and the severe safety concerns of duvelisib. The applicant has further amended the indication to only include patients with refractory FL after at least two prior systemic therapies.

Thus, in principle this single pivotal study would not be considered comprehensive and the ORR for duvelisib in this single-arm trial is not outstanding; the indication in "Relapsed or refractory follicular lymphoma (FL) after at least one prior systemic therapy" is not considered justified. At the request of the CHMP the indication was amended to specify "refractory" FL patients, "after at least two prior systemic therapies".

Historically, in a comparable study (101-09; IRC assessed) of the PI3K inhibitor idelalisib the ORR was 57.6% in the iNHL cohort and 55.6% (40/72) in the FL subset with 16.7% (12/72) obtaining a CR (Zydelig SmPC) and received the indication as monotherapy for FL refractory to two prior therapies. The median number of prior therapies in the study was four (Gopal et al., 2014).

In a phase 3 study (GADOLIN) the combination Gazyvaro + bendamustine followed by Gazyvaro maintenance, which is indicated for refractory FL, the median PFS by IRC is not reached (22.5 – NR months) and the PFS in the bendamustine comparator arm was 13.8 months (see Gazyvaro SmPC). The median age was 63 years and the median number of prior therapies two.

The treatment landscape of R/R FL has changed since start of the pivotal trial (24 June 2013) with the PI3K inhibitor idelalisib as treatment option for double-refractory FL (ESMO guideline 2016). The currently proposed indication is partially overlapping with idelalisib (Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment). The studied population consisted mostly of FL patients refractory to rituximab and chemotherapy (e.g. double refractory) and no previous PI3 kinase treatment with 2 prior treatments. This patient population has become very rare due to changes in the treatment landscape. With the proposed indication (after at least 2 lines), the question with respect to the expected efficacy of duvelisib in patients previously treated with idelalisib remains unaddressed and the efficacy of duvelisib after idelalisib is questioned. In light of the severe toxicity of duvelisib and the unlikely efficacy of duvelisib after idelalisib treatment, a warning has been added to SmPC section 4.4. regarding previous use of idelalisib. The indication was amended to only include *refractory* FL, as the B/R in relapsed FL patients was not considered justified given the potentially long remission in these patients, the severe safety concerns of duvelisib and other efficacious options.

All in all, there are several limitations with respect to the presented data for FL in a single arm study with ORR as primary endpoint. Although an RCT would have been preferred it is acknowledged that at study initiation a suitable effective comparator was not readily available. In a similar development programme for Zydelig (idelalisib) a full approval was given for both CLL and FL in 2014. During that procedure the CHMP has accepted the single-arm data for the FL population with ORR as primary endpoint.

The applicant will request advice from the CHMP SAWP on the design of a randomised trial VS-0145-327 which will report post-authorisation.

2.5.4. Conclusions on the clinical efficacy

The presented results are supportive of the restricted indication in CLL in patients having received ≥ 2 prior lines of therapy whereas stating the fact that patients having received prior PI3 kinase, bcl-2, or BTK inhibitor treatment were not part of the study population.

The applicant accepted a recommendation from the CHMP to provide the final OS results for Study IPI-145-07 for both the ITT and finally approved subgroup as soon as available (estimated July 2021).

The revised indication in FL referring to treatment after at least two prior systemic therapies and the limitation to *refractory* FL patients is agreed.

The applicant has agreed to the recommendation of the CHMP to provide results from a phase 3 randomised trial in FL (Study VS-0145-327). As the design of study VS-0145-327 is not yet clarified, the applicant has also agreed to seek scientific advice, an outline of further steps has been proposed.

2.6. Clinical safety

Patient exposure

The Summary of Clinical Safety (SCS) provided an Integrated Summary of Safety (ISS) from 4 studies (Studies IPI-145-02, IPI-145-06, IPI-145-07 and IPI-145-12) of duvelisib monotherapy in subjects with haematologic malignancies. Specifically, the data presented include the clinical studies mainly conducted in subjects with CLL/SLL and FL at the recommended 25 mg twice daily (BID) dose in total 442 patients of which 303 had CLL/SLL and 96 had FL. The cut-off for the integrated summary of safety, also named Study VS-0145-328, was 19 July 2017. With the 3-year updated ISS data (Study VS-0145-328) the All Heme 25 mg BID Group (N = 443), had a median duration of exposure of 40.00 weeks (range: 0.3 to 311.0 weeks) as opposed to 39 weeks at the time of the application. A total of 277 patients (62.5%) were treated for ≥ 6 months, 170 (38.4%) were treated for ≥ 1 year, 109 (24.6%) were treated for ≥ 1.5 years, and importantly for the evaluation of long-term safety 72 patients (16.3%) were treated for ≥ 2 years, of which 54 were CLL patients and 7 were FL patients.

Table 61 Integrated studies

Study Number	Study Title	Number of Subjects Receiving Duvelisib
Integrated Studies in Subjects with Haematologic Malignancies [n = 586]		
IPI-145-02	A Phase 1 Study Evaluating Duvelisib in Subjects with Advanced Haematologic Malignancies	210
IPI-145-06	A Phase 2, Single-arm Study Evaluating Duvelisib in Subjects with Refractory Indolent Non-Hodgkin Lymphoma (iNHL)	129
IPI-145-07	A Phase 3, Randomized Study Comparing Duvelisib to Ofatumumab in Subjects with Relapsed or Refractory CLL/SLL	158
IPI-145-12	An Optional Crossover Extension of Study IPI-145-07	89
Abbreviations: CLL= chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma Source: ISS Table 1.1		

Table 62 Distribution of subjects by Analysis population (SAS)

Population	All Heme		CLL/SLL		FL	
	25 mg BID N=442	All Doses N=586	25 mg BID N=303	All Doses N=330	25 mg BID N=96	All Doses N=107
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
IPI-145-02	66 (14.9)	210 (35.8)	28 (9.2)	55 (16.7)	13 (13.5)	24 (22.4)
IPI-145-06	129 (29.2)	129 (22.0)	28 (9.2)	28 (8.5)	83 (86.5)	83 (77.6)
IPI-145-07	158 (35.7)	158 (27.0)	158 (52.1)	158 (47.9)	0	0
IPI-145-12	89 (20.1)	89 (15.2)	89 (29.4)	89 (27.0)	0	0

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukaemia; Heme = haematologic malignancies; FL = follicular lymphoma; SLL = small lymphocytic lymphoma.

Note: Denominators for percentages are based on the number of subjects in each analysis group for the Safety Analysis Set.

The median number of prior therapies was 2.0 in the phase 3 CLL study (both arms), in All CLL 25 mg BID, and All Heme 25 mg BID and 3.0 in the FL 25 mg BID population.

Table 63 Extent of exposure

Category	All Heme		CLL/SLL		FL	
	25 mg BID Duvelisib (N=442)	All Doses Duvelisib (N=586)	25 mg BID Duvelisib (N=303)	All Doses Duvelisib (N=330)	25 mg BID Duvelisib (N=96)	All Doses Duvelisib (N=107)
Duration of Exposure (weeks) [a]						
n	442	586	303	330	96	107
Mean	48.11	42.53	50.52	50.13	33.49	34.11
SD	39.772	40.895	37.483	38.504	33.114	38.258
Median	39.00	26.86	45.29	43.64	24.14	20.00
Min, Max	0.3, 229.7	0.3, 236.7	0.9, 203.9	0.9, 203.9	0.3, 170.3	0.3, 236.7
Number of Cycles Started, n (%)						
≥1	442 (100)	586 (100)	303 (100)	330 (100)	96 (100)	107 (100)
≥2	421 (95.2)	542 (92.5)	294 (97.0)	321 (97.3)	88 (91.7)	97 (90.7)
≥4	366 (82.8)	440 (75.1)	260 (85.8)	283 (85.8)	71 (74.0)	76 (71.0)
≥6	298 (67.4)	345 (58.9)	218 (71.9)	234 (70.9)	50 (52.1)	53 (49.5)
≥8	258 (58.4)	284 (48.5)	190 (62.7)	202 (61.2)	41 (42.7)	43 (40.2)
≥10	234 (52.9)	257 (43.9)	178 (58.7)	188 (57.0)	32 (33.3)	34 (31.8)
≥12	201 (45.5)	218 (37.2)	157 (51.8)	165 (50.0)	22 (22.9)	24 (22.4)
Number of Cycles Started						
n	442	586	303	330	96	107
Mean	12.5	11.1	13.1	13.0	8.8	8.9
SD	9.93	10.23	9.35	9.60	8.28	9.59
Median	10.0	7.0	12.0	11.5	7.0	5.0
Min, Max	1, 58	1, 60	1, 51	1, 51	1, 43	1, 60
Relative Dose Intensity [b]						
n	442	586	303	330	96	107
Mean	88.33	85.46	88.67	87.71	88.15	88.12
SD	17.937	21.017	17.916	18.598	17.009	18.116
Median	97.60	96.25	97.70	97.60	97.30	97.30
Min, Max	0.0, 123.0	0.0, 141.3	0.0, 123.0	0.0, 123.0	39.7, 100.00	39.7, 141.3
Number of Subjects Receiving Duvelisib, n (%)						
≥1 day	442 (100)	586 (100)	303 (100)	330 (100)	96 (100)	107 (100)
≥2 months	389 (88.0)	477 (81.4)	275 (90.8)	299 (90.6)	77 (80.2)	84 (78.5)

Category	All Heme		CLL/SLL		FL	
	25 mg BID Duvelisib (N=442)	All Doses Duvelisib (N=586)	25 mg BID Duvelisib (N=303)	All Doses Duvelisib (N=330)	25 mg BID Duvelisib (N=96)	All Doses Duvelisib (N=107)
≥4 months	314 (71.0)	369 (63.0)	228 (75.2)	246 (74.5)	55 (57.3)	58 (54.2)
≥6 months	269 (60.9)	298 (50.9)	198 (65.3)	210 (63.6)	44 (45.8)	46 (43.0)
≥12 months	160 (36.2)	177 (30.2)	123 (40.6)	131 (39.7)	18 (18.8)	20 (18.7)
Dose Reduction or Dose Hold, n (%)						
No	110 (24.9)	145 (24.7)	72 (23.8)	74 (22.4)	32 (33.3)	33 (30.8)
Yes	332 (75.1)	441 (75.3)	231 (76.2)	256 (77.6)	64 (66.7)	74 (69.2)
Due to TEAE	317 (71.7)	413 (70.5)	220 (72.6)	241 (73.0)	62 (64.6)	71 (66.4)
Dose Reduction, n (%)						
No	336 (76.0)	420 (71.7)	229 (75.6)	240 (72.7)	74 (77.1)	81 (75.7)
Yes	106 (24.0)	166 (28.3)	74 (24.4)	90 (27.3)	22 (22.9)	26 (24.3)
Due to TEAE	97 (21.9)	151 (25.8)	66 (21.8)	79 (23.9)	22 (22.9)	26 (24.3)
Dose Hold, n (%)						
No	113 (25.6)	153 (26.1)	75 (24.8)	79 (23.9)	32 (33.3)	33 (30.8)
Yes	329 (74.4)	433 (73.9)	228 (75.2)	251 (76.1)	64 (66.7)	74 (69.2)
Due to TEAE	315 (71.3)	408 (69.6)	218 (71.9)	237 (71.8)	62 (64.6)	71 (66.4)
Dose Increase, n (%)						
No	426 (96.4)	562 (95.9)	294 (97.0)	316 (95.8)	92 (95.8)	102 (95.3)
Yes	16 (3.6)	24 (4.1)	9 (3.0)	14 (4.2)	4 (4.2)	5 (4.7)

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukaemia; FL = follicular lymphoma; Heme = haematologic malignancies; max = maximum; min = minimum; SD = standard deviation; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

All Heme All Doses Group = all subjects with any haematologic malignancy treated with duvelisib monotherapy (Study IPI-145-02, Study IPI-145-06, Study IPI-145-07, Study IPI-145-12)

CLL/SLL All Doses Group = all subjects with CLL/SLL treated with duvelisib monotherapy (Study IPI-145-02, Study IPI-145-06, Study IPI-145-07, and Study IPI-145-12)

FL All Doses Group = all subjects with FL treated with duvelisib monotherapy (Study IPI-145-02 and Study IPI-145-06) Dose Reduction = Yes, if the study drug was reduced for any reason; dose partially taken was not considered a reduction. Dose Hold = Yes, if the study drug was not taken for any reason.

Note: Denominators for percentages are based on the number of subjects in each dose group for the Safety Analysis Set.

Duration of Exposure (weeks) = (date of last dose – date of first dose + 1)/7, rounded to one decimal.

Relative dose intensity = 100% * total dose received / planned cumulative dose for the duration of treatment based on the initial dose assignment.

Source: ISS Table 1.8, ISS Table 1.8.1, ISS Table 1.8.2

Four subjects had been treated with ibrutinib prior to treatment with duvelisib.

Adverse events

CLL/SLL – pivotal phase 3 study IPI-145-07:

Table 64 Overall Summary of TEAEs (All – treated Analysis set)

Category	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
All Causalities		
Subjects with a TEAE	156 (98.7)	144 (92.9)
Subjects with a TEAE ≥ Grade 3	138 (87.3)	75 (48.4)
Subjects with a TESAE	115 (72.8)	50 (32.3)
Subjects with a TEAE Leading to Treatment Discontinuation	57 (36.1)	9 (5.8)
Subjects with a TEAE Resulting in Dose Hold	123 (77.8)	15 (9.7)
Subjects with a TEAE Leading to Dose Reduction	46 (29.1)	2 (1.3)
Subjects with a TEAE Resulting in Dose Hold or Reduction	125 (79.1)	16 (10.3)
Subjects with a TEAE with an Outcome of Death	19 (12.0)	7 (4.5)
Treatment Related		
Subjects with a TEAE	142 (89.9)	111 (71.6)
Subjects with a TEAE ≥ Grade 3	118 (74.7)	47 (30.3)
Subjects with a TESAE	84 (53.2)	16 (10.3)
Subjects with a TEAE Leading to Treatment Discontinuation	45 (28.5)	2 (1.3)
Subjects with a TEAE Resulting in Dose Hold	108 (68.4)	9 (5.8)
Subjects with a TEAE Leading to Dose Reduction	43 (27.2)	2 (1.3)
Subjects with a TEAE Resulting in Dose Hold or Reduction	111 (70.3)	10 (6.5)
Subjects with a TEAE with an Outcome of Death	4 (2.5)	0

Abbreviations: TEAE = treatment-emergent adverse event.

Treatment-emergent Adverse Events (TEAEs)

CLL/SLL – pivotal phase 3 study IPI-145-07:

In the phase 3 study in CLL (Table 29/CSR-07, below), the incidence of various AEs by SOC and/or PT in the duvelisib arm were generally higher than in the ofatumumab arm. For haematologic TEAEs the incidence for the duvelisib arm compared to the ofatumumab arm were: neutropenia: 32.9% vs 20.6%; anaemia: 22.8% vs 10.3%; and thrombocytopenia: 14.6% vs 5.8%. Many events fall under the heading Adverse events of Special Interest (AESI) and are discussed later.

