Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for idelalisib

Proprietary Product Name: Zydelig

Sponsor: Gilead Sciences Pty Ltd

First round report: January 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

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List of abbreviations

Abbreviations	Meaning
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the curve
BD	Twice daily
CLL	Chronic Lymphocytic Leukaemia
Cmax	Maximum concentration
CMI	Consumer Medicines Information
CR	Complete Response
CT	X-Ray Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DOR	Duration of Response
EMA	European Medicines Agency
EOS	End of Study
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
HRQL	Health Related Quality of Life
ICH	International Conference on Harmonisation
IRC	Independent Review Committee

Abbreviations	Meaning
ITT	Intention to Treat
IV	Intravenous
IWCLL	International Workshop on CLL
LDH	Lactate Dehydrogenase
LNR	Lymph Node Response
LVD	Longest Vertical Dimension
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NHL	Non-Hodgkins Lymphoma
OD	Once daily
ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamics or Progressive Disease
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PP	Per protocol
PR	Partial Response
QoL	Quality of Life
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SPD	Sum of the Products of Perpendicular Diameters

Abbreviations	Meaning
Tmax	Time of maximum concentration
TTR	Time to Response
ULN	Upper Limit of Normal
Vss	Volume of distribution at steady state

1. Introduction

This is an abbreviated application to extend the indications of the product.

1.1. Drug class and therapeutic indication

Idelalisib is an inhibitor of phosphoinositide 3-kinase δ isoform (PI3δ kinase). PI3δ kinase is part of the B-cell receptor (BCR) signalling pathway, which is crucial for B-cell proliferation and survival. PI3 kinase signalling is constitutively activated in CLL.[1]

The currently approved indications are:

> *Zydelig in combination with rituximab is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) for whom chemo immunotherapy is not considered suitable, either:*
>
> § *Upon relapse after at least one prior therapy, or*
>
> § *As first-line treatment in the presence of 17p deletion or TP53 mutation.*
>
> *Zydelig is indicated as monotherapy for the treatment of patients with refractory follicular lymphoma who have received at least two prior systemic therapies.*

The application seeks to amend the CLL/SLL indication as follows:

> *Zydelig in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) for whom chemo immunotherapy is not considered suitable, either:*
>
> § *Upon relapse after at least one prior therapy, or*
>
> § *As first-line treatment in the presence of 17p deletion or TP53 mutation.*

Hence the application is seeking approval for use of idelalisib in combination with ofatumumab for the treatment of CLL/SLL. No change to the follicular lymphoma indication is proposed.

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

· 100 and 150 mg tablets.

No new dosage forms or strengths are proposed.

1.3. Dosage and administration

The idelalisib dose proposed for use in combination with ofatumumab is 150 mg BD, which is the same dose approved for the existing indications. For all indications the dose may be reduced to 100 mg BD in the event of toxicity.

[1] Blunt MD and Steele AJ. Pharmacological targeting of PI3K isoforms as a therapeutic strategy in chronic lymphocytic leukaemia. *Leuk Res Rep.* 4: 60-3 (2015).

2. Clinical rationale

CLL/SLL is a haematological malignancy that results from a clonal proliferation and accumulation of mature B-lymphocytes. It is typically a disease of the elderly with median age at diagnosis between 67 and 72 years, and is more common in males than females at a ratio of 1.7 to 1.[2] According to Cancer Australia,[3] there were 1,174 new cases of CLL in Australia in 2011, and in 2012 it caused 342 deaths. CLL and SLL are considered to be different presentations of the same disease. In CLL significant numbers of abnormal lymphocytes are found in blood and bone marrow, whereas in SLL they are predominantly found in lymph nodes and bone marrow.[4]

Clinical symptoms and signs of CLL/SLL include weakness, fatigue, night sweats, fever, weight loss, frequent infections, lymphadenopathy, splenomegaly and hepatomegaly. Abnormal laboratory tests in CLL include a lymphocytosis in blood (≥ 5.0 x 10^9 cells/L) and bone marrow (>30%).[5] Cytopaenias (mainly anaemia and thrombocytopaenia) may occur, especially in advanced disease. Autoimmune phenomena such as haemolytic anaemia and immune thrombocytopaenia may also occur. Hypogammaglobulinaemia occurs in a proportion of patients.