Table 65 TEAEs Occurring in ≥ 10% Subjects on Either Treatment Arm and/or ≥ 5% Higher on Either Treatment Arm, by SOC and PT – All Causalities (All-Treated Analysis Set)

System Organ Class Preferred Term	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
Subjects with ≥ 1 TEAE	156 (98.7)	144 (92.9)
Blood and lymphatic system disorders	**85 (53.8)**	**53 (34.2)**
Neutropenia	52 (32.9)	32 (20.6)
Anaemia	36 (22.8)	16 (10.3)
Thrombocytopenia	23 (14.6)	9 (5.8)
Febrile neutropenia	11 (7.0)	3 (1.9)
Gastrointestinal disorders	**116 (73.4)**	**58 (37.4)**
Diarrhoea	80 (50.6)	19 (12.3)
Nausea	37 (23.4)	17 (11.0)
Constipation	26 (16.5)	13 (8.4)
Vomiting	23 (14.6)	10 (6.5)
Colitis	21 (13.3)	2 (1.3)
Abdominal pain	16 (10.1)	3 (1.9)
Paraesthesia oral	0	10 (6.5)
General disorders and administration site conditions	**82 (51.9)**	**57 (36.8)**
Pyrexia	45 (28.5)	16 (10.3)
Fatigue	20 (12.7)	19 (12.3)
Asthenia	18 (11.4)	17 (11.0)
Oedema peripheral	15 (9.5)	7 (4.5)
Infections and infestations	**109 (69.0)**	**67 (43.2)**
Pneumonia	29 (18.4)	9 (5.8)
Upper respiratory tract infection	25 (15.8)	12 (7.7)
Bronchitis	21 (13.3)	13 (8.4)
Nasopharyngitis	12 (7.6)	4 (2.6)
Respiratory tract infection	11 (7.0)	3 (1.9)
Injury, poisoning and procedural complications	**28 (17.7)**	**42 (27.1)**
Infusion related reaction	2 (1.3)	30 (19.4)
Investigations	**56 (35.4)**	**31 (20.0)**
Weight decreased	18 (11.4)	3 (1.9)
Aspartate aminotransferase increased	14 (8.9)	3 (1.9)
Alanine aminotransferase increased	12 (7.6)	3 (1.9)
Metabolism and nutrition disorders	**56 (35.4)**	**31 (20.0)**
Decreased appetite	20 (12.7)	5 (3.2)
Hypokalaemia	15 (9.5)	3 (1.9)
Nervous system disorders	**45 (28.5)**	**41 (26.5)**
Paraesthesia	7 (4.4)	15 (9.7)
Respiratory, thoracic and mediastinal disorders	**68 (43.0)**	**46 (29.7)**
Cough	33 (20.9)	22 (14.2)
Dyspnoea	16 (10.1)	9 (5.8)
Pneumonitis	10 (6.3)	0
Skin and subcutaneous tissue disorders	**67 (42.4)**	**48 (31.0)**
Rash	16 (10.1)	18 (11.6)
Vascular disorders	**25 (15.8)**	**26 (16.8)**
Hypertension	12 (7.6)	4 (2.6)

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated subjects in each treatment group. A treatment- emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence.
Source Table 14.3.1.2

Source: CSR-

Table 66 TEAEs in ≥ 5% of Subjects (CLL/SLL)

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=303) n (%)	All Doses Duvelisib (N=330) n (%)
Subjects with Any TEAE	297 (98.0)	324 (98.2)
Blood and lymphatic system disorders	**155 (51.2)**	**171 (51.8)**
Neutropenia	95 (31.4)	103 (31.2)
Anaemia	55 (18.2)	65 (19.7)
Thrombocytopenia	43 (14.2)	47 (14.2)
Febrile neutropenia	21 (6.9)	26 (7.9)
Gastrointestinal disorders	**215 (71.0)**	**237 (71.8)**
Diarrhoea	137 (45.2)	151 (45.8)
Nausea	59 (19.5)	68 (20.6)
Constipation	40 (13.2)	43 (13.0)
Vomiting	39 (12.9)	47 (14.2)
Colitis	35 (11.6)	37 (11.2)
Abdominal pain	28 (9.2)	29 (8.8)
Abdominal pain upper	16 (5.3)	16 (4.8)
Dyspepsia	15 (5.0)	16 (4.8)
General disorders and administration site conditions	**153 (50.5)**	**174 (52.7)**
Pyrexia	76 (25.1)	89 (27.0)
Fatigue	44 (14.5)	53 (16.1)
Asthenia	33 (10.9)	35 (10.6)
Oedema peripheral	27 (8.9)	35 (10.6)
Infections and infestations	**195 (64.4)**	**217 (65.8)**
Pneumonia	49 (16.2)	58 (17.6)
Upper respiratory tract infection	40 (13.2)	47 (14.2)
Bronchitis	28 (9.2)	31 (9.4)
Respiratory tract infection	19 (6.3)	19 (5.8)
Nasopharyngitis	16 (5.3)	17 (5.2)
Urinary tract infection	15 (5.0)	17 (5.2)
Investigations	**116 (38.3)**	**134 (40.6)**
Alanine aminotransferase increased	28 (9.2)	35 (10.6)
Aspartate aminotransferase increased	28 (9.2)	35 (10.6)
Weight decreased	25 (8.3)	29 (8.8)
Lipase increased	17 (5.6)	17 (5.2)
Neutrophil count decreased	16 (5.3)	21 (6.4)
Metabolism and nutrition disorders	**110 (36.3)**	**128 (38.8)**
Decreased appetite	43 (14.2)	49 (14.8)
Hypokalaemia	26 (8.6)	34 (10.3)
Hyperkalaemia	18 (5.9)	23 (7.0)
Dehydration	15 (5.0)	16 (4.8)
Musculoskeletal and connective tissue disorders	**86 (28.4)**	**98 (29.7)**

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=303) n (%)	All Doses Duvelisib (N=330) n (%)
Arthralgia	24 (7.9)	31 (9.4)
Back pain	18 (5.9)	19 (5.8)
Myalgia	15 (5.0)	18 (5.5)
Nervous system disorders	**82 (27.1)**	**89 (27.0)**
Headache	23 (7.6)	26 (7.9)
Dizziness	16 (5.3)	17 (5.2)
Renal and urinary disorders	**45 (14.9)**	**50 (15.2)**
Renal failure acute	15 (5.0)	16 (4.8)
Respiratory, thoracic and mediastinal disorders	**127 (41.9)**	**151 (45.8)**
Cough	57 (18.8)	69 (20.9)
Dyspnoea	27 (8.9)	34 (10.3)
Skin and subcutaneous tissue disorders	**136 (44.9)**	**155 (47.0)**
Rash	44 (14.5)	48 (14.5)
Pruritus	17 (5.6)	19 (5.8)
Rash maculo-papular	17 (5.6)	23 (7.0)
Night sweats	15 (5.0)	18 (5.5)
Vascular disorders	**45 (14.9)**	**51 (15.5)**
Hypertension	17 (5.6)	19 (5.8)

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.2.1.2

Table 67 TEAEs in ≥ 5% of Subjects (FL)

System Organ Class/Preferred Term	25 mg BID Duvelisib (N=96) n (%)	All Doses Duvelisib (N=107) n (%)
Subjects with Any TEAE	95 (99.0)	106 (99.1)
Blood and lymphatic system disorders	**49 (51.0)**	**57 (53.3)**
Anaemia	25 (26.0)	28 (26.2)
Neutropenia	24 (25.0)	29 (27.1)
Thrombocytopenia	17 (17.7)	18 (16.8)
Febrile neutropenia	8 (8.3)	9 (8.4)
Leukopenia	5 (5.2)	5 (4.7)
Eye disorders	**12 (12.5)**	**12 (11.2)**
Dry eye	5 (5.2)	5 (4.7)
Gastrointestinal disorders	**70 (72.9)**	**80 (74.8)**
Diarrhoea	45 (46.9)	51 (47.7)
Nausea	31 (32.3)	36 (33.6)
Vomiting	21 (21.9)	22 (20.6)
Abdominal pain	16 (16.7)	18 (16.8)
Constipation	12 (12.5)	13 (12.1)
Stomatitis	7 (7.3)	8 (7.5)
Abdominal pain upper	5 (5.2)	5 (4.7)
Colitis	5 (5.2)	5 (4.7)
Dry mouth	5 (5.2)	5 (4.7)
Mouth ulceration	5 (5.2)	5 (4.7)
General disorders and administration site conditions	**62 (64.6)**	**71 (66.4)**
Fatigue	25 (26.0)	31 (29.0)
Pyrexia	25 (26.0)	32 (29.9)
Oedema peripheral	14 (14.6)	16 (15.0)
Asthenia	10 (10.4)	10 (9.3)
Chills	7 (7.3)	10 (9.3)
Disease progression	7 (7.3)	7 (6.5)
Infections and infestations	**53 (55.2)**	**58 (54.2)**
Oral candidiasis	7 (7.3)	8 (7.5)
Upper respiratory tract infection	7 (7.3)	8 (7.5)
Bronchitis	5 (5.2)	5 (4.7)
Urinary tract infection	5 (5.2)	6 (5.6)
Investigations	**45 (46.9)**	**55 (51.4)**
Alanine aminotransferase increased	17 (17.7)	24 (22.4)
Aspartate aminotransferase increased	15 (15.6)	22 (20.6)
Lipase increased	9 (9.4)	9 (8.4)
Blood alkaline phosphatase increased	8 (8.3)	10 (9.3)
Weight decreased	8 (8.3)	8 (7.5)
Blood lactate dehydrogenase increased	6 (6.3)	6 (5.6)

System Organ Class/Preferred Term	25 mg BID Duvelisib (N=96) n (%)	All Doses Duvelisib (N=107) n (%)
Metabolism and nutrition disorders	**38 (39.6)**	**42 (39.3)**
Hypokalaemia	12 (12.5)	13 (12.1)
Decreased appetite	10 (10.4)	12 (11.2)
Dehydration	8 (8.3)	8 (7.5)
Hypomagnesaemia	8 (8.3)	8 (7.5)
Hyperuricaemia	6 (6.3)	7 (6.5)
Hypophosphataemia	5 (5.2)	5 (4.7)
Musculoskeletal and connective tissue disorders	**38 (39.6)**	**41 (38.3)**
Back pain	14 (14.6)	14 (13.1)
Arthralgia	11 (11.5)	11 (10.3)
Pain in extremity	8 (8.3)	9 (8.4)
Musculoskeletal pain	6 (6.3)	7 (6.5)
Myalgia	5 (5.2)	7 (6.5)
Nervous system disorders	36 (37.5)	40 (37.4)
Headache	21 (21.9)	24 (22.4)
Dysgeusia	6 (6.3)	7 (6.5)
Dizziness	5 (5.2)	6 (5.6)
Psychiatric disorders	12 (12.5)	14 (13.1)
Insomnia	7 (7.3)	9 (8.4)
Respiratory, thoracic and mediastinal disorders	45 (46.9)	53 (49.5)
Cough	26 (27.1)	30 (28.0)
Dyspnoea	8 (8.3)	12 (11.2)
Oropharyngeal pain	7 (7.3)	10 (9.3)
Dyspnoea exertional	5 (5.2)	6 (5.6)
Pneumonitis	5 (5.2)	6 (5.6)
Rhinorrhoea	5 (5.2)	5 (4.7)
Skin and subcutaneous tissue disorders	48 (50.0)	56 (52.3)
Rash	21 (21.9)	23 (21.5)
Night sweats	9 (9.4)	10 (9.3)
Dry skin	7 (7.3)	7 (6.5)
Pruritus	7 (7.3)	7 (6.5)
Vascular disorders	16 (16.7)	18 (16.8)
Hypotension	4 (4.2)	6 (5.6)

Abbreviations: BID = twice daily; FL = follicular lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.2.1.1

Table 68 TEAEs in ≥ 5% of Subjects (All Heme)

System Organ Class/Preferred Term	25 mg BID Duvelisib (N=442) n (%)	All Doses Duvelisib (N=586) n (%)
Subjects with Any TEAE	**435 (98.4)**	**578 (98.6)**
Blood and Lymphatic System Disorders	**225 (50.9)**	**292 (49.8)**
Neutropenia	131 (29.6)	161 (27.5)
Anaemia	89 (20.1)	122 (20.8)
Thrombocytopenia	62 (14.0)	89 (15.2)
Febrile neutropenia	29 (6.6)	45 (7.7)
Gastrointestinal Disorders	**317 (71.7)**	**425 (72.5)**
Diarrhoea	206 (46.6)	261 (44.5)
Nausea	104 (23.5)	151 (25.8)
Vomiting	69 (15.6)	95 (16.2)
Constipation	57 (12.9)	79 (13.5)
Abdominal pain	53 (12.0)	68 (11.6)
Colitis	47 (10.6)	57 (9.7)
Abdominal pain upper	23 (5.2)	28 (4.8)
Stomatitis	21 (4.8)	38 (6.5)
General Disorders and Administration Site Conditions	**247 (55.9)**	**358 (61.1)**
Pyrexia	115 (26.0)	175 (29.9)
Fatigue	84 (19.0)	144 (24.6)
Oedema peripheral	54 (12.2)	85 (14.5)
Asthenia	47 (10.6)	58 (9.9)
Chills	26 (5.9)	48 (8.2)
Disease progression	14 (3.2)	35 (6.0)
Infections and Infestations	**276 (62.4)**	**364 (62.1)**
Pneumonia	60 (13.6)	79 (13.5)
Upper respiratory tract infection	52 (11.8)	70 (11.9)
Bronchitis	34 (7.7)	38 (6.5)
Urinary tract infection	22 (5.0)	34 (5.8)
Investigations	**184 (41.6)**	**282 (48.1)**
Alanine aminotransferase increased	53 (12.0)	113 (19.3)
Aspartate aminotransferase increased	49 (11.1)	107 (18.3)
Weight decreased	38 (8.6)	56 (9.6)
Lipase increased	27 (6.1)	28 (4.8)
Neutrophil count decreased	23 (5.2)	45 (7.7)
Blood alkaline phosphatase increased	15 (3.4)	34 (5.8)
Metabolism and Nutrition Disorders	**169 (38.2)**	**250 (42.7)**
Decreased appetite	63 (14.3)	93 (15.9)
Hypokalaemia	43 (9.7)	67 (11.4)
Dehydration	28 (6.3)	41 (7.0)
Hyperkalaemia	22 (5.0)	34 (5.8)

System Organ Class/Preferred Term	25 mg BID Duvelisib (N=442) n (%)	All Doses Duvelisib (N=586) n (%)
Hypomagnesaemia	22 (5.0)	38 (6.5)
Hyperglycaemia	18 (4.1)	30 (5.1)
Musculoskeletal and Connective Tissue Disorders	**149 (33.7)**	**206 (35.2)**
Arthralgia	46 (10.4)	67 (11.4)
Back pain	36 (8.1)	47 (8.0)
Pain in extremity	25 (5.7)	40 (6.8)
Myalgia	22 (5.0)	34 (5.8)
Nervous System Disorders	**139 (31.4)**	**199 (34.0)**
Headache	52 (11.8)	77 (13.1)
Dizziness	29 (6.6)	46 (7.8)
Psychiatric Disorders	**53 (12.0)**	**82 (14.0)**
Insomnia	21 (4.8)	36 (6.1)
Respiratory, Thoracic and Mediastinal Disorders	**201 (45.5)**	**298 (50.9)**
Cough	101 (22.9)	145 (24.7)
Dyspnoea	41 (9.3)	72 (12.3)
Pneumonitis	22 (5.0)	27 (4.6)
Oropharyngeal pain	18 (4.1)	33 (5.6)
Skin and Subcutaneous Tissue Disorders	**207 (46.8)**	**299 (51.0)**
Rash	73 (16.5)	89 (15.2)
Pruritus	28 (6.3)	42 (7.2)
Night sweats	25 (5.7)	40 (6.8)
Rash maculo-papular	21 (4.8)	50 (8.5)
Dry skin	17 (3.8)	30 (5.1)
Vascular disorders	**75 (17.0)**	**100 (17.1)**
Hypertension	24 (5.4)	31 (5.3)
Hypotension	18 (4.1)	32 (5.5)

Abbreviations: BID = twice daily; Heme = haematologic malignancies; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.2.1

The results in the pooled CLL/SLL 25 mg BID (n=303) were comparable to the phase 3 study in CLL (n=158; these are included in the 303 patients).

Generally, the AEs in the pooled FL population, the pooled CLL/SLL, and the All Heme 25 mg BID population are of the same order as in the RCT (IPI-145-07).

The incidence and prevalence of TEAE and serious TEAE over time of the 25 mg BID duvelisib all Heme population is shown in Table 35.

Table 69 Incidence and prevalence of TEAE and Serious TEAE over time

All Heme 25 mg BID Duvelisib (N = 443)					
Time frame	**<12 Weeks (N = 443) n (%)**	**12 to <24 Weeks (N = 404) n (%)**	**≥24 Weeks (N = 307) n (%)**	**≥ 1 year to <2 years (N=191) n %**	**≥ 2 years (N=78) n %**
Subjects with Any TEAE (incidence)	397 (89.6)	315 (78.0)	264 (86.0)	166 (86.9)	66 (84.6)
Subjects with Any Serious TEAE (incidence)	102 (23.0)	101 (25.0)	117 (38.1)	62 (32.5)	32 (41.0)
Subjects with Any TEAE (prevalence)	397 (89.6)	361 (89.4)	286 (93.2)	182 (95.3)	77 (98.7)
Subjects with Any Serious TEAE (prevalence)	102 (23.0)	121 (30.0)	135 (44.0)	69 (36.1)	33 (42.3)

Treatment-related Adverse Events (TRAEs)

No table of treatment-related adverse events is presented in the SCS. From the two pivotal studies (07 for CLL and 06 for FL) generally the events correspond to the adverse events of special interest (AESIs) and are similar between the two trials especially when considering that the FL study is a single-arm trial.

CLL/SLL – pivotal phase 3 study IPI-145-07:

Table 70 Treatment-Related TEAEs Occurring in ≥ 5% of Subjects on Either Treatment Arm, by SOC and PT (All-Treated Analysis Set)

System Organ Class Preferred Term	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
Subjects with ≥ 1 TEAE	142 (89.9)	111 (71.6)
Blood and lymphatic system disorders	**66 (41.8)**	**34 (21.9)**
Neutropenia	44 (27.8)	26 (16.8)
Anaemia	18 (11.4)	3 (1.9)
Thrombocytopenia	12 (7.6)	3 (1.9)
Febrile neutropenia	8 (5.1)	2 (1.3)
Gastrointestinal disorders	**93 (58.9)**	**23 (14.8)**
Diarrhoea	65 (41.1)	4 (2.6)
Nausea	23 (14.6)	9 (5.8)
Colitis	19 (12.0)	0
Vomiting	12 (7.6)	4 (2.6)
Constipation	9 (5.7)	2 (1.3)

Table cont.

System Organ Class Preferred Term	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
General disorders and administration site conditions	**44 (27.8)**	**28 (18.1)**
Fatigue	13 (8.2)	10 (6.5)
Pyrexia	13 (8.2)	7 (4.5)
Asthenia	10 (6.3)	7 (4.5)
Oedema peripheral	9 (5.7)	2 (1.3)
Infections and infestations	**43 (27.2)**	**23 (14.8)**
Pneumonia	11 (7.0)	6 (3.9)
Injury, poisoning and procedural complications	**3 (1.9)**	**31 (20.0)**
Infusion-related reaction	0	29 (18.7)
Investigations	**36 (22.8)**	**11 (7.1)**
Aspartate aminotransferase increased	11 (7.0)	0
Alanine aminotransferase increased	9 (5.7)	0
Weight decreased	9 (5.7)	0
Metabolism and nutrition disorders	**21 (13.3)**	**7 (4.5)**
Decreased appetite	14 (8.9)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**31 (19.6)**	**7 (4.5)**
Cough	11 (7.0)	1 (0.6)
Pneumonitis	8 (5.1)	0
Skin and subcutaneous tissue disorders	**35 (22.2)**	**30 (19.4)**
Rash	11 (7.0)	14 (9.0)

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated subjects in each treatment group. A treatment- emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence. TEAEs with a relationship of Possible, Probable, or Definite per Investigator are considered related to study treatment.
Source: Table 14.3.1.3

FL – phase 2 study IPI-145-06

Table 25 displays the TEAEs occurring in ≥ 4 (3%) subjects in the overall FAS that were assessed by investigators as related to duvelisib.

Table 71 Treatment-Related Treatment-Emergent Adverse Events Occurring in ≥ 3% of Subjects by SOC and PT (FAS)

System Organ Class/Preferred Term	Overall N = 129 n (%)
Subjects with at Least 1 Treatment-Related TEAE	**116 (89.9)**
Blood and lymphatic system disorders	**49 (38.0)**
Neutropenia	36 (27.9)
Thrombocytopenia	18 (14.0)
Anaemia	16 (12.4)
Febrile neutropenia	8 (6.2)
Leukopenia	4 (3.1)
Gastrointestinal disorders	**60 (46.5)**
Diarrhoea	43 (33.3)
Nausea	17 (13.2)
Vomiting	9 (7.0)
Colitis	6 (4.7)
Abdominal pain	5 (3.9)
Dry mouth	5 (3.9)
General disorders and administration site conditions	**39 (30.2)**
Fatigue	21 (16.3)
Pyrexia	11 (8.5)
Asthenia	7 (5.4)
Infections and infestations	**31 (24.0)**
Pneumonia	7 (5.4)
Oral candidiasis	4 (3.1)

System Organ Class/Preferred Term	Overall N = 129 n (%)
Investigations	**42 (32.6)**
Alanine aminotransferase increased	16 (12.4)
Aspartate aminotransferase increased	12 (9.3)
Lipase increased	7 (5.4)
Neutrophil count decreased	6 (4.7)
Blood alkaline phosphatase increased	5 (3.9)
Blood lactate dehydrogenase increased	5 (3.9)
Weight decreased	4 (3.1)
Metabolism and nutrition disorders	**27 (20.9)**
Decreased appetite	13 (10.1)
Hypokalaemia	4 (3.1)
Hypophosphataemia	4 (3.1)
Nervous system disorders	**20 (15.5)**
Headache	10 (7.8)
Respiratory, thoracic and mediastinal disorders	**25 (19.4)**
Cough	8 (6.2)
Pneumonitis	5 (3.9)
Skin and subcutaneous tissue disorders	**37 (28.7)**
Rash	16 (12.4)
Pruritus	6 (4.7)

Note: Subjects were counted once within each system organ class and preferred term. Percentages are based on the number of subjects in the Full Analysis Set.
Source: Table 14.3.1.3, Table 14.3.1.22, Table 14.3.1.23, Table 14.3.1.24, Listing 16.2.7.1

≥ *Grade 3 AEs*

Clearly ≥ grade 3 TEAE occurred more frequently in the duvelisib arm compared to the ofatumumab arm in the RCT: This was apparent for PTs in the SOC Blood and lymphatic system disorders, infections (in particular pneumonia), colitis/diarrhoea, increased transaminases, and pneumonitis (Table 31/CSR-07). The frequencies were similar in the pooled studies for both CLL/SLL (Table 17/SCS) and FL (Table 21/SCS).

CLL/SLL – pivotal phase 3 study IPI-145-07:

Table 72 Severe (≥ Grade 3) TEAEs Occurring in ≥2 % Subjects, by SOC and PT – All Causalities and Treatment-Related (All-Treated Analysis Set)

System Organ Class Preferred Term	Duvelisib (N=158) n (%)		Ofatumumab (N=155) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Subjects with at Least 1 TEAE ≥ Grade 3	138 (87.3)	118 (74.7)	75 (48.4)	47 (30.3)
Blood and lymphatic system disorders	**67 (42.4)**	**52 (32.9)**	**38 (24.5)**	**27 (17.4)**
Neutropenia	48 (30.4)	40 (25.3)	27 (17.4)	22 (14.2)
Anaemia	20 (12.7)	8 (5.1)	8 (5.2)	1 (0.6)
Thrombocytopenia	12 (7.6)	4 (2.5)	3 (1.9)	3 (1.9)
Febrile neutropenia	11 (7.0)	8 (5.1)	3 (1.9)	2 (1.3)
Leukocytosis	4 (2.5)	4 (2.5)	0	0
Gastrointestinal disorders	**51 (32.3)**	**42 (26.6)**	**4 (2.6)**	**1 (0.6)**
Diarrhoea	23 (14.6)	21 (13.3)	2 (1.3)	0
Colitis	19 (12.0)	18 (11.4)	1 (0.6)	0
General disorders and administration site conditions	**18 (11.4)**	**0**	**8 (5.2)**	**0**
Pyrexia	4 (2.5)	0	1 (0.6)	0
Asthenia	3 (1.9)	2 (1.3)	4 (2.6)	0
Infections and infestations	**53 (33.5)**	**25 (15.8)**	**17 (11.0)**	**7 (4.5)**
Pneumonia	22 (13.9)	10 (6.3)	2 (1.3)	2 (1.3)
Bronchitis	5 (3.2)	1 (0.6)	1 (0.6)	0
Injury, poisoning and procedural complications	**5 (3.2)**	**1 (0.6)**	**7 (4.5)**	**6 (3.9)**
Infusion related reaction	0	0	6 (3.9)	6 (3.9)
Investigations	**21 (13.3)**	**17 (10.8)**	**6 (3.9)**	**3 (1.9)**
Aspartate aminotransferase increased	5 (3.2)	5 (3.2)	0	0
Alanine aminotransferase increased	4 (2.5)	4 (2.5)	0	0
Lipase increased	4 (2.5)	4 (2.5)	1 (0.6)	0
Metabolism and nutrition disorders	**22 (13.9)**	**5 (3.2)**	**7 (4.5)**	**3 (1.9)**
Hypokalaemia	8 (5.1)	2 (1.3)	0	0
Hyponatraemia	4 (2.5)	0	1 (0.6)	0
Renal and urinary disorders	**7 (4.4)**	**1 (0.6)**	**2 (1.3)**	**0**
Renal failure acute	4 (2.5)	1 (0.6)	2 (1.3)	0
Respiratory, thoracic and mediastinal disorders	**17 (10.8)**	**10 (6.3)**	**4 (2.6)**	**0**
Dyspnoea	4 (2.5)	1 (0.6)	0	0
Pneumonitis	4 (2.5)	4 (2.5)	0	
Skin and subcutaneous tissue disorders	**21 (13.3)**	**18 (11.4)**	**4 (2.6)**	**4 (2.6)**
Toxic skin eruption	4 (2.5)	4 (2.5)	0	0

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated subjects in each treatment group. A treatment- emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence. TEAEs with a relationship of Possible, Probable, or Definite per Investigator are considered related to study treatment.
Source: Table 14.3.1.4, Table 14.3.1.5

Integrated summary:

Table 73 Grade 3 or Higher TEAEs in ≥ 2% of Subjects (CLL/SLL)

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=303) n (%)	All Doses Duvelisib (N=330) n (%)
Subjects with Any TEAE Grade 3 or Higher	262 (86.5)	287 (87.0)
Blood and lymphatic system disorders	**128 (42.2)**	**138 (41.8)**
Neutropenia	87 (28.7)	92 (27.9)
Anaemia	33 (10.9)	38 (11.5)
Thrombocytopenia	26 (8.6)	29 (8.8)
Febrile neutropenia	21 (6.9)	26 (7.9)
Leucocytosis	8 (2.6)	9 (2.7)
Pancytopenia	6 (2.0)	6 (1.8)
Gastrointestinal disorders	**88 (29.0)**	**93 (28.2)**
Diarrhoea	44 (14.5)	46 (13.9)
Colitis	30 (9.9)	32 (9.7)
General disorders and administration site conditions	**35 (11.6)**	**39 (11.8)**
Pyrexia	7 (2.3)	9 (2.7)
Disease progression	6 (2.0)	7 (2.1)
Fatigue	5 (1.7)	8 (2.4)
Infections and infestations	**94 (31.0)**	**108 (32.7)**
Pneumonia	39 (12.9)	46 (13.9)
Bronchitis	8 (2.6)	8 (2.4)
Sepsis	8 (2.6)	9 (2.7)
Investigations	**55 (18.2)**	**64 (19.4)**
Neutrophil count decreased	13 (4.3)	18 (5.5)
Aspartate aminotransferase increased	10 (3.3)	13 (3.9)
Lipase increased	10 (3.3)	10 (3.0)
Alanine aminotransferase increased	9 (3.0)	10 (3.0)
Metabolism and nutrition disorders	**39 (12.9)**	**49 (14.8)**
Hypokalaemia	13 (4.3)	18 (5.5)
Hyponatraemia	8 (2.6)	10 (3.0)
Hyperkalaemia	6 (2.0)	7 (2.1)
Hypophosphataemia	6 (2.0)	10 (3.0)
Renal and urinary disorders	**15 (5.0)**	**17 (5.2)**
Renal failure acute	9 (3.0)	10 (3.0)
Respiratory, thoracic and mediastinal disorders	**31 (10.2)**	**38 (11.5)**
Pneumonitis	6 (2.0)	9 (2.7)
Dyspnoea	5 (1.7)	7 (2.1)
Skin and subcutaneous tissue disorders	**33 (10.9)**	**34 (10.3)**
Rash	9 (3.0)	9 (2.7)

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1 and graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.16.1.2

Source: SCS

Table 74 Grade 3 or Higher TEAEs in ≥ 2% of Subjects (FL)

System Organ Class/Preferred Term	25 mg BID Duvelisib (N=96) n (%)	All Doses Duvelisib (N=107) n (%)
Subjects with Any TEAE Grade 3 or Higher	82 (85.4)	93 (86.9)
Blood and lymphatic system disorders	**35 (36.5)**	**42 (39.3)**
Neutropenia	21 (21.9)	26 (24.3)
Anaemia	13 (13.5)	15 (14.0)
Thrombocytopenia	10 (10.4)	10 (9.3)
Febrile neutropenia	8 (8.3)	9 (8.4)
Leukopenia	3 (3.1)	3 (2.8)
Pancytopenia	2 (2.1)	2 (1.9)
Gastrointestinal disorders	**24 (25.0)**	**26 (24.3)**
Diarrhoea	16 (16.7)	17 (15.9)
Vomiting	6 (6.3)	6 (5.6)
Colitis	4 (4.2)	4 (3.7)
Nausea	3 (3.1)	4 (3.7)
Abdominal pain	2 (2.1)	3 (2.8)
General disorders and administration site conditions	**17 (17.7)**	**17 (15.9)**
Disease progression	7 (7.3)	7 (6.5)
Fatigue	6 (6.3)	6 (5.6)
Asthenia	3 (3.1)	3 (2.8)
Hepatobiliary disorders	4 (4.2)	4 (3.7)
Hepatotoxicity	2 (2.1)	2 (1.9)
Infections and infestations	**19 (19.8)**	**21 (19.6)**
Pneumonia	3 (3.1)	3 (2.8)
Bronchopneumonia	2 (2.1)	2 (1.9)
Sepsis	2 (2.1)	2 (1.9)
Investigations	**25 (26.0)**	**30 (28.0)**
Alanine aminotransferase increased	9 (9.4)	13 (12.1)
Lipase increased	8 (8.3)	8 (7.5)
Aspartate aminotransferase increased	7 (7.3)	12 (11.2)
Platelet count decreased	3 (3.1)	3 (2.8)
Amylase increased	2 (2.1)	2 (1.9)
Blood bilirubin increased	2 (2.1)	2 (1.9)
Neutrophil count decreased	2 (2.1)	2 (1.9)
Metabolism and nutrition disorders	**15 (15.6)**	**16 (15.0)**

System Organ Class/Preferred Term	25 mg BID Duvelisib (N=96) n (%)	All Doses Duvelisib (N=107) n (%)
Hyperuricaemia	3 (3.1)	4 (3.7)
Hypophosphataemia	3 (3.1)	3 (2.8)
Hyperglycaemia	2 (2.1)	2 (1.9)
Hypokalaemia	2 (2.1)	2 (1.9)
Hyponatraemia	2 (2.1)	2 (1.9)
Renal and urinary disorders	**6 (6.3)**	**6 (5.6)**
Renal failure acute	4 (4.2)	4 (3.7)
Renal failure	2 (2.1)	2 (1.9)
Respiratory, thoracic and mediastinal disorders	**7 (7.3)**	**8 (7.5)**
Pneumonitis	4 (4.2)	5 (4.7)
Skin and subcutaneous tissue disorders	**10 (10.4)**	**12 (11.2)**
Rash	3 (3.1)	3 (2.8)
Rash generalised	2 (2.1)	3 (2.8)
Vascular disorders	**4 (4.2)**	**5 (4.7)**
Hypotension	2 (2.1)	3 (2.8)

Abbreviations: BID = twice daily; FL = follicular lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1 and graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.16.1.1

Adverse Events of Special Interest (AESIs)

In the SCS the AESIs are presented but without the separate results from the only randomised study for comparison. It is apparent that safety is going to be a major issue for the potential approval of duvelisib in CLL/SLL and/or FL and safety therefore has to be comprehensively presented. As the PTs for the AESIs in the SCS are pooled presenting the PTs from the various tables from the CSR (IPI-145-07) may not reflect the entire picture, and the applicant is requested to present the data for all AESIs in study IPI-145-07 using pooled PTs for both arms (duvelisib and ofatumumab) and include them in the tables for AESIs in the SCS (25 mg BID) preferably in the order All Heme (N=442), All FL (N=96), All CLL/SLL (N=303), CLL study 145-07 duvelisib arm (N=158) and the comparator ofatumumab (N=155) for ease of comparison. The applicant has presented the information as requested – see tables below.

Table 75 Adverse Events of Special Interest - regarding frequency-adjusted AESIs for study 07

AESI Grouping	Duvelisib N =158 N (N/P-Y)	Ofatumumab N=155 N (N/P-Y)	Duvelisib/Ofatumumab Rate Ratio
Pneumonitis	13 (0.078)	1 (0.018)	4.33
Rash	42 (0.296)	23 (0.482)	0.61
Transaminase elevation	18 (0.114)	6 (0.109)	1.05
Diarrhea/colitis	90 (0.767)	21 (0.409)	1.88
Neutropenia	53 (0.412)	35 (0.725)	0.57
Infections and infestations	109 (1.188)	67 (1.534)	0.77

Diarrhoea-Colitis

A customised PT grouping was used to identify the selected adverse events of AESI Diarrhoea-Colitis for each population (All Heme, CLL/SLL, and FL [each 25 mg BID]): *Colitis, Colitis erosive, Colitis microscopic, Colitis ulcerative, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Diarrhoea, and Diarrhoea haemorrhagic.* The incidence of the AESI diarrhoea-colitis reported with duvelisib was 50.2% in the All Heme group, 49.0% in the 96 subjects with FL, 49.8% in the 303 subjects with CLL, and 57.0% in Study IPI-145-07 compared to 13.5% in the ofatumumab arm.

In the duvelisib treatment arm with colitis 21/23 patients had Grade 3 or 4 colitis: Of the 23 patients, 10 (43%) had an onset within 6 months of initiating treatment; 10 (43%) subjects had an onset between 6 and 12 months of starting treatment; and 3 (13%) subjects had an onset after 1 year on treatment demonstrating that colitis may occur at any time during treatment, and is not limited to the initial treatment period. This is also confirmed by the integrated analysis were the median time to onset for ≥ Grade 3 was 227 days.

In the Integrated summary population 20% (89/442) patients had an SAE with 1 death and 79/442 events being Grade 3 or 4. No Grade 5 colitis occurred in the RCT. None of the colitis TEAEs resulted in death.