There are currently two systems used for staging CLL – the Rai (Table 1) and Binet (Table 2) systems. Both these systems are based on physical examination and haematology parameters. Higher stages are associated with worse prognosis. Other factors associated with poor prognosis include elevated serum beta-2 microglobulin, elevated serum thymidine kinase, absence of mutations in immunoglobulin heavy chain variable (IGHV) region genes and cellular expression of CD38, CD49d and ZAP-70. Various cytogenetic abnormalities are also associated with poor clinical outcomes, particularly deletion of the long arm of chromosome 11 [del (11q)], deletion of the short arm of chromosome 17 [del (17p)] or mutations in the TP53 gene.[6]

Table 1: Rai staging system for CLL.

Stage	Modified Rai category	Features	Median survival (yr)
0	Low risk	Lymphocytosis[a]	13+
I	Intermediate risk	Lymphocytosis + enlarged nodes	8
II		Lymphocytosis + enlarged spleen or liver	
III	High risk	Lymphocytosis + anemia[b]	2
IV		Lymphocytosis + thrombocytopenia[c]	

[a] Absolute lymphocyte count in blood ≥5000/mm^3 with flow cytometry findings of predominance of monoclonal B-cells with characteristic features of CLL (CD19+, CD20+, CD5+, CD23+).
[b] Hemoglobin <11 g/dL, with or without anemia or enlargement of lymph nodes, spleen, or liver.
[c] Platelets <100,000/mm^3, with or without anemia or enlargement of lymph nodes, spleen, or liver.

[2] Hallek M. Chronic lymphocytic leukemia: 2013 update on diagnosis, risk stratification and treatment. *Am J Hematol.* 88: 804-816 (2013).
[3] Cancer Australia, Chronic lymphocytic leukaemia statistics.
[4] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Non-Hodgkin's Lymphomas – Version 1.2016.
[5] Rai KR and and Patel DV. Chronic lymphocytic leukemia. In: Hoffman R, Benz EJ, Shattil SJ et al (eds). Hematology - Basic Principles and Practice. 3rd ed. Philadelphia: Churchill Livingstone, 2000, pp 1350-1363.
[6] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Non-Hodgkin's Lymphomas – Version 1.2016.

Table 2: Binet staging system for CLL.

Stage	Features	Median survival (y)
A	Hemoglobin ≥10 g/dL, platelets ≥100,000/mm^3, and ≤2 palpably enlarged lymphoid sites[a]	15
B	Hemoglobin ≥10 g/dL, platelets ≥100,000/mm^3, and >2 palpably enlarged lymphoid sites[a]	5
C	Hemoglobin <10 g/dL or platelets <100,0000/mm^3, regardless of the number of palpably enlarged lymphoid areas	3

[a] Of the following five sites: cervical, axillary and inguinal lymph nodes, and spleen and liver.

Agents that are currently registered in Australia for the treatment of CLL include alkylating agents (chlorambucil, bendamustine, cyclophosphamide), purine analogues (fludarabine, cladribine), monoclonal antibodies directed against CD20 (rituximab, ofatumumab, obinutuzumab), a monoclonal antibody directed against CD52 (alemtuzumab) and an inhibitor of Bruton's tyrosine kinase (ibrutinib).

Recommended treatment of CLL/SLL depends on a number of factors including patient functional status, age, the presence or absence of certain cytogenetic abnormalities [del (11q), del (17p) or TP53 mutation] and the presence or absence of significant comorbidities. For previously untreated patients, aged < 70 and in good physical condition and without adverse cytogenetic abnormalities, combination therapy with a chemotherapy agent and a monoclonal antibody ("chemoimmunotherapy") is usually recommended– e.g. fludaribine + cyclophosphamide + rituximab (FCR).