Table 76 Overview of Subjects with TEAEs of AESI Diarrhoea-Colitis and Individual Grouped PTs, Safety Analysis Set, All Subgroups (25 mg BID)

Subjects with:	All Heme 25 mg BID (N=442) n (%)	CLL/SLL 25 mg BID (N=303) n (%)	FL 25 mg BID (N=96) n (%)
AESI-Diarrhoea-Colitis	222 (50.2)	151 (49.8)	47 (49.0)
Colitis	47 (10.6)	35 (11.6)	5 (5.2)
Enterocolitis	5 (1.1)	3 (1.0)	1 (1.0)
Colitis microscopic	2 (0.5)	1 (0.3)	0
Colitis ulcerative	2 (0.5)	2 (0.7)	0
Diarrhoea	206 (46.6)	137 (45.2)	45 (46.9)
Diarrhoea haemorrhagic	1 (0.2)	1 (0.3)	0
≥ Grade 3 AESI-Diarrhoea-Colitis	101 (22.9)	71 (23.4)	19 (19.8)
Serious (All Grade) AESI-Diarrhoea-Colitis	81 (18.3)	59 (19.5)	12 (12.5)
AESI-Diarrhoea-Colitis Leading to a Hold or Reduction of Dose			
Dose hold	101 (22.9)	73 (24.1)	16 (16.7)
Dose reduction	27 (6.1)	19 (6.3)	5 (5.2)
AESI-Diarrhoea-Colitis Leading to Treatment Discontinuation	43 (9.7)	33 (10.9)	4 (4.2)
AESI-Diarrhoea-Colitis Resulting in Death	1	0	0

Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = haematologic malignancies; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Only TEAEs of this category of Adverse Events of Special Interest that were reported by subjects are included in this table.

Adverse Events are graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher.

a. Includes Definitely, Possibly, Probably, unknown, or missing relationship.

Source: MAA Safety TLFs Table 2.30, Table 2.30.1, Table 2.30.2, Table 2.32, Table 2.32.1, Table 2.32.2, Table 2.34, Table 2.34.1, Table 2.34.2, Table 2.34.1.1, Table 2.34.2.1, Table 2.34.3.1, Table 2.35, Table 2.35.1, Table 2.35.2, Table 2.36.3, Table 2.36.3.1, Table 2.36.3.2; ISS Table 2.2.1

All Heme 25 mg BID-population: For Grade 3 or higher events, the majority were recovered/resolved or recovered/resolved with sequelae (137 events, 93%). Five events (3%) were not recovered/not resolved, 4 (3%) had a change in grade, and 1 outcome was fatal.

Infection (Including Pneumonia)

For the AESI Infections PTs of the entire SOC are included. There were more infectious adverse events in the duvelisib arm of the pivotal randomised study (145-07) compared to the ofatumumab arm; 69.0% vs 43.2% and for SAEs 38.0% vs 12.9%. For Pneumonia the corresponding percentages were 18.4% vs 5.8% and for SAEs 14.6% vs 3.2%. The difference between the two arms were also higher for ≥ Grade 3 infections with the incidence of SOC Infections being 33.5% vs 11.0% (duvelisib vs ofatumumab) and the corresponding

results for Pneumonia 13.9% (N=22) vs 1.3% (N=2). All subjects (N=10) with Infectious TEAEs leading to death were duvelisib treated, no patients in the ofatumumab arm died due to an infection.

Table OC153-1: Frequency of Adverse Events, Serious Adverse Events, and Grade 3+ Adverse Events in the Infections and Infestations System Organ Class

Event	Duvelisib % (N)	Ofatumumab % (N)	Duvelisib Subjects/P-Y	Ofatumumab Subjects/P-Y	Rate Ratio Duvelisib/ Ofatumumab
SOC Infection - AE	69.0 (109)	43.2 (67)	1.235	1.535	0.80
SOC Infection - SAE	38.0 (60)	12.9 (20)	0.424	0.377	1.12
SOC Infection -Gr3+	33.5 (53)	11.0 (17)	0.356	0.318	1.12

Abbreviations: AE = adverse event; Gr = Grade; P-Y = patient-years; SAE = serious adverse event.
Source: CSR-07 Tables: 14.3.1.2 AEs, 14.3.1.11 SAEs, 14.3.1.4 Gr3+ AEs. T_14_3_1_2_tpy_teae_d120.rtf-AEs; teae_ser_d120.rtf-SAEs; teae_g3.rtf Gr 3+AEs

Table 48: Overview of Subjects with TEAEs (≥ 2% by All Heme) of AESI Infection and Individual Grouped PTs, Safety Analysis Set, All Subgroups (25 mg BID)

Subjects with:	All Heme 25 mg BID (N=442) n (%)	CLL/SLL 25 mg BID (N=303) n (%)	FL 25 mg BID (N=96) n (%)
AESI-Infection	276 (62.4)	195 (64.4)	53 (55.2)
Pneumonia	60 (13.6)	49 (16.2)	4 (4.2)
Upper respiratory tract infection	52 (11.8)	40 (13.2)	7 (7.3)
Bronchitis	34 (7.7)	28 (9.2)	5 (5.2)
Urinary tract infection	22 (5.0)	15 (5.0)	5 (5.2)
Respiratory tract infection	21 (4.8)	19 (6.3)	1 (1.0)
Nasopharyngitis	20 (4.5)	16 (5.3)	2 (2.1)
Oral candidiasis	20 (4.5)	10 (3.3)	7 (7.3)
Sinusitis	15 (3.4)	11 (3.6)	2 (2.1)
Influenza	13 (2.9)	10 (3.3)	2 (2.1)
Gastroenteritis	12 (2.7)	10 (3.3)	2 (2.1)
Herpes zoster	12 (2.7)	7 (2.3)	3 (3.1)
Sepsis	10 (2.3)	8 (2.6)	2 (2.1)
≥ Grade 3 AESI-Infection	119 (26.9)	94 (31.0)	19 (19.8)
Serious AESI-Infection	137 (31.0)	106 (35.0)	20 (20.8)
AESI-Infection Leading to a Hold or Reduction of Dose			
Dose hold	95 (21.5)	74 (24.4)	12 (12.5)
Dose reduction	8 (1.8)	5 (1.7)	3 (3.1)
AESI-Infection Leading to Treatment Discontinuation	24 (5.4)	19 (6.3)	3 (3.1)
AESI-Infection Resulting in Death	18 (4.1)	16 (5.3)	2 (2.1)

Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = haematologic malignancies; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Only TEAEs of this category of Adverse Events of Special Interest that were reported by ≥2% of subjects in the All Heme 25 mg BID Group are included in this table.

Adverse Events are graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher.

a. Includes Definitely, Possibly, Probably, unknown, or missing relationship.

Source: ISS Table 2.21.3, ISS Table 2.21.3.2, ISS Table 2.21.3.1, ISS Table 2.22.3, ISS Table 2.22.3.2, ISS Table 2.22.3.1

Non-infectious Pneumonitis (Pneumonitis)

Thirteen (8.2%) subjects on the duvelisib treatment arm had an AESI of pneumonitis and one in the ofatumumab arm (0.6%); PT Lung infiltration.

Table 77 Frequencies of AESI of pneumonitis for CLL and FL: 25mg BID duvelisib

	ISS Data			Study IPI-145-07				
	All Heme (N=442) n (%)	FL (N=96) n (%)	CLL/SLL (N=303) n (%)	Duvelisib (N=158) N (%)	Ofatumumab (N=155) N (%)	Duvelisib N (N/P-Y)	Ofatumumab N (N/P-Y)	Duvelisib/Ofatumumab Rate Ratio
AESI: Pneumonitis	**30 (6.8)**	**5 (5.2)**	**20 (6.6)**	**13 (8.2)**	**1 (0.6)**	**13 (0.078)**	**1 (0.018)**	**4.33**
Pneumonitis	22 (5.0)	5 (5.2)	13 (4.3)	10 (6.3)	0	10 (0.060)	0	-
Interstitial lung disease	5 (1.1)	0	5 (1.7)	3 (1.9)	0	3 (0.017)	0	-
Lung infiltration	3 (0.7)	0	2 (0.7)	0	1 (0.6)	0	1 (0.018)	-

Source: ISS source: ISS Table 2.2.1, Table 2.2.1.1 and Table 2.2.1.2; Table 14.3.1.2_tpy_si_d120 (data on file)
Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; ISS = integrated safety summary; N/P-Y = number of subjects per patient-year; SLL = small lymphocytic lymphoma.

Table 78 Overview of Subjects with TEAEs of AESI Pneumonitis and Individual Grouped PTs, Safety Analysis Set, All Subgroups (25 mg BID)

Subjects with:	All Heme 25 mg BID (N=442) n (%)	CLL/SLL 25 mg BID (N=303) n (%)	FL 25 mg BID (N=96) n (%)
AESI-Pneumonitis	30 (6.8)	20 (6.6)	5 (5.2)
Pneumonitis	22 (5.0)	13 (4.3)	5 (5.2)
Interstitial lung disease	5 (1.1)	5 (1.7)	0
Lung infiltration	3 (0.7)	2 (0.7)	0
≥ Grade 3 AESI-Pneumonitis	16 (3.6)	10 (3.3)	4 (4.2)
Serious AESI-Pneumonitis	20 (4.5)	13 (4.3)	4 (4.2)
AESI-Pneumonitis Leading to a Hold or Reduction of Dose			
Dose hold	21 (4.8)	13 (4.3)	4 (4.2)
Dose reduction	3 (0.7)	2 (0.7)	0
AESI-Pneumonitis Leading to Treatment Discontinuation	15 (3.4)	10 (3.3)	3 (3.1)
AESI-Pneumonitis Resulting in Death	1 (0.2)	1 (0.3)	0

Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = haematologic malignancies; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.
Note: Adverse Events are coded using MedDRA version 16.1. Only TEAEs of this category of Adverse Events of Special Interest that were reported by subjects are included in this table.
Adverse Events are graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher.
a. Includes Definitely, Possibly, Probably, unknown, or missing relationship.

Severe Cutaneous Reactions (AESI Rash)

There were more AESIs Rash in the CLL arm compared to the ofatumumab arm; 42 (26.6%) vs 23 (14.8%). The incidence in the entire CLL/SLL cohort of 303 patients was 29.7%, and are also of the same magnitude in

the FL population (N=96; 31.3%). This also pertains to the ≥ Grade 3 and serious AEs. Four subjects had severe TEAEs of toxic skin eruption probably or definitely related to duvelisib treatment.

Table 79 Overview of Subjects with TEAEs (≥2% by All Heme) of AESI Rash and Individual Grouped PTs, Safety Analysis Set, All Subgroups (25 mg BID)

Subjects with:	All Heme 25 mg BID (N=442) n (%)	CLL/SLL 25 mg BID (N=303) n (%)	FL 25 mg BID (N=96) n (%)
AESI-Rash	136 (31.2)	90 (29.7)	30 (31.3)
MedDRA PT Rash	73 (16.5)	44 (14.5)	21 (21.9)
Rash maculo-papular	21 (4.8)	17 (5.6)	1 (1.0)
Rash erythematous	13 (2.9)	8 (2.6)	3 (3.1)
Dermatitis	10 (2.3)	8 (2.6)	2 (2.1)
Rash pruritic	9 (2.0)	4 (1.3)	2 (2.1)
≥ Grade 3 AESI-Rash	41 (9.3)	28 (9.2)	10 (10.4)
Serious AESI-Rash	23 (5.2)	15 (5.0)	7 (7.3)
AESI-Rash Leading to a Hold or Reduction of Dose			
Dose hold	39 (8.8)	28 (9.2)	9 (9.4)
Dose reduction	11 (2.5)	9 (3.0)	1 (1.0)
AESI-Rash Leading to Treatment Discontinuation	16 (3.6)	12 (4.0)	4 (4.2)
AESI-Rash Resulting in Death	2 (0.5)	0	2 (2.1)

Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = haematologic malignancies; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Only TEAEs of this category of Adverse Events of Special Interest that were reported in ≥2% of subjects in the All Heme 25 mg BID Group are included in this table.

AESI = Adverse Event of Special Interest; Adverse Events are graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher.

a. Includes Definitely, Possibly, Probably, unknown, or missing relationship.

Serious adverse events and deaths

Deaths

In the randomised study fatal TEAEs (between first dose and 30 days after last dose) were reported for 19 in the duvelisib arm (12.0%) and 7 (4.5%) in the ofatumumab arm. Two patients in the ofatumumab arm had progressive disease counted as an TEAE. Two patients died after the cut-off date of 19 July 2017.

Table 80 IPI-145-07 Subjects with TEAEs Resulting in Death, by SOC and PT - All Causalities (All-Treated Analysis Set)

System Organ Class Preferred Term	Duvelisib (N=158) n (%)		Ofatumumab (N=155) n (%)	
	All Causalities	Related to Treatment	All Causalities	Related to Treatment
Subjects with ≥ 1 TEAE Resulting in Death, excluding disease progression	19 (12.0)	4 (2.5); Possible, Related	5 (3.2)	0; Not Related
Subjects with ≥1 TEAE Resulting in Death	19 (12.0)	4 (2.5); Possible, Related	7 (4.5)	0; Not Related
Cardiac disorders	1 (0.6)	0; Not Related	0	0; Not Related
Cardiac failure	1 (0.6)	0; Not Related	0	0; Not Related
General disorders and administration site conditions	4 (2.5)	1 (0.6); Possible, Related	2 (1.3)	0; Not Related
Death	1 (0.6)	0; Not Related	0	0; Not Related
General physical health deterioration	1 (0.6)	1 (0.6); Possible, Related	0	0; Not Related
Multi-organ failure	1 (0.6)	0; Not Related	0	0; Not Related
Sudden death	1 (0.6)	0; Not Related	0	0; Not Related
Disease progression	0	0; Not Related	2 (1.3)	0; Not Related
Hepatobiliary disorders	0	0; Not Related	1 (0.6)	0; Not Related
Hepatic failure	0	0 Not Related	1 (0.6)	0; Not Related
Infections and infestations	10 (6.3)	3 (1.9); Possible, Related	0	0; Not Related
Bronchopulmonary aspergillosis	2 (1.3)	0; Not Related	0	0; Not Related
Pneumonia staphylococcal	2 (1.3)	2 (1.3); Possible, Related	0	0; Not Related
Bronchitis	1 (0.6)	0; Not Related	0	0; Not Related
Enterococcal sepsis	1 (0.6)	0; Not Related	0	0; Not Related
Escherichia sepsis	1 (0.6)	0; Not Related	0	0; Not Related
Pneumonia bacterial	1 (0.6)	0; Not Related	0	0; Not Related
Pneumonia pseudomonas aeruginosa	1 (0.6)	0; Not Related	0	0; Not Related
Pseudomonal sepsis	1 (0.6)	0; Not Related	0	0; Not Related
Sepsis	1 (0.6)	1 (0.6); Possible, Related	0	0; Not Related
Septic shock	1 (0.6)	0; Not Related	0	0; Not Related
Injury, poisoning and procedural complications	0	0; Not Related	1 (0.6)	0; Not Related
Fall	0	0; Not Related	1 (0.6)	0; Not Related

System Organ Class Preferred Term	Duvelisib (N=158) n (%)		Ofatumumab (N=155) n (%)	
	All Causalities	Related to Treatment	All Causalities	Related to Treatment
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0; Not Related	2 (1.3)	0; Not Related
Glioblastoma multiforme	0	0; Not Related	1 (0.6)	0; Not Related
Squamous cell carcinoma	0	0; Not Related	1 (0.6)	0; Not Related
Nervous system disorders	3 (1.9)	0; Not Related	0	0; Not Related
Haemorrhagic stroke	2 (1.3)	0; Not Related	0	0; Not Related
Mental impairment	1 (0.6)	0; Not Related	0	0; Not Related
Renal and urinary disorders	0	0; Not Related	1 (0.6)	0; Not Related
Renal failure acute	0	0; Not Related	1 (0.6)	0; Not Related
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0; Not Related	0	0; Not Related
Chronic obstructive pulmonary disease	1 (0.6)	0; Not Related	0	0; Not Related

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated subjects in each treatment group. A treatment- emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence.

A total of 42 (9.5%) subjects in the All Heme 25 mg BID Group died on treatment or within 30 days of last dose of duvelisib.

Table 81 Summary of all deaths in the All Heme 25 mg BID Group and All Heme. All Doses Group.

Number of Deaths	Category	25 mg BID Duvelisib (N=442) n (%)	All Doses Duvelisib (N=586) n (%)
On Treatment	Overall	42 (9.5)	67 (11.4)
	PD	16 (3.6)	33 (5.6)
	AE	24 (5.4)	32 (5.5)
	Other	1 (0.2)	1 (0.2)
	Unknown	1 (0.2)	1 (0.2)
Survival Follow-up	Overall	98 (22.2)	163 (27.8)
	PD	50 (11.3)	90 (15.4)
	AE	12 (2.7)	16 (2.7)
	Not PD	3 (0.7)	17 (2.9)
	Other	19 (4.3)	19 (3.2)
	Unknown	14 (3.2)	21 (3.6)

Abbreviations: AE = Adverse Event; BID = twice daily; Heme = haematologic malignancies; PD = Progressive Disease;

Note: Deaths on treatment are defined as deaths occurring between first dose and within 30 days after last dose. Deaths in follow-up are defined as deaths occurring > 30 days after last dose. For subjects in Study IPI-145-02, the Survival Follow- up deaths are classified according to the eCRF question: "Was Death due to disease progression?" As a result, all deaths from that study that were not due to PD are categorized as Not PD. In Studies IPI-145-06, IPI-145-07, and IPI-145-12, the data were captured as PD, AE, Other, and Unknown.

Source: ISS Table 3.1

Table 82 Summary of TEAEs with outcome of Death (CLL)

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=303) n (%)	All Doses Duvelisib (N=330) n (%)
Subjects with Any TEAE Resulting in Death	37 (12.2)	42 (12.7)
Cardiac disorders	**3 (1.0)**	**4 (1.2)**
Cardiac failure	2 (0.7)	2 (0.6)
Cardio-respiratory arrest	1 (0.3)	1 (0.3)
Cardiac arrest	0	1 (0.3)
General disorders and administration site conditions	**12 (4.0)**	**13 (3.9)**
Disease progression	6 (2.0)	7 (2.1)
General physical health deterioration	2 (0.7)	2 (0.6)
Multi-organ failure	2 (0.7)	2 (0.6)
Death	1 (0.3)	1 (0.3)
Oedema	1 (0.3)	1 (0.3)
Sudden death	1 (0.3)	1 (0.3)
Infections and infestations	**16 (5.3)**	**18 (5.5)**
Bronchopulmonary aspergillosis	2 (0.7)	2 (0.6)
Pneumonia staphylococcal	2 (0.7)	2 (0.6)
Sepsis	2 (0.7)	3 (0.9)
Septic shock	2 (0.7)	2 (0.6)
Bronchitis	1 (0.3)	1 (0.3)
Enterococcal sepsis	1 (0.3)	1 (0.3)
Escherichia sepsis	1 (0.3)	1 (0.3)
Pneumocystis jirovecii pneumonia	1 (0.3)	1 (0.3)
Pneumonia bacterial	1 (0.3)	1 (0.3)
Pneumonia pseudomonas aeruginosa	1 (0.3)	2 (0.6)
Pneumonia respiratory syncytial viral	1 (0.3)	1 (0.3)
Pseudomonal sepsis	1 (0.3)	2 (0.6)
Urosepsis	1 (0.3)	1 (0.3)
Viral infection	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders	**0**	**1 (0.3)**
Metabolic acidosis	0	1 (0.3)
Nervous system disorders	**3 (1.0)**	**3 (0.9)**
Haemorrhagic stroke	2 (0.7)	2 (0.6)
Mental impairment	1 (0.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**4 (1.3)**	**5 (1.5)**
Respiratory failure	2 (0.7)	3 (0.9)
Apnoea	1 (0.3)	1 (0.3)
Chronic obstructive pulmonary disease	1 (0.3)	1 (0.3)
Lung infiltration	1 (0.3)	1 (0.3)
Vascular disorders	**1 (0.3)**	**1 (0.3)**
Aortic dissection	1 (0.3)	1 (0.3)

Table 83 Summary of TEAEs with outcome of Death (FL)

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=96) n (%)	All Doses Duvelisib (N=107) n (%)
Subjects with Any TEAE Resulting in Death	11 (11.5)	11 (10.3)
Cardiac disorders	**1 (1.0)**	**1 (0.9)**
Cardiac failure congestive	1 (1.0)	1 (0.9)
General disorders and administration site conditions	**7 (7.3)**	**7 (6.5)**
Disease progression	7 (7.3)	7 (6.5)
Infections and infestations	**2 (2.1)**	**2 (1.9)**
Scrotal infection	1 (1.0)	1 (0.9)
Sepsis syndrome	1 (1.0)	1 (0.9)
Skin and subcutaneous tissue disorders	**2 (2.1)**	**2 (1.9)**
Drug reaction with eosinophilia and systemic symptoms	1 (1.0)	1 (0.9)
Toxic epidermal necrolysis	1 (1.0)	1 (0.9)

Abbreviations: BID = twice daily; FL = follicular lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.5.1.1

Serious Adverse Events:

In the randomised study (IPI-145-07) SAEs (PT) were reported in 115 (72.8%) subjects treated with duvelisib and 50 (32.3%) subjects treated with ofatumumab. The previously described AESIs are the most prevalent SAEs in the duvelisib arm: SOC Infections (38.0%), pneumonia (14.6%), colitis (12.0%), diarrhoea (10.1%), and febrile neutropenia (6.3%). In the ofatumumab arm the SOC Infections occurred in 12.9%, and no SAEs (PT) occurred in > 5% of subjects.

There were twice as many SAEs in the duvelisib arm, and this includes the previously described, and from other PI3K inhibitors well-known, AESIs of pneumonia, colitis, diarrhoea, and febrile neutropenia.

In the ISS population for CLL/SLL the frequencies for the SAEs were comparable, and for the FL population Infections were clearly lower than in the CLL/SLL population (20.8% vs 38.0%), which is not unexpected, as CLL patients are considered more immune-incompetent (Riches et al., 2012).

CLL/SLL – pivotal phase 3 study IPI-145-07:

Table 84 Serious TEAEs Occurring in ≥2% Subjects Overall, by SOC and PT – All Causalities and Treatment-Related (All-Treated Analysis Set)

System Organ Class Preferred Term	Duvelisib (N=158) n (%)		Ofatumumab (N=155) n (%)	
	All Causalities	Treatment Related	All Causalities	Treatment Related
Subjects with ≥ 1 TESAE	115 (72.8)	84 (53.2)	50 (32.3)	16 (10.3)
Blood and lymphatic system disorders	**17 (10.8)**	**8 (5.1)**	**7 (4.5)**	**2 (1.3)**
Febrile neutropenia	10 (6.3)	6 (3.8)	3 (1.9)	2 (1.3)
Gastrointestinal disorders	**45 (28.5)**	**37 (23.4)**	**5 (3.2)**	**1 (0.6)**
Colitis	19 (12.0)	18 (11.4)	1 (0.6)	0
Diarrhoea	16 (10.1)	13 (8.2)	1 (0.6)	0
General disorders and administration site conditions	**15 (9.5)**	**5 (3.2)**	**4 (2.6)**	**0**
Pyrexia	7 (4.4)	2 (1.3)	1 (0.6)	0
General physical health deterioration	4 (2.5)	1 (0.6)	0	0
Infections and infestations	**60 (38.0)**	**23 (14.6)**	**20 (12.9)**	**8 (5.2)**
Pneumonia	23 (14.6)	10 (6.3)	5 (3.2)	3 (1.9)
Bronchitis	5 (3.2)	2 (1.3)	1 (0.6)	0
Gastroenteritis	4 (2.5)	0	1 (0.6)	0
Renal and urinary disorders	**7 (4.4)**	1 (0.6)	**2 (1.3)**	**0**
Renal failure acute	4 (2.5)	1 (0.6)	2 (1.3)	0
Respiratory, thoracic and mediastinal disorders	**17 (10.8)**	13 (8.2)	**3 (1.9)**	**0**
Pneumonitis	6 (3.8)	6 (3.8)	0	0
Skin and subcutaneous tissue disorders	**10 (6.3)**	10 (6.3)	**0**	**0**
Toxic skin eruption	4 (2.5)	4 (2.5)	0	0

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated subjects in each treatment group. A treatment-emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence.
Source: Table 14.3.1.11, Table 14.3.1.12

Integrated summary:

Table 85 TESAEs in ≥ 2% of Subjects (CLL/SLL)

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=303) n (%)	All Doses Duvelisib (N=330) n (%)
Subjects with Any Serious TEAE	206 (68.0)	228 (69.1)
Blood and lymphatic system disorders	35 (11.6)	42 (12.7)
Febrile neutropenia	19 (6.3)	24 (7.3)
Pancytopenia	6 (2.0)	6 (1.8)
Gastrointestinal disorders	74 (24.4)	78 (23.6)
Colitis	29 (9.6)	31 (9.4)
Diarrhoea	29 (9.6)	32 (9.7)
General disorders and administration site conditions	31 (10.2)	34 (10.3)
Pyrexia	12 (4.0)	13 (3.9)
Disease progression	6 (2.0)	7 (2.1)
General physical health deterioration	6 (2.0)	6 (1.8)
Infections and infestations	106 (35.0)	118 (35.8)
Pneumonia	40 (13.2)	45 (13.6)
Sepsis	8 (2.6)	9 (2.7)
Bronchitis	7 (2.3)	7 (2.1)
Renal and urinary disorders	13 (4.3)	14 (4.2)
Renal failure acute	8 (2.6)	8 (2.4)
Respiratory, thoracic and mediastinal disorders	29 (9.6)	34 (10.3)
Pneumonitis	8 (2.6)	11 (3.3)

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; TESAE = treatment-emergent serious adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.6.1.2

Table 86 TESAEs in ≥ 2% of Subjects (CLL/FL)

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=96) n (%)	All Doses Duvelisib (N=107) n (%)
Subjects with Any Serious TEAE	56 (58.3)	61 (57.0)
Blood and lymphatic system disorders	**11 (11.5)**	**13 (12.1)**
Febrile neutropenia	6 (6.3)	7 (6.5)
Anaemia	2 (2.1)	3 (2.8)
Thrombocytopenia	2 (2.1)	2 (1.9)
Cardiac disorders	**3 (3.1)**	**3 (2.8)**
Atrial fibrillation	2 (2.1)	2 (1.9)
Gastrointestinal disorders	**18 (18.8)**	**20 (18.7)**
Diarrhoea	9 (9.4)	10 (9.3)
Vomiting	3 (3.1)	3 (2.8)
Abdominal pain	2 (2.1)	3 (2.8)
Colitis	2 (2.1)	2 (1.9)
Nausea	2 (2.1)	3 (2.8)
General disorders and administration site conditions	**15 (15.6)**	**16 (15.0)**
Disease progression	7 (7.3)	7 (6.5)
Pyrexia	4 (4.2)	5 (4.7)
Fatigue	2 (2.1)	2 (1.9)
Infections and infestations	**20 (20.8)**	**22 (20.6)**
Pneumonia	3 (3.1)	3 (2.8)
Bronchopneumonia	2 (2.1)	2 (1.9)
Influenza	2 (2.1)	2 (1.9)
Oral candidiasis	2 (2.1)	2 (1.9)
Sepsis	2 (2.1)	2 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (4.2)**	**4 (3.7)**
Squamous cell carcinoma of skin	2 (2.1)	2 (1.9)
Renal and urinary disorders	**6 (6.3)**	**6 (5.6)**
Renal failure acute	4 (4.2)	4 (3.7)
Renal failure	2 (2.1)	2 (1.9)
Respiratory, thoracic and mediastinal disorders	**7 (7.3)**	**8 (7.5)**
Pneumonitis	4 (4.2)	5 (4.7)
Pleural effusion	2 (2.1)	2 (1.9)
Skin and subcutaneous tissue disorders	**7 (7.3)**	**7 (6.5)**
Rash	2 (2.1)	2 (1.9)
Rash generalised	2 (2.1)	2 (1.9)

Abbreviations: BID = twice daily; FL = follicular lymphoma; TESAE = treatment-emergent serious adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.6.1.1

Laboratory findings

Haematology:

Table 87 Haematology Results, Shift from ≤ Grade 2 at Baseline to Worst Post-Baseline Grade (≥ Grade 3) or Grade 3 at Baseline to Grade 4 Post-Baseline in ≥ 2% of Subjects (All-Treated Analysis Set)

Test (unit)	Treatment	Baseline Grade	New Grade 3/4 on Treatment		
			3 n (%)	4 n (%)	Total n (%)
Hemoglobin (g/L) Decreased	Duvelisib (N=158)	0	4 (2.5)	0	4 (2.5)
		1	7 (4.5)	0	7 (4.5)
		2	20 (12.7)	0	20 (12.7)
		3	--	0	0
		Total	31 (19.7)	0	31/157 (19.7)
	Ofatumumab (N=155)	0	0	0	0
		1	5 (3.2)	0	5 (3.2)
		2	5 (3.2)	0	5 (3.2)
		3	--	0	0
		Total	10 (6.5)	0	10/154 (6.5)
Leukocytes (10^9/L) Decreased	Duvelisib (N=158)	0	6 (3.8)	0	6 (3.8)
		1	4 (2.5)	0	4 (2.5)
		2	0	0	0
		3	--	0	0
		Total	10 (6.4)	0	10/157 (6.4)
	Ofatumumab (N=155)	0	8 (5.2)	2 (1.3)	10 (6.5)
		1	1 (0.6)	1 (0.6)	2 (1.3)
		2	2 (1.3)	0	2 (1.3)
		3	--	0	0
		Total	11 (7.1)	3 (1.9)	14/154 (9.1)
Lymphocytes (10^9/L) Decreased	Duvelisib (N=158)	0	4 (2.6)	2 (1.3)	6 (3.9)
		1	0	0	0
		2	0	0	0
		3	0	2 (1.3)	2 (1.3)
		Total	4 (2.6)	4 (2.6)	8/155 (5.2)
	Ofatumumab (N=155)	0	3 (2.0)	2 (1.3)	5 (3.3)
		1	1 (0.7)	0	1 (0.7)
		2	1 (0.7)	0	1 (0.7)
		3	0	0	0
		Total	5 (3.3)	2 (1.3)	7/153 (4.6)

Test (unit)	Treatment	Baseline Grade	New Grade 3/4 on Treatment		
			3 n (%)	4 n (%)	Total n (%)
Neutrophils (10^9/L) Decreased	Duvelisib (N=158)	0	23 (14.8)	32 (20.6)	55 (35.5)
		1	1 (0.6)	3 (1.9)	4 (2.6)
		2	5 (3.2)	6 (3.9)	11 (7.1)
		3	--	6 (3.9)	6 (3.9)
		Total	29 (18.7)	47 (30.3)	76/155 (49.0)
	Ofatumumab (N=155)	0	23 (15.1)	19 (12.5)	42 (27.6)
		1	2 (1.3)	4 (2.6)	6 (3.9)
		2	3 (2.0)	1 (0.7)	4 (2.6)
		3	--	3 (2.0)	3 (2.0)
		Total	28 (18.4)	27 (17.8)	55/152 (36.2)
Platelets (10^9/L) Decreased	Duvelisib (N=158)	0	3 (1.9)	2 (1.3)	5 (3.2)
		1	9 (5.7)	3 (1.9)	12 (7.6)
		2	3 (1.9)	3 (1.9)	6 (3.8)
		3	--	2 (1.3)	2 (1.3)
		Total	15 (9.6)	10 (6.4)	25/157 (15.9)
	Ofatumumab (N=155)	0	2 (1.3)	1 (0.6)	3 (1.9)
		1	2 (1.3)	0	2 (1.3)
		2	5 (3.2)	0	5 (3.2)
		3	--	3 (1.9)	3 (1.9)
		Total	9 (5.8)	4 (2.6)	13/154 (8.4)

Note: Percentages are based on the number of all-treated subjects in each treatment group with non-missing values for that test at Baseline and post- Baseline. A severity grade of 4 is not applicable for hemoglobin decreased.
Source: Table 14.3.4.1

Neutropenia

Table OC152-5: Frequencies of AESI of Neutropenia for CLL/SLL and FL: 25 mg BID Duvelisib

	ISS Data			Study IPI-145-07				
	All Heme (N=442) n (%)	FL (N=96) n (%)	CLL/SLL (N=303) n (%)	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)	Duvelisib N (N/P-Y)	Ofatumumab N (N/P-Y)	Duvelisib/Ofatumumab Rate Ratio
AESI-Neutropenia	**151 (34.2)**	**27 (28.1)**	**108 (35.6)**	**53 (33.5)**	**35 (22.6)**	**53 (0.412)**	**35 (0.725)**	**0.57**
Neutropenia	131 (29.6)	24 (25.0)	95 (31.4)	52 (32.9)	32 (20.6)	52 (0.402)	32 (0.655)	0.61
Neutrophil count decreased	23 (5.2)	3 (3.1)	16 (5.3)	2 (1.3)	3 (1.9)	2 (0.012)	3 (0.054)	0.22

Source: ISS Table 2.2.1, Table 2.2.1.1 and Table 2.2.1.2; Table 14.3.1.2_tpy_si_d120 (data on file)
Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; ISS = integrated safety summary; N/PY = number of subjects per patient-year; SLL = small lymphocytic lymphoma.

Table 88 Overview of Subjects with TEAEs of AESI Neutropenia and Individual Grouped PTs, Safety Analysis Set, All Subgroups (25 mg BID)

Subjects with:	All Heme 25 mg BID (N=442) n (%)	CLL/SLL 25 mg BID (N=303) n (%)	FL 25 mg BID (N=96) n (%)
AESI-Neutropenia	151 (34.2)	108 (35.6)	27 (28.1)
Neutropenia	131 (29.6)	95 (31.4)	24 (25.0)
Neutrophil count decreased	23 (5.2)	16 (5.3)	3 (3.1)
≥ Grade 3 AESI-Neutropenia	132 (29.9)	97 (32.0)	23 (24.0)
Serious AESI-Neutropenia	3 (0.7)	3 (1.0)	0
AESI-Neutropenia Leading to a Hold or Reduction of Dose			
Dose hold	40 (9.0)	30 (9.9)	7 (7.3)
Dose reduction	13 (2.9)	9 (3.0)	2 (2.1)
AESI-Neutropenia Leading to Treatment Discontinuation	3 (0.7)	2 (0.7)	1 (1.0)
AESI-Neutropenia Resulting in Death	0	0	0
Treatment-Related AESI-Neutropenia Resulting in Death [a]	0	0	0

Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = haematologic malignancies; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Only TEAEs of this category of Adverse Events of Special Interest that were reported are included in this table.