Previously submitted data had demonstrated that idelalisib in combination with rituximab was effective as a second line regimen in CLL/SLL, and as a first line regimen in subjects with del (17p) or TP53 mutation, who have poor outcomes with standard chemoimmunotherapy regimens. Ofatumumab is another anti-CD20 monoclonal antibody registered for the treatment of CLL/SLL. The efficacy and safety of the combination of idelalisib and ofatumumab would therefore be of clinical interest.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 1 pivotal efficacy/safety study (GS-US-312-0119) of idelalisib in combination with ofatumumab.
- An updated study report of one previously evaluated phase 1/2 study (study 101-07) that included some data on the use of idelalisib in combination with ofatumumab.
- Study reports of various other studies not directly relevant to the new indication. Some of these studies had previously been evaluated by TGA. The safety data from these studies have been reviewed in this evaluation.
- A validation study (Report 15-001) of a previously developed population pharmacokinetic model using PK data from the pivotal study.
- Tables of safety data from four ongoing, blinded, placebo-controlled Phase 3 studies of idelalisib (GS-US-312-0115, GS-US-312-0123, GS-US-313-0124, and GS-US-313-0125) in CLL and indolent NHL. These data were all blinded (i.e. it was not possible to determine whether a reported adverse event occurred in a placebo-treated or idelalisib-treated patient). The

data were therefore not evaluable. According to the sponsor no new safety concerns have been identified to date from the blinded data.

- Literature references.

3.2. Paediatric data

The submission did not contain any paediatric data.

Comment: As CLL/SLL is a disease of adults the absence of paediatric data is acceptable.

3.3. Good clinical practice

The study reports included in this submission all contained assurances that the studies were conducted in accordance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki.

4. Pharmacokinetics

Limited PK sampling was performed in the pivotal study included in this submission (GS-US-312-0119). Results are summarised in Table 3.

Table 3: Idelalisib plasma PK concentration (ng/Ml) PK analysis set.

	Sampling Time											
	Week 1 Pre-Dose	Week 1 1.5 hours Post-Dose	Week 3 Pre-Dose	Week 3 1.5 hours Post-Dose	Week 5 Pre-Dose	Week 5 1.5 hours Post-Dose	Week 8 Pre-Dose	Week 8 1.5 hours Post-Dose	Week 12 Pre-Dose	Week 12 1.5 hours Post-Dose	Week 24 Pre-Dose	Week 24 1.5 hours Post-Dose
N	2	163	153	149	138	140	135	134	126	128	112	114
Mean	596.7	2494.4	621.3	2349.6	487.4	2305.1	550.8	2191.0	446.3	2193.2	599.3	2093.9
SD	711.77	1235.22	645.17	1031.69	462.53	1060.04	472.65	912.85	432.47	1020.59	665.54	1069.48
% CV	119.3	49.5	103.8	43.9	94.9	46.0	85.8	41.7	96.9	46.5	111.1	51.1
Median	596.7	2510.0	420.0	2240.0	357.5	2180.0	398.0	2155.0	302.5	2070.0	372.5	2070.0
Min	BLQ	BLQ	31.3	200.0	BLQ	44.4	BLQ	147.0	BLQ	BLQ	BLQ	45.5
Max	1100.0	6100.0	3710.0	7030.0	3210.0	6370.0	2730.0	4760.0	2010.0	6110.0	3760.0	4720.0
Q1	93.4	1730.0	239.0	1760.0	222.0	1730.0	234.0	1640.0	186.0	1585.0	204.0	1410.0
Q3	1100.0	3360.0	669.0	2950.0	597.0	2985.0	780.0	2770.0	502.0	2795.0	724.0	2730.0
N (LN-scale)	2	163	153	149	138	140	135	134	126	128	112	114
Geom. Mean	320.5	1917.3	428.3	2088.4	363.0	1962.4	401.4	1926.2	325.2	1850.8	396.3	1681.1
95% CI(L)	0.0	1636.2	373.9	1912.6	320.1	1746.6	349.5	1738.5	283.5	1630.7	335.0	1442.2
95% CI(U)	2.0433E5	2246.6	490.6	2280.3	411.7	2204.9	461.0	2134.2	373.0	2100.6	468.7	1959.6
# BLQ	166	2	0	0	2	0	7	0	7	2	7	0

Note: the PK analysis set includes subjects in the safety analysis set who have baseline and on-study measurements to provide interpretable results, with treatment group designated according to the actual treatment received.

In addition, the sponsor conducted various population PK and population PK/PD analyses of subjects enrolled in the pivotal study using previously developed population PK models. Results for these analyses are summarised below.

Table 4: Effect of ofatumumab on idelalisib PK.

Idelalisib PK Mean (%CV)	Idelalisib + Ofatumumab (Study GS-US-312-0119) (N = 171)	Idelalisib Monotherapy [a] (Study 101-02) (N = 61)
AUC_{tau} (ng•h/mL)	11633.9 (32.0)	10598.1 (40.8)
C_{max} (ng/mL)	2103.4 (28.5)	1861.4 (43.3)
C_{tau} (ng/mL)	404.8 (60.9)	381.3 (57.9)

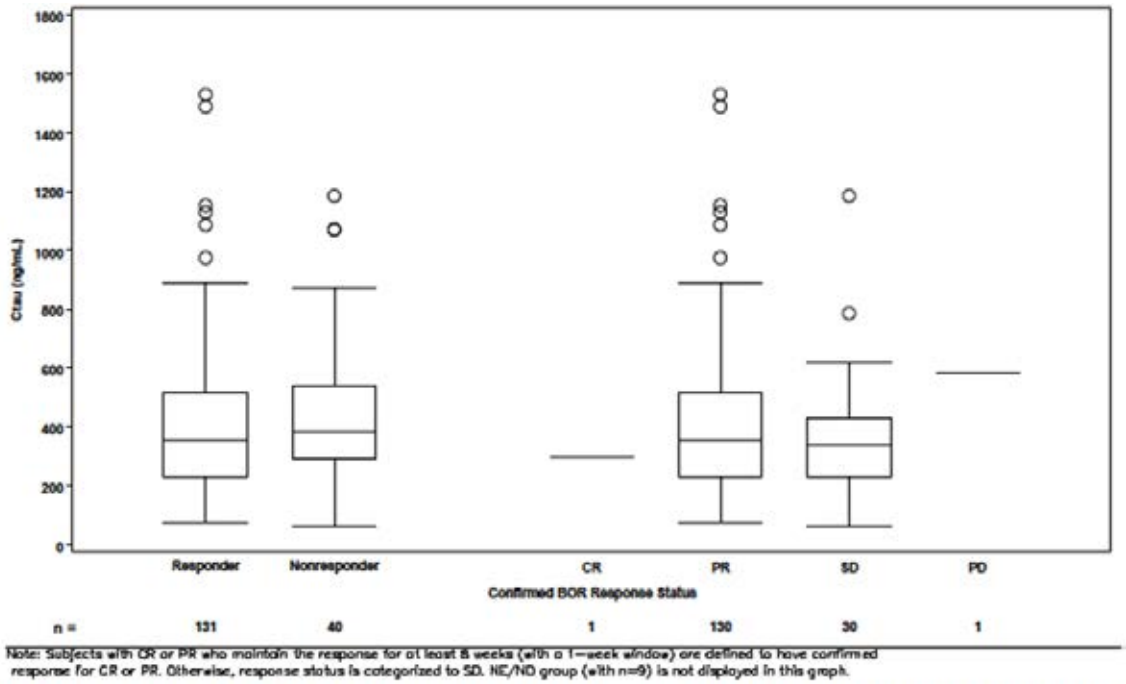
AUC_{tau} represents half the $AUC_{0\text{-}24h}$ values shown in the source table.
a Subjects in Study 101-02 with CLL, NHL, acute myeloid leukemia, or multiple myeloma who received idelalisib 150 mg BID monotherapy are included. Idelalisib monotherapy source: original marketing application, m5.3.4.2, PK/PD Table 1.2.

Table 5: Effect of intrinsic factors on idelalisib PK.