Adverse Events are graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher.

a. Includes Definitely, Possibly, Probably, unknown, or missing relationship.

Source: ISS Table 2.21.4, ISS Table 2.21.4.2, ISS Table 2.21.4.1, ISS Table 2.22.4, ISS Table 2.22.4.2, ISS Table 2.22.4.1

Clinical Chemistry

In the integrated summary in subjects receiving duvelisib 25 mg BID, lipase increased was the most frequently reported shift from Baseline to a post-Baseline ≥ Grade 3 (All Heme 16.0%; CLL/SLL 13.3%; FL 23.6%). Among subjects in the All Heme group with new ≥ Grade 3 lipase increased (n=55), only 2 subjects experienced a TEAE of pancreatitis (1 Grade 2, non-serious, and 1 Grade 3, SAE). In the randomised study lipase increased was not listed in the corresponding "shift" table. Increased lipase was seen more frequently in the duvelisib compared to the ofatumumab arm: 5.1% vs 1.9% (All causes), 2.5% vs 0.6% (≥ Grade 3), respectively, and 1 SAE of lipase increased, and 1 SAE of pancreatitis, Grade 3, in the duvelisib arm.

In the integrated summary in the All Heme 25 mg BID Group, new maximum shifts to post-Baseline Grade ≥ 3 values in 5% of subjects included ALT increased (7.7%) (7.0% in the duvelisib arm in study 145-07 and 0 in the ofatumumab arm), hyponatraemia (6.7%) (7.1% in the duvelisib arm in study 145-07 and 3.3% in the ofatumumab arm), hypokalaemia (6.9%) (8.3% in the duvelisib arm in study 145-07 and 0 in the ofatumumab arm), AST increased (5.5%) (3.2% in the duvelisib arm in study 145-07 and 1.3% in the ofatumumab arm), and hypophosphataemia (5.4%) (3.2% in the duvelisib arm in study 145-07 and 3.4% in the ofatumumab arm): New maximum shifts in clinical chemistry values to post-Baseline Grade ≥ 3 values

were similar across All Heme, CLL/SLL, and FL groups and the duvelisib arm in study 145-07 and clearly larger than in the ofatumumab for all but hypophosphatemia.

Transaminase Elevation

Table OC152-4: Frequencies of AESI of Transaminase Elevations for CLL/SLL and FL: 25 mg BID Duvelisib

	ISS Data			Study IPI-145-07				
	All Heme (N=442) N (%)	**FL (N=96) N (%)**	**CLL/SLL (N=303) N (%)**	**Duvelisib (N=158) N (%)**	**Ofatumumab (N=155) N (%)**	**Duvelisib N (N/P-Y)**	**Ofatumumab N (N/P-Y)**	**Duvelisib/Ofatumumab Rate Ratio**
AESI-Transaminase Elevation	**67 (15.1)**	**20 (20.8)**	**38 (12.5)**	**18 (11.4)**	**6 (3.9)**	**18 (0.114)**	**6 (0.109)**	**1.04**
Alanine amino transferase increased	53 (12.0)	17 (17.7)	28 (9.2)	12 (7.6)	3 (1.9)	12 (0.073)	3 (0.054)	1.35
Aspartate amino-transferase increased	49 (11.1)	15 (15.6)	28 (9.2)	14 (8.9)	3 (1.9)	14 (0.086)	3 (0.054)	1.59
Transaminases increased	7 (1.6)	0	7 (2.3)	4 (2.5)	0	4 (0.024)	0	-
Hepatotoxicity	3 (0.7)	3 (3.1)	0	0	0	0	0	-
Hepatocellular injury	1 (0.2)	0	1 (0.3)	1 (0.6)	0	1 (0.006)	0	-
Hyper transaminasaemia	1 (0.2)	0	0	0	0	0	0	-
Hepatic failure	0	0	0	0	1 (0.6)	0	1 (0.018)	0.0

Source: ISS source: ISS Table 2.2.1, Table 2.2.1.1 and Table 2.2.1.2; Table 14.3.1.2_tpy_si_d120 (data on file)
Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; ISS = integrated safety summary; N/P-Y = number of subjects per patient-year; SLL = small lymphocytic lymphoma.

Table 89 Overview of Subjects with TEAEs of AESI Transaminase Elevation and Individual Grouped PTs, Safety Analysis Set, All Subgroups (25 mg BID)

Subjects with:	All Heme 25 mg BID (N=442) n (%)	CLL/SLL 25 mg BID (N=303) n (%)	FL 25 mg BID (N=96) n (%)
AESI-Transaminase Elevation	67 (15.1)	38 (12.5)	20 (20.8)
Alanine aminotransferase increased	53 (12.0)	28 (9.2)	17 (17.7)
Aspartate aminotransferase increased	49 (11.1)	28 (9.2)	15 (15.6)
Transaminases increased	7 (1.6)	7 (2.3)	0
Hepatotoxicity	3 (0.7)	0	3 (3.1)
Hepatocellular injury	1 (0.2)	1 (0.3)	0
Hypertransaminasaemia	1 (0.2)	0	0
≥ Grade 3 AESI-Transaminase Elevation	34 (7.7)	18 (5.9)	11 (11.5)
Serious AESI-Transaminase Elevation	4 (0.9)	2 (0.7)	0
AESI-Transaminase Elevation Leading to a Hold or Reduction of Dose			
Dose hold	31 (7.0)	17 (5.6)	11 (11.5)
Dose reduction	18 (4.1)	10 (3.3)	7 (7.3)
AESI-Transaminase Elevation Leading to Treatment Discontinuation	6 (1.4)	3 (1.0)	2 (2.1)
AESI-Transaminase Elevation Resulting in Death	0	0	0

Abbreviations: AESI = adverse event of special interest; BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = haematologic malignancies; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Only TEAEs of this category of Adverse Events of Special Interest that were reported by subjects are included in this table.

Adverse Events are graded according to NCI-CTCAE version 4.03; missing grades are reported as Grade 3 or higher.

a. Includes Definitely, Possibly, Probably, unknown, or missing relationship.

Source: ISS Table 2.21.8, ISS Table 2.21.8.1, ISS Table 2.21.8.2, ISS Table 2.22.8, ISS Table 2.22.8.1, ISS Table 2.22.8.2, MAA Safety TLFs Table 2.1, MAA Safety TLFs Table 2.1.2, MAA Safety TLFs 2.1.1

Table 90 shows the median time to onset and the median duration of the TEAESI.

Table 90 Time and duration of treatment-emergent AEs of Special Interest Duvelisib (All Heme 25 mg BID group)

AESI	All Heme 25 mg BID (N=442) n (%)	≥Grade 3 n (%)	Median time to onset (days)	Median duration (days)
Diarrhoea-Colitis	222 (50.2)	101 (22.9)	123	15

Infection (including pneumonia)	276 (62.4)	119 (26.9)	85	16
Neutropenia	151 (34.2)	132 (29.9)	49	23
Non-Infectious Pneumonitis (Pneumonitis)	30 (6.8)	16 (3.6)	130	32.5
Severe cutaneous reaction (Rash)	136 (31.2)	41 (9.3)	88.5	27
Transaminase elevation	67 (15.1)	34 (7.7)	57	15

Safety in special populations

Age

No clinically meaningful differences in the incidence of TEAEs or TESAEs by age and age group in the All Heme, CLL/SLL, and FL groups can be seen.

Gender

In general, TEAEs appeared to be well balanced between gender on both treatment arms. There were gender differences but as numbers are small and the ISS by gender identified no clinically meaningful differences in the incidence of TEAEs or TESAEs in the All Heme, CLL/SLL, and FL groups, no meaningful conclusions can be drawn.

Immunological events

Not Applicable

Safety related to drug-drug interactions and other interactions

The drug-drug interaction (DDI) potential of duvelisib was evaluated *in vitro* in liver fractions and in 3 clinical studies in healthy subjects (IPI-145-01, IPI-145-10, and IPI-145-11). In these studies, duvelisib exposures were significantly affected by a strong inhibitor and inducer of CYP3A. An additional DDI study of Repeated Dosing of Etravirine on the Pharmacokinetics, Safety, and Tolerability of a Single-dose of Duvelisib in Healthy Subjects (VS-0145-131) was conducted in 2019 (see the pharmacology section for additional details).

Discontinuation due to AEs

In the pivotal phase 3 study in CLL 57 patients (36.1%) in the duvelisib arm and 9 patients (5.8%) in the ofatumumab arm discontinued treatment due to an adverse event according to Table 28/CSR-07 (In section Adverse events), which is quite a large difference reflecting the toxicity of duvelisib. From a clinical point of view, it is highly likely that many of the patients that chose to discontinue [13 (8.2%) in the duvelisib arm

and 7 (4.5%) in the ofatumumab arm] may have done so due to intolerable side effects, particularly for the duvelisib arm, since the treatment is administered at home and not at the hospital, as is the case for ofatumumab, which for the latter may lead to particularly elderly patients opting out of the treatment due to inconvenience rather than adverse events. Death as the reason for discontinuation occurred more frequently in the duvelisib arm [12 (8.2%)] compared to the ofatumumab arm [7 (4.5%)].

CLL/SLL – pivotal phase 3 study IPI-145-07:

Table 91 All TEAEs Resulting in Study Treatment Discontinuation, by SOC and PT- All Causalities (All-Treated Analysis Set)

System Organ Class Preferred Term	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
Subjects with ≥ 1 TEAE Resulting in Treatment Discontinuation	57 (36.1)	9 (5.8)
Blood and lymphatic system disorders	**4 (2.5)**	**1 (0.6)**
Neutropenia	2 (1.3)	0
Febrile neutropenia	1 (0.6)	0
Idiopathic thrombocytopenic purpura	1 (0.6)	0
Haemolytic anaemia	0	1 (0.6)
Gastrointestinal disorders	**17 (10.8)**	**0**
Colitis	8 (5.1)	0
Diarrhoea	8 (5.1)	0
Gastritis	1 (0.6)	0
General disorders and administration site conditions	**3 (1.9)**	**1 (0.6)**
Fatigue	1 (0.6)	0
General physical health deterioration	1 (0.6)	0
Oedema peripheral	1 (0.6)	0
Disease progression	0	1 (0.6)
Hepatobiliary disorders	**0**	**1 (0.6)**
Hepatic failure	0	1 (0.6)
Immune system disorders	**0**	**1 (0.6)**
Drug hypersensitivity	0	1 (0.6)
Infections and infestations	**11 (7.0)**	**0**
Pneumonia	2 (1.3)	0
Pneumonia staphylococcal	2 (1.3)	0
Aspergillus infection	1 (0.6)	0
Bronchitis	1 (0.6)	0
Bronchopulmonary aspergillosis	1 (0.6)	0
Enterococcal sepsis	1 (0.6)	0
Escherichia sepsis	1 (0.6)	0
Pneumonia pseudomonas aeruginosa	1 (0.6)	0
Pseudomonal sepsis	1 (0.6)	0
Pseudomonas bronchitis	1 (0.6)	0
Sepsis	1 (0.6)	0
Injury, poisoning and procedural complications	**0**	**2 (1.3)**
Fall	0	1 (0.6)
Infusion related reaction	0	1 (0.6)
Investigations	**1 (0.6)**	**0**
Transaminases increased	1 (0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (1.3)**	**2 (1.3)**
Intestinal adenocarcinoma	1 (0.6)	0
Ovarian cancer	1 (0.6)	0
Glioblastoma multiforme	0	1 (0.6)
Squamous cell carcinoma	0	1 (0.6)
Nervous system disorders	**4 (2.5)**	**0**
Ageusia	1 (0.6)	0
Dementia	1 (0.6)	0

System Organ Class Preferred Term	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
Haemorrhagic stroke	1 (0.6)	0
Mental impairment	1 (0.6)	0
Renal and urinary disorders	**0**	**1 (0.6)**
Renal failure acute	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**7 (4.4)**	**0**
Pneumonitis	3 (1.9)	0
Interstitial lung disease	2 (1.3)	0
Lung disorder	1 (0.6)	0
Respiratory failure	1 (0.6)	0
Skin and subcutaneous tissue disorders	**8 (5.1)**	**0**
Toxic skin eruption	2 (1.3)	0
Dermatitis	1 (0.6)	0
Dermatitis exfoliative	1 (0.6)	0
Dermatitis exfoliative generalised	1 (0.6)	0
Rash	1 (0.6)	0
Rash maculo-papular	1 (0.6)	0
Rash papular	1 (0.6)	0

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated subjects in each treatment group. A treatment-emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence.
Source: Table 14.3.1.20.

Table 92 TEAEs resulting in dose hold or reduction by SOC (≥10%) and PT (≥ 5%)- all causalities (all treated analysis set)

System Organ Class Preferred Term	Dose Hold or Dose Reduction	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
Subjects with ≥ 1 TEAE Resulting in Dose Hold or Dose Reduction	Hold	123 (77.8)	15 (9.7)
	Reduction	46 (29.1)	2 (1.3)
	Hold or Reduction	*125 (79.1)*	*16 (10.3)*
Blood and lymphatic system disorders	Hold	29 (18.4)	3 (1.9)
	Reduction	8 (5.1)	0
	Hold or Reduction	*30 (19.0)*	*3 (1.9)*
Febrile neutropenia	Hold	8 (5.1)	1 (0.6)
	Reduction	2 (1.3)	0
	Hold or Reduction	*8 (5.1)*	*1 (0.6)*
Neutropenia	Hold	19 (12.0)	2 (1.3)
	Reduction	6 (3.8)	0
	Hold or Reduction	*21 (13.3)*	*2 (1.3)*
Gastrointestinal disorders	Hold	52 (32.9)	1 (0.6)
	Reduction	14 (8.9)	0
	Hold or Reduction	*53 (33.5)*	*1 (0.6)*
Colitis	Hold	17 (10.8)	0
	Reduction	4 (2.5)	0
	Hold or Reduction	*17 (10.8)*	*0*
Diarrhoea	Hold	36 (22.8)	0
	Reduction	11 (7.0)	0
	Hold or Reduction	*37 (23.4)*	*0*
General disorders and administration site conditions	Hold	23 (14.6)	0
	Reduction	3 (1.9)	0
	Hold or Reduction	*24 (15.2)*	*0*
Pyrexia	Hold	12 (7.6)	0
	Reduction	1 (0.6)	0
	Hold or Reduction	*12 (7.6)*	*0*
Infections and infestations	Hold	43 (27.2)	10 (6.5)
	Reduction	4 (2.5)	0
	Hold or Reduction	*43 (27.2)*	*10 (6.5)*
Pneumonia	Hold	17 (10.8)	3 (1.9)
	Reduction	1 (0.6)	0
	Hold or Reduction	*17 (10.8)*	*3 (1.9)*
Investigations	Hold	17 (10.8)	2 (1.3)
	Reduction	9 (5.7)	0

System Organ Class Preferred Term	Dose Hold or Dose Reduction	Duvelisib (N=158) n (%)	Ofatumumab (N=155) n (%)
	Hold or Reduction	***17 (10.8)***	***2 (1.3)***
Respiratory, thoracic and mediastinal disorders	**Hold**	**15 (9.5)**	**0**
	Reduction	**4 (2.5)**	**0**
	Hold or Reduction	***16 (10.1)***	***0***
Skin and subcutaneous tissue disorders	**Hold**	**20 (12.7)**	**0**
	Reduction	**8 (5.1)**	**0**
	Hold or Reduction	***21 (13.3)***	***0***

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted only once within each Dose Hold or Dose Reduction category within each system organ class and within each preferred term. Percentages are based on the number of all-treated subjects in each treatment group. A treatment-emergent AE (TEAE) is defined as an AE that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the AE was used to determine treatment emergence. Dose held for ofatumumab and dose interruption for duvelisib was classified as dose hold.
Source: Table 14.3.1.17

The most frequently reported (> 2%) TEAEs leading to duvelisib discontinuation in the All Heme 25 mg BID Group were colitis (4.8%), diarrhoea (4.5%), and pneumonitis (2.3%). Gastrointestinal disorders was the SOC with the greatest number of subjects reporting at least 1 TEAE leading to treatment discontinuation.