Idelalisib PK Mean (%CV)	< 65 Years (N = 66)	65 to 75 Years (N = 71)	> 75 Years (N = 34)
AUC_{tau} (ng•h/mL)	10805.9 (25.4)	11832.3 (33.2)	12827.0 (35.9)
C_{max} (ng/mL)	2025.3 (23.9)	2127.8 (30.0)	2204.2 (32.2)
C_{tau} (ng/mL)	346.8 (51.1)	413.4 (61.0)	499.6 (63.4)
GS-563117 PK Mean (%CV)			
AUC_{tau} (ng•h/mL)	40647.2 (49.2)	44598.9 (49.6)	38133.3 (45.9)
C_{max} (ng/mL)	4131.1 (45.8)	4355.6 (46.0)	3809.2 (45.8)
C_{tau} (ng/mL)	2540.2 (57.3)	2946.8 (56.0)	2448.0 (47.5)

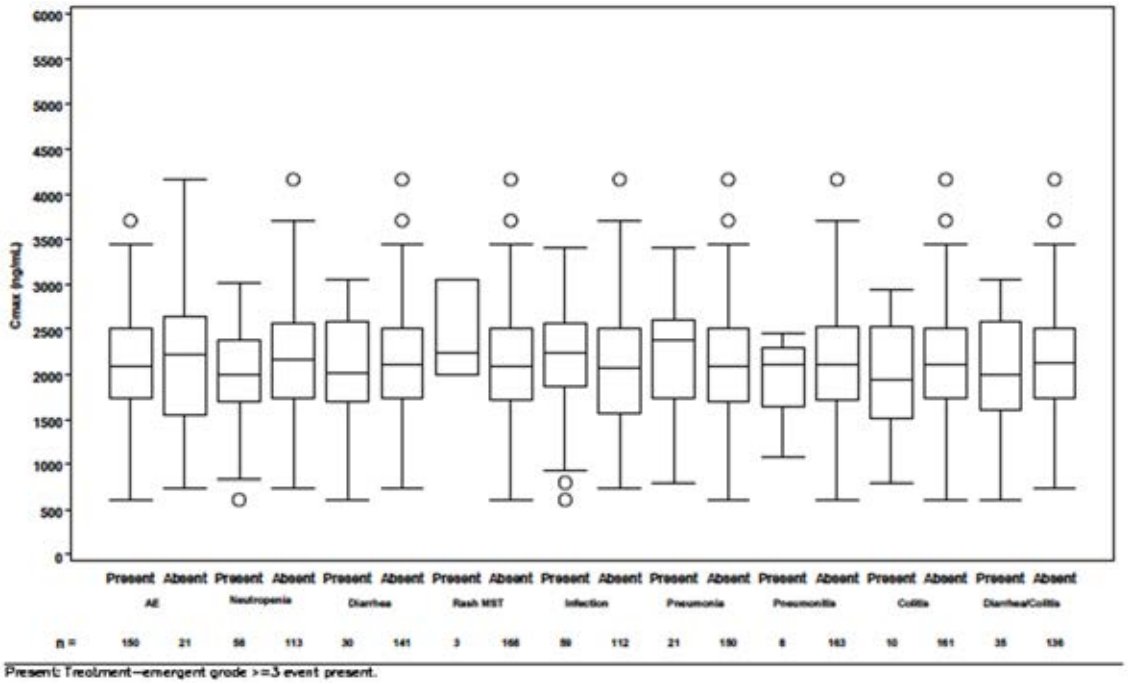
AUC_{tau} represents half the $AUC_{0\text{-}24h}$ values shown in the source table.

Figure 1: Study GS-US-312-0119: exposure-efficacy relationship, box plot of idelalisib C_{tau} stratified by BOR.



BOR = best overall response, CR = complete response, PR = partial response, SD = stable disease, NE = not evaluable, ND = no disease

Figure 2: Study GS-US-312-0119: exposure-safety relationship, box plot of idelalisib C_{max} for subjects with ≥ Grade 3 AEs of interest.



Conclusions drawn from these PK data were:

- Idelalisib trough and peak plasma concentrations remain reasonably stable over 24 weeks when the drug is administered in combination with ofatumumab;
- Co-administration of ofatumumab with idelalisib does not appear to significantly affect the PK of idelalisib;
- No relationships could be established between systemic exposure to idelalisib and efficacy outcomes;
- No relationships could be established between systemic exposure to idelalisib and the occurrence of common AEs.