Table 93 TEAEs Leading to Treatment Discontinuation in ≥ 2 Subjects (All Heme)

System Organ Class/ Preferred Term	25 mg BID Duvelisib (N=442) n (%)	All Doses Duvelisib (N=586) n (%)
Subjects with Any TEAE Resulting in Discontinuation of Study Drug	156 (35.3)	210 (35.8)
Blood and lymphatic system disorders	**8 (1.8)**	**10 (1.7)**
Neutropenia	3 (0.7)	4 (0.7)
Gastrointestinal disorders	**47 (10.6)**	**58 (9.9)**
Colitis	21 (4.8)	24 (4.1)
Diarrhoea	20 (4.5)	25 (4.3)
Stomatitis	3 (0.7)	4 (0.7)
Enterocolitis	2 (0.5)	2 (0.3)
General disorders and administration site conditions	**9 (2.0)**	**20 (3.4)**
Disease progression	5 (1.1)	16 (2.7)
Infections and infestations	**24 (5.4)**	**34 (5.8)**
Pneumonia	6 (1.4)	9 (1.5)
Pneumocystis jirovecii pneumonia	2 (0.5)	3 (0.5)
Pneumonia staphylococcal	2 (0.5)	2 (0.3)
Escherichia sepsis	1 (0.2)	2 (0.3)
Pseudomonal sepsis	1 (0.2)	2 (0.3)
Investigations	**10 (2.3)**	**22 (3.8)**
Alanine aminotransferase increased	4 (0.9)	14 (2.4)
Aspartate aminotransferase increased	3 (0.7)	5 (0.9)
Lipase increased	2 (0.5)	2 (0.3)
Transaminases increased	2 (0.5)	2 (0.3)
Musculoskeletal and connective tissue disorders	**4 (0.9)**	**6 (1.0)**
Polyarthritis	1 (0.2)	2 (0.3)
Renal and urinary disorders	**3 (0.7)**	**3 (0.5)**
Renal failure acute	2 (0.5)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	**19 (4.3)**	**23 (3.9)**
Pneumonitis	10 (2.3)	12 (2.0)
Interstitial lung disease	4 (0.9)	4 (0.7)
Respiratory failure	2 (0.5)	2 (0.3)
Skin and subcutaneous tissue disorders	**21 (4.8)**	**24 (4.1)**
Rash	4 (0.9)	4 (0.7)
Toxic skin eruption	3 (0.7)	3 (0.5)
Rash generalised	2 (0.5)	3 (0.5)
Rash maculo-papular	2 (0.5)	3 (0.5)
Rash erythematous	1 (0.2)	2 (0.3)

Abbreviations: BID = twice daily; Heme = haematologic malignancies; TEAE = treatment-emergent adverse event.

Note: Adverse Events are coded using MedDRA version 16.1. Subjects are counted once within each System Organ Class and Preferred Term. Percentages are based on the number of subjects in each analysis group for the Safety Analysis Set. System Organ Classes are sorted alphabetically, and Preferred Terms are sorted in decreasing frequency of the Duvelisib 25 mg BID analysis group.

Source: ISS Table 2.3.1

Safety in special populations

Table 94 AEs by Age Group in Elderly Populations (among subjects treated with duvelisib 25 mg BID enrolled in studies IPI-145-02, IPI-145-06, IPI-145-07, IPI-145-12)

MedDRA Terms	Age <65 number (percentage) N=172	Age 65-74 number (percentage) N=166	Age 75-84 number (percentage) N=96	Age 85+ number (percentage) N=8
Total AEs Total Subjects with AEs	2746 171 (99.4)	2625 166 (100)	1672 97 (100)	108 8 (100)
Serious AEs – Total Total Subjects with Serious AEs	250 109 (63.4)	273 116 (69.9)	188 77 (79.4)	11 7 (87.5)
- Fatal[a]	21 (12.2)	18 (10.8)	15 (15.5)	3 (37.5)
- Hospitalisation/prolong existing hospitalisation [b]	88 (51.2)	100 (60.2)	61 (62.9)	5 (62.5)
- Life-threatening [b]	13 (7.6)	8 (4.8)	7 (7.2)	0
- Disability/incapacity [b]	3 (1.7)	0	1 (1.0)	2 (25.0)
- Other (medically significant) [b]	18 (10.5)	20 (12.0)	11 (11.3)	2 (25.0)
AE leading to drop-out	63 (36.6)	70 (42.2)	47 (48.5)	2 (25.0)
Psychiatric disorders [c]	21 (12.2)	19 (11.4)	14 (14.4)	2 (25.0)
Nervous system disorders [c]	48 (27.9)	63 (38.0)	29 (29.9)	3 (37.5)
Accidents and injuries [c]	0	0	0	0
Cardiac disorders [c]	12 (7.0)	22 (13.3)	23 (23.7)	3 (37.5)
Vascular disorders [c]	21 (12.2)	36 (21.7)	22 (22.7)	1 (12.5)
Cerebrovascular disorders [d]	3 (1.7)	5 (3.0)	3 (3.1)	0
Infections and infestations [c]	113 (65.7)	107 (64.5)	66 (68.0)	6 (75.0)
Anticholinergic syndrome [e]	0	0	0	0
Quality of life decreased [e]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [f,g]	13 (7.6)	24 (14.5)	21 (21.6)	2 (25.0)
Other AEs appearing more frequently in older patients (as analysed in Module 2.7.4)				
Hyperglycaemic disorders [1]	7 (4.1)	13 (7.8)	6 (6.2)	1 (12.5)
Hypertension [2]	9 (5.2)	9 (5.4)	6 (6.2)	1 (12.5)
Bleeding events [3]	25 (14.5)	26 (15.7)	27 (27.8)	1 (12.5)
Cardiac arrhythmias [4]	7 (4.1)	13 (7.8)	11 (11.3)	2 (25.0)

Data cut-off: 20 July 2020

Note: All summaries are based on treatment-emergent adverse events.

[a]: AEs with outcome of death during the study period.

[b]: Subcategories of seriousness not collected in study IPI-145-02.

[c]: Determined by MedDRA System Organ Class (SOC)

[d]: Determined by MedDRA Higher Level Terms (HLTs) of: Central nervous system vascular disorder, Central nervous system aneurysms, Central nervous system haemorrhages and cerebrovascular accidents, Central nervous system vascular disorders NEC, Cerebrovascular venous and sinus thrombosis, Transient cerebrovascular events, Traumatic central nervous system haemorrhages

[e]: MedDRA Preferred Term

[f]: Postural hypotensions includes MedDRA Preferred Term of Orthostatic hypotension. Fracture includes MedDRA Preferred Terms of Ankle fracture, Cervical vertebral fracture, Facial bones fracture, Femur fracture, Pathological fracture, Pelvic fracture, Rib fracture, Spinal compression fracture, Spinal fracture, Sternal fracture, Thoracic vertebral fracture, Traumatic fracture, Upper limb fracture, Wrist fracture. Fall, Ataxia, Syncope and Black outs are based on MedDRA

Preferred Terms.
[g] Total subjects with at least one event
[1]: Based on search of MedDRA preferred terms: Diabetic retinopathy, Blood glucose increased, Diabetes mellitus, Hyperglycaemia, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Impaired fasting glucose, Glucose tolerance impaired, Diabetic hyperosmolar coma, Diabetic neuropathy, Diabetic nephropathy, Diabetic foot, Diabetic complication.
[2]: Based on search of MedDRA preferred terms: Hypertensive Cardiomyopathy, Hypertensive heart disease, Essential hypertension, Hypertension
[3: Based on MedDRA Standardised MedDRA Query (SMQ) for Haemorrhage terms (excl laboratory terms)
[4]: Based on search of MedDRA preferred terms: Arrhythmia, Arrhythmia supraventricular, Atrial fibrillation, Atrial flutter, Bradyarrhythmia, Bradycardia, Sinus bradycardia, Atrial tachycardia, Paroxysmal arrhythmia, Sinus arrhythmia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Ventricular tachycardia, Cardiac flutter, Extrasystoles, Heart rate irregular.

Post marketing experience

Duvelisib was authorised for the marketing in the USA on 24 September 2018 under the brand name Copiktra for the treatment of adult patients with: Relapsed or refractory CLL or SLL after at least 2 prior therapies, and Relapsed or refractory FL after at least 2 prior systemic therapies.

Overall, approximately 1254 subjects have been exposed to duvelisib as monotherapy or in combination with another agent; the patient exposure to duvelisib during the current reporting interval from 24 Sep 2018 to 23 March 2019 is estimated at approximately 23.5 patient-years. There were no new risks identified during the reporting period.

2.6.1. Discussion on clinical safety

The total safety database of subjects with hematologic malignancies exposed to duvelisib compromised 586 patients of which 442 received duvelisib 25 mg BID (All Heme). The cut-off for the integrated summary of safety, also named Study VS-0145-328, was 19 July 2017. This study was an obligation to the FDA, who also required update of this study after an additional 2 years on treatment with a final report submission date of 11/2020. The cut-off date was 19 July 2020. The results are discussed below.

While the pooled safety databases are valuable to obtain a general safety profile of duvelisib, safety data with the IPI-145-07 study in CLL is considered most important since the included control arm allows to put safety data in context. Safety comparison in the FL population is hampered by the single arm trial design.

A discrepancy in effect between subjects with 1 prior treatment compared to subjects >2 prior therapies in study IPI-145-07 has been observed. A higher incidence of toxicity is expected after several treatment lines, but this could not be confirmed for either CLL or FL although the limited number of FL patients with 1 prior therapy hampers thorough assessment.

The number of patients exposed for a minimum of one-year is considered to be acceptable for the safety database. However, the number of patients treated for 6 months at dose level intended for clinical use, is limited to 269 patients of whom 106 patients needed a dose reduction. The relatively limited extent of population exposure at the 25 mg BID dose level impairs the detection of uncommon and (very) rare adverse events. There was a substantial difference between median exposure among the CLL and FL population (i.e. 45 weeks vs. 24 weeks). This is explained by the high proportion of PD and shorter time to discontinuation due to PD in the FL group.

The treatment landscape has changed over time as discussed in the efficacy section. The pivotal studies were performed in a study population, which does not exist anymore. Patients previously treated with PI3 kinase

inhibitors or BTK inhibitors (e.g. idelalisib and ibrutinib) were excluded from the pivotal studies. The safety of duvelisib in the current treatment landscape is therefore unknown, which is reflected in the SmPC (section 4.4).

In study IPI-145-07, the incidence of various AEs by SOC and/or PT in the duvelisib arm (N=158) were generally higher than in the ofatumumab arm (N=155), which was also the case for SAEs. Overall, the AEs in the pooled FL population (N=93), the pooled CLL/SLL (N=303), and the All Heme 25 mg BID population (N=442) are of the same order as in the RCT.

The primary safety issues identified with duvelisib include serious, including fatal, infections, diarrhoea or colitis, cutaneous reactions, and pneumonitis, along with serious hepatotoxicity and neutropenia all of which are well-known adverse events of special interest (AESIs) for the PI3K inhibitor idelalisib, which is approved for FL and CLL.

There was a considerably higher incidence of *diarrhoea-colitis, infectious*, *neutropenia, and rash* adverse events in the duvelisib arm compared to the ofatumumab arm even after exposure time is taken into account. Both Grade 3+ events and SAEs for this AESI were more frequent with duvelisib than with ofatumumab. Diarrhoea-colitis is considered an important identified risk of duvelisib.

In the duvelisib arm in the RCT *Pneumonitis/Interstitial lung disease* adverse events were recorded for approximately 8-9% (13-14 patients) of which 5% were SAEs and 4.4% led to discontinuation as opposed to 0% (all AEs) in the ofatumumab arm.

The incidence of the AESI-Transaminase elevation is clearly higher in the duvelisib arm compared to the ofatumumab arm in the RCT: 18 (11.4%) and 6 (3.9%), respectively, and even higher in the All FL 25 mg BID group 20/96 (20.8%). In the randomised study fatal TEAEs were reported for 19/158 (12.0%) in the duvelisib arm and 5/155 (3.2%) in the ofatumumab arm. Given the higher rate of deaths in the duvelisib arm compared to the ofatumumab arm and the overall safety profile the indication in CLL and FL has been amended to include patients after at least two prior therapies.

Inclusion of pancreatitis in the Summary of safety concerns in the RMP as an 'Important identified or potential risk' has been agreed.

Photosafety measurements have been incorporated based on preclinical findings of duvelisib via several amendments across the clinical studies. However, based on the nonclinical safety margin and clinical information, it is agreed that additional risk management activities for photosensitivity are not required and inclusion of photosensitivity in the SmPC was not needed.

In the RCT in CLL 57 patients (36.1%) in the duvelisib arm and 9 patients (5.8%) in the ofatumumab arm discontinued treatment due to an adverse event, which is quite a large difference reflecting the toxicity of duvelisib.

Looking at the AESI transaminase elevation this is clearly more prevalent in the duvelisib arm compared to the ofatumumab arm:18 (11.4%) and 6 (3.9%), respectively. In the duvelisib arm one increased transaminase AE was considered an SAE and one led to discontinuation. No subjects on study met the criteria for Hy's Law. In the CLL/SLL group in the integrated summary the incidence of the AESI-Transaminase elevation was comparable to the CLL arm in study IPI-145-07 (12.8% vs 11.4%) whereas in the All FL 25 mg BID group the incidence was higher; 20.8%. There was one event of Hepatic failure in the All CLL/SLL 25 mg BID group.

The data presented from the initial application are as of the cut-off of 19 July 2017. The applicant has updated Study VS-0145-328 (consisting of safety from studies IPI-145-02, IPI-145-06, IPI-145-07 and IPI-145-12 corresponding to the ISS) with a cut-off on July 19, 2020. Since the 19 July 2017 data cut-off, only 1 additional subject received duvelisib; this is a subject in the CLL/SLL 25 mg BID Group who was randomised to ofatumumab in Study IPI-145-07 and subsequently crossed over to Study IPI-145-12 to receive duvelisib. A total of 443 subjects included in the integrated safety dataset received at least 1 dose of duvelisib 25 mg (of which 304/443 [68.6%] subjects are in the CLL/SLL Group and 96/443 [21.7%] subjects are in the FL Group). These 443 subjects had a total of 498.0 patient-years of exposure as opposed to 479 patient-years in the ISS at the time of the application. Data from the final updated ISS (Study VS-0145-328) have been evaluated for the various adverse event subtypes.

With the 3-year updated ISS data (Study VS-0145-328) the All Heme 25 mg BID Group (N = 443), had a median duration of exposure of 40.00 weeks (range: 0.3 to 311.0 weeks) as opposed to 39 weeks at the time of the application. A total of 277 patients (62.5%) were treated for ≥ 6 months, 170 (38.4%) were treated for ≥ 1 year (160 at the time of the application), 109 (24.6%) were treated for ≥ 1.5 years, and importantly for the evaluation of long-term safety 72 patients (16.3%) were treated for ≥ 2 years, of which 54 were CLL patients and 7 were FL patients.

The updated safety data from Study VS-0145-328 (443 received duvelisib 25 mg BID in the All Heme group) did not reveal any meaningful changes or new AEs. A slight increase in all AEs (All, ≥Grade 3, SAEs, Deaths, AESIs), as would be expected with time, was seen. It is agreed that there were no clinically meaningful changes between the cumulative 2017 and 2020 data and no new adverse events were found.

In the post marketing setting following US approval overall, approximately 1254 subjects have been exposed to duvelisib as monotherapy or in combination with another agent; the patient exposure to duvelisib during the current reporting interval from 24 Sep 2018 to 23 Mar 2019 is estimated at approximately 23.5 patient-years. There were no new risks identified during the reporting period. In addition, there was no significant change in the frequency or severity of AEs characterised as important identified risks and important potential risks. Based on the data obtained through the end of the review period, no new safety relevant information was identified regarding the safety concerns and the safety profile of duvelisib.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The most frequent clinically important adverse reactions related to the use of the duvelisib are infections, diarrhoea/colitis, neutropenia, rash, transaminase increased, and pneumonitis.

Duvelisib has a safety profile with a high frequency of adverse events including AESIs, SAEs, deaths, and discontinuations in the duvelisib arm compared to the ofatumumab arm.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Serious infections Serious diarrhoea/colitis Severe cutaneous reactions Pneumonitis
Important potential risks	Hepatotoxicity Embryo-foetal toxicity Drug-drug interaction with CYP3A substrates
Missing information	Safety in patients with severe hepatic impairment Long term safety follow-up

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	Risk minimisation measures
Important Identified Risks	
Serious infections	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* *Advice regarding dose modifications in included in section 4.2. Advice regarding counselling, monitoring and prophylactic treatment is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Serious diarrhoea/colitis	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* Advice regarding dose modifications in *included in section 4.2. Advice on how to counsel patients is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Severe cutaneous reactions	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* *Advice regarding dose modifications in included in section 4.2. Advice on how to counsel patients is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Pneumonitis	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* Advice regarding dose modifications in included in section 4.2. *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Important Potential Risks	

Safety concern	Risk minimisation measures
Hepatotoxicity	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* *Advice regarding dose modifications in included in section 4.2. Monitoring of hepatic function during treatment with COPIKTRA is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Embryo-foetal toxicity	**Routine risk minimisation measures**: *SmPC section 4.4, 4.6* *PL section 2* *Advice regarding the use of contraception in included in section 4.4 and advice that it is preferable to avoid the use of COPIKTRA during pregnancy is included in section 4.6.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Drug-drug interaction with CYP3A substrates	**Routine risk communication**: *SmPC section 4.4, 4.5, 5.2* *PL section 2* *Advice regarding the need to avoid co-administration of midazolam with COPIKTRA and the need to avoid concomitant treatment of duvelisib with sensitive CYP3A substrates and use of alternative medicinal products that are less sensitive to CYP3A4 inhibition is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Missing Information	
Safety in patients with severe hepatic impairment	**Routine risk minimisation measures**: *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*
Long term safety follow-up	**Routine risk minimisation measures**: *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the

international birth date (IBD). The IBD is 24.09.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of duvelisib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers duvelisib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Data in this MAA support the following indications:

- Relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies.
- Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies.

3.1.2. Available therapies and unmet medical need

Therapy for CLL has evolved from monotherapy with alkylating agents (chlorambucil, bendamustine) and purine analogues (fludarabine) to immunotherapy (anti-CD52 monoclonal antibody alemtuzumab and anti-CD20 monoclonal antibody ofatumumab) and chemoimmunotherapy combinations (rituximab, ofatumumab as well as obinutuzumab in combination with purine and alkylating agents). Since 2014, novel targeted agents have been approved initially in the relapsed and some later in the previously untreated setting and include ibrutinib, idelalisib, and venetoclax.

Even with the availability of these novel treatments, most patients will eventually relapse. Furthermore, not all patients tolerate or respond to these treatments, and resistance will emerge over time. In addition, the response rate tends to be lower and the duration of response (DOR) becomes progressively shorter with each subsequent line of therapy (Fischer et al., 2011; Carton et al., 2014; Keating et al., 2002, Wierda et al., 2010; Catovsky et al, 2007). In conclusion, there remains an unmet medical need for additional novel therapies, especially for patients with previously treated CLL.

Over the past several decades, substantial advances have been made in event-free survival, progression-free survival (PFS), and overall survival (OS) of patients with FL. These survival improvements are mostly attributed to progress in the delivery of effective anti-lymphoma therapies and improvements in supportive care (Casulo et al., 2015). The vast majority of patients treated for FL will have an initial response to therapy with 40 to 80 percent demonstrating a complete response, depending on the initial regimen used. However, conventional therapy for FL is not curative and most of these patients will ultimately develop progressive disease. In addition, less than 10 percent of patients treated with initial chemoimmunotherapy will not respond to treatment (ie, refractory disease). Even with the newer available treatments, most patients with FL will eventually relapse or become intolerant to therapy. In addition, the rate of response and DOR progressively diminish with each subsequent line of therapy. All approved therapies in FL are associated with toxicities that may preclude their use in patients with certain comorbidities. Additional options are needed to treat this unmet medical need.

3.1.3. Main clinical studies

The pivotal study IPI-145-07 in CLL (DUO trial) is an open-label, multicentre, randomised (1:1) phase 3 study comparing the efficacy of duvelisib (N=158) (continuous until disease progression or unacceptable toxicity, whichever came first) to ofatumumab (N=155) [6-7 months (max 12 infusions) treatment according

to the previously approved indication] in relapsed or refractory CLL/SLL patients who had previously received ≥1 therapy.

The pivotal study IPI-145-06 in FL is a Phase 2, open-label, single arm efficacy and safety study of duvelisib monotherapy administered orally to subjects with relapsed/refractory iNHL, including the subtypes of FL (n = 83), small lymphocytic lymphoma (SLL) (n = 28), and MZL (n = 18) for a total of 129 subjects. This study was designed to evaluate the effect of duvelisib 25 mg BID monotherapy in subjects with iNHL refractory to rituximab and to either chemotherapy or radioimmunotherapy (RIT).

3.2. Favourable effects

In the CLL study IPI-145-07 the median PFS (ITT population) for duvelisib was 13.3 months (95% CI: 12.1, 16.8) and for ofatumumab 9.9 months (95% CI: 9.2, 11.3) with a hazard ratio of 0.52 (95% CI: 0.39, 0.70; p < 0.0001) and thus the study met its primary endpoint demonstrating statistically significant superiority of duvelisib over ofatumumab for PFS per IRC.

Approximately 60% of subjects received at least two prior therapies. Median PFS was 16.4 months (95% CI: 12.0, 20.5) for duvelisib versus 9.1 months for ofatumumab (95% CI: 7.9, 10.7), with a hazard ratio of 0.4 (95% CI: 0.27, 0.59). Even though subjects with 17p del/TP53 mutation represent a high-risk group of CLL, the median PFS (ITT population) for duvelisib was only slightly lower (12.7 months subjects with mutation versus 14.7 months for subjects without mutation), also reflected in the ORR. Approximately 60% of subjects 17p-patients received at least two prior therapies. Median PFS was 12.8 months (95% CI: 8.9, 22.1) for duvelisib versus 8.7 months for ofatumumab (95% CI: 5.3, 12.6), with a hazard ratio of 0.36 (95% CI: 0.18, 0.72).

In the trial IPI-145-06 in iNHL the ORR for the FAS (N= 129) was 45.7% (59/129; 95% CI: 36.9, 54.7) per IRC assessment. All responses (59) were PRs. The FL population (N=83) did not meet the expected ORR for the FAS as ORR (FL) was 42.2% (35/83; 95% CI: 31.4, 53.5) with 1 CR and 34 PRs. The ORR for the subgroup of ≥ 2 prior therapies was 29/73 (39.7%; 95% CI: 29,52). The median DOR for the responders in IPI-145-06 was 10.0 months, but the estimated median DoR is uncertain due to early censoring. Results are in line with those reported for the IRC-based analysis as this was app. 10 months for both the ITT and patients with more than 2 prior regimens.

3.3. Uncertainties and limitations about favourable effects

For CLL patients with only 1 prior therapy the median PFS was 12.7 months (95% CI: 9.1, 17.8) for duvelisib versus 12.0 months for ofatumumab (95% CI: 9.6, 12.8) with a hazard ratio of 0.8 (95% CI: 0.5, 1.28). The overall efficacy seems to be driven by the 60% of patients having received ≥ 2 prior therapies. Thus, duvelisib seems to work better in heavily pre-treated CLL patients contrary to what is generally seen with regards to efficacy. A further limitation of the studied population is the fact patients with prior treatment with BTK-, bcl-2, and idelalisib were excluded. It is also acknowledged that comparison of the efficacy of duvelisib in CLL after ≥ 2 prior treatment to ofatumumab, which was acceptable at the time of the trial initiation, may not be representative in the current context.

The median OS of IPI-145-07 was not estimable in either treatment arm and results are difficult to assess due to use of further anticancer therapy in both arms. Of note, patients in the duvelisib arm may have been more likely to continue with currently approved therapies as next line than those in the ofatumumab arm. The applicant is recommended to provide the results of the final OS analysis after all subjects have been

followed for a minimum of five years (expected July 2021) for both the ITT and approved subgroup as a post-marketing submission. A limitation of the studied population is the fact that patients with prior treatment with BTK-, bcl-2, and idelalisib were excluded.

The data for the follicular lymphoma indication is based on a single-arm trial: All in all, there are limitations with respect to the presented data for FL in a single arm study with ORR as primary endpoint. An RCT would have been preferred even though it is acknowledged that at study initiation a suitable effective comparator was not readily available. Randomised Study 327 is currently under discussion with the prospect of obtaining CHMP Scientific advice; results will be reported post-authorisation in line with a CHMP recommendation.

3.4. Unfavourable effects

In the only phase 3 study in patients with CLL, the incidence of various AEs by SOC and/or PT in the duvelisib arm (N=158) were generally higher than in the ofatumumab arm (N=155), which was also the case for SAEs.

Almost all patients in both the duvelisib and ofatumumab arm experienced a TEAE (98.7% vs. 92.9%). TEAEs with >10% higher incidence in the duvelisib arm compared to ofatumumab were: neutropenia (32.9% vs. 20.6%), anaemia (32.9% vs. 20.6%), diarrhoea (50.6% vs. 12.3%), nausea (23.4% vs. 11%), constipation (16.5% vs. 8.4%), colitis (13.3% vs. 1.3%), abdominal pain (10.1% vs. 1.9%), pyrexia (28.5% vs. 10.3%), pneumonia (18.4% vs. 5.8%) and weight decreased (11.4% vs. 1.9%).

TEAES ≥ grade 3 (87.3% vs. 48.4%) and TESAEs (72.8% vs. 32.3%) were reported with substantial higher frequency in the duvelisib arm compared to ofatumumab. Highest differences in TEAE of ≥grade 3 between duvelisib and ofatumumab were seen in the SOCs Blood and lymphatic system disorders (42.4 vs. 24.5%), Gastrointestinal disorders (32.3 vs. 2.6%) and Infections and infestations (33.5 vs. 11.0%). Treatment related TEAEs ≥ grade 3 were reported in 74.7% vs. 30.3%, related TESAEs in 53.2% vs. 10.3%. Hematologic and gastro-intestinal events were the most frequently reported treatment related TEAEs.

TEAEs leading to dose reduction or dose hold were reported more frequently in the duvelisib arm: 79.1% vs. 10.3%. In the duvelisib arm, diarrhoea was the most common TEAE to result in dose hold or reduction (23.4%), followed by neutropenia (13.3%), pneumonia (10.8%), and colitis (10.8%). TEAEs leading to treatment discontinuation: 36.1% vs. 5.8%. TEAEs leading to discontinuation were divided over all SOCs, most frequently being GI disorders.

TEAEs with an outcome of death: 12% (n=19) vs. 4.5% (n=7). Fatal TEAEs occurring in more than one subject included: bronchopulmonary aspergillosis (n = 2), pneumonia staphylococcal (n = 2), and haemorrhagic stroke (n = 2). Four subjects experienced fatal treatment related TEAEs: pneumonia staphylococcal (n = 2), general physical health deterioration and sepsis (n = 1, each).

Overall, the AEs in the pooled FL population (N=93), the pooled CLL/SLL (N=303), and the All Heme 25 mg BID population (N=442) are of the same order as in the RCT. The updated safety data from Study VS-0145-328 (443 received duvelisib 25 mg BID in the All Heme group) did not show any meaningful changes or new AEs. A slight increase in all AEs (All, ≥Grade 3, SAEs, Deaths, AESIs), as would be expected with time, was seen.

Almost all patients experienced a TEAE (99.2%). The most common TEAEs were diarrhoea (44.2%), neutropenia (31.8%), nausea (28.7%), fatigue (24.0%), cough (24.0%), anaemia (22.5%), thrombocytopenia (20.9%), pyrexia (20.9%), rash (17.8%), and vomiting (17.1%). TEAEs Grade 3 or higher (83.7%) and TESAEs (57.4%) were reported in a substantial part of the study population. Treatment related

TEAEs ≥ grade 3 were reported in 67.4% and related TESAEs in 35.7%. The most common ≥Grade 3 TEAEs were neutropenia (23.3%), diarrhoea (14.7%), anaemia (11.6%), and thrombocytopenia (10.1%). TESAEs were mostly reported in the infections and infestations SOC (22.5%), as well as the blood and lymphatic system disorders SOC (12.4%) and gastrointestinal disorders SOC (15.5%).

TEAEs leading to dose reduction or dose hold were reported in 64.3%. Nineteen (19, 14.7%) subjects had at least 1 TEAE that led to duvelisib dose reduction. TEAEs leading to duvelisib reduction in ≥ 2 subjects were: febrile neutropenia (n=3; 2.3%), neutropenia (n=2; 1.6%), diarrhoea (n=7; 5.4%), AST increased (n=2; 1.6), and ALT increased (n=2; 1.6%). TEAEs leading to treatment discontinuation occurred in 24%. TEAEs leading to duvelisib discontinuation in ≥ 2 patients were disease progression (n=4), pneumonia (n=2), pneumonitis (n=3), and rash generalised (n=2).

TEAEs with an outcome of death were reported in 10.9% (n=14) of the patients in study IPL-145-06, of which 11 occurred in the FL group. Four of the 14 deaths on treatment were assessed by the investigator as related to duvelisib: drug reaction with eosinophilia and systemic symptoms (FL), sepsis syndrome / toxic epidermal necrolysis (FL), septic shock (SLL), and viral infection (SLL).

3.5. Uncertainties and limitations about unfavourable effects

In patients treated with duvelisib the main uncertainties are related to the limitations of the studied population as patients with prior treatment with BTK-, bcl-2, and idelalisib were excluded.

Safety comparison in the FL population is hampered by the single arm trial design as well as the short exposure (24 weeks) in this population.

3.6. Effects Table

Effects Table for Copiktra in CLL after two prior therapies (Data cut-off: 19 MAY 2017)

Effect	Short Description	Unit	Duvelisib	Ofatumumab	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS (ITT)	Progression free survival by independent review	Months 95% CI	13.3 (12.1,16.8)	9.9 (9.2,11.3)	Heterogeneous patient population might make the assessment of the benefit/risk difficult. Hazard ratio (95% CI): 0.52 (0.39, 0.69)	
ORR	Overall response rate	N (%)	118/160 (73.8)	72/159 (45.3)	DUV: 1 CR, 117 PR OFA: 1 CR, 71 PR	
PFS in patients after ⩾2 prior Treatments	Progression free survival by independent review	Months	**16.4 (12.0, 20.5)**	**9.1 (7.9, 10.7)**	Hazard Ratio for Duvelisib/Ofatumumab (95% CI): 0.4 (0.27, 0.59)	

Effect	Short Description	Unit	Duvelisib	Ofatumumab	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Diarrhoea-colitis	Pooled PTs	% AEs % SAEs	66.5 24.0	14.2 1.8		
Infection	SOC	% AEs % SAEs	69.0 38.0	43.2 12.9		
Neutropenia	PT (not laboratory)	% AEs % ≥ Grade 3	32.9 30.4	20.6 17.4		
Pneumonitis	Pooled PTs	% AEs	8.2	0		
Severe cutaneous reactions	Pooled PTs	% AEs	30.4	16.1		
Increased trans-aminases		% AST % ALT % AST/ALT	8.9 7.6 2.5	1.9 1.9 0		
Deaths due to TEAEs		N (%)	19-21* (12.0-13.3)	5 (3.2)	*The exact number awaits the answer to an OC	
SAEs		%	72.8	32.3		
Discontinua-tions due to TEAEs		%	34.1	3.9	From CSR-07, Table 14.1.1.2.	

Abbreviations: PTs; Preferred Terms, SAEs; Serious adverse events, TEAEs; Treatment emergent AEs

Effects Table for Copiktra in FL after one prior therapy (Data cut-off: 18-MAY-2018)

Effect	Short Description	Unit	Duvelisib	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR in FL	Overall response rate (CR+PR) by IWG criteria.	N (%) 95% CI	83 42.2 (31.4, 53.5)	0	Phase 2, single-arm study. 129 subjects with indolent Non-Hodgkin lymphoma of which 83 had follicular lymphoma.	
Unfavourable Effects in FL patients						
Infection*	SOC	% AE % SAEs	55.2 20.8			
Neutro-penia*	PT (not laboratory)	% AE	25.0			

Effect	Short Description	Unit	Duvelisib	Control	Uncertainties/ Strength of evidence	References
Increased trans-aminases*		% AST % ALT	15.6 17.7			
The other AEs (Diarrhoea-colitis, pneumonitis, cutaneous reactions) listed for the RCT in CLL were comparable; see table above.						
Deaths due to TEAEs*		N (%)	11/96 11.5			
SAEs*		%	58.3			
Discontinua-tions due to TEAEs*		%	29.2			

Abbreviations:
Notes: *Pooled FL 25 mg BID; 83 patients from the pivotal study IPI-145-06 and 13 patients from study IPI-145-02.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of duvelisib in CLL after ≥ 2 prior treatment as measured by a longer median PFS of 16.4 months compared to 9.1 months for ofatumumab, and a HR of 0.4 is clinically relevant as an alternative option in the further lines of CLL treatment, notwithstanding the challenges in the context of the present-day treatment landscape.

The primary data for the FL indication is collected from a single arm Phase 2 Study IPI-145-06. The clinical data underlying the FL indication is based on a limited number of patients (n=96 subjects) and derived from a subgroup analysis of a single arm trial. In the primary analysis of ORR per IRC in 83 patients with refractory FL duvelisib demonstrated an ORR of 42% (95% CI: 31, 54). Phase 3 Randomised study VS-014-327 in FL was issued by the FDA in response to marketing approval in the US. However, the study design needs further clarification and no subjects have been enrolled within this protocol. The applicant agreed with CHMP recommendations and is initiating discussions with the CHMP in view of seeking scientific advice on the study design and will provide the results as soon as available.

Of note, the treatment landscape of R/R FL has changed since start of the pivotal trial (24 June 2013) with the PI3K inhibitor idelalisib as a treatment option for double-refractory FL (ESMO guideline 2016). The studied population consisted mainly of FL patients refractory to rituximab and chemotherapy (e.g. double refractory) and no previous PI3 kinase treatment. This patient population has become very rare due to changes in the treatment landscape. The indication was amended to only include *refractory* FL, as best representing the clinical benefit of duvelisib in the studied population.

The primary safety issues identified with duvelisib include serious, including fatal, infections, diarrhoea or colitis, cutaneous reactions, and pneumonitis, along with serious hepatotoxicity and neutropenia.

The updated safety data from Study VS-0145-328 (443 received duvelisib 25 mg BID in the All Heme group) did not show any meaningful changes or new AEs. A slight increase in all AEs (All, ≥Grade 3, SAEs, deaths, AESIs), as would be expected with time, was seen.

3.7.2. Balance of benefits and risks

The benefit/risk balance for Copiktra in the relapsed or refractory CLL setting after at least two prior lines of therapy is positive.

In the refractory FL indication and considering uncertainties discussed, the benefit/risk balance for Copiktra in the refractory setting after two prior lines of therapy is positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Copiktra is positive.

4. Recommendations

Similarity with authorised orphan medicinal products>

The CHMP is of the opinion that Copiktra is not similar to Gazyvaro (obinutuzumab) and Imbruvica (ibrutinib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Copiktra is favourable in the following indications: Relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies; Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see section 4.2 of the SmPC).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that duvelisib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.