5. Pharmacodynamics

No new pharmacodynamic data were included in the submission. In the pivotal study blood samples were collected for the measurement of plasma cytokines and chemokines, serum markers of iron metabolism and CLL cell DNA, RNA and protein. The study report did not contain analyses of these parameters. It indicated that a separate biomarker analysis report would be submitted.

6. Dosage selection for the pivotal studies

The dose of idelalisib used in the pivotal study was 150 mg BD. This is the same regimen used for the currently approved indications and was based on previously evaluated Phase 1 studies.

The choice of ofatumumab dose (1000 mg) was not discussed in the study report for the pivotal study. However, this dose was used in an earlier phase 1/2 study (101-07) where the stated justification was that the 1000 mg dose is common when ofatumumab is used in combination regimens.

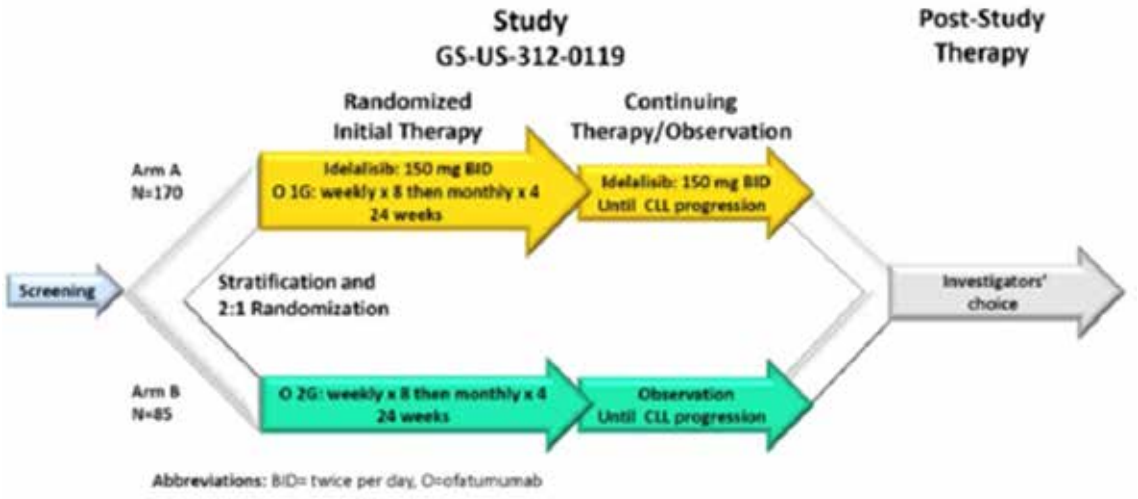
7. Clinical efficacy

7.1. Pivotal efficacy study (GS-US-312-0119)

7.1.1. Study design, objectives, locations and dates

Study GS-US-312-0119 was a phase 3, randomised open-label controlled trial with two parallel groups. Subjects were randomised (2:1) to receive either the combination of ofatumumab with idelalisib (Group A) or ofatumumab monotherapy (Group B). A study schema is shown in Figure 3.

Figure 3: Study GS-US-312-0119 – Study schema.



The primary objective of the study was to evaluate the effect of the addition of idelalisib to ofatumumab on progression-free survival (PFS) in subjects with previously treated CLL.

The secondary objectives were to:

- Evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumour control;
- Evaluate the effect of the addition of idelalisib to ofatumumab on the onset, magnitude, and duration of tumour control for subjects with 17p deletion and/or TP53 mutation;
- Assess the effect of the addition of idelalisib to ofatumumab on measures of subject well being, including overall survival (OS), health-related quality of life (HRQL), and performance status;
- Assess the effects of the addition of idelalisib to ofatumumab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib;
- Characterize the effect of ofatumumab on idelalisib exposure through the evaluation of idelalisib plasma concentrations over time;
- Describe the safety profile observed with the addition of idelalisib to ofatumumab;
- Estimate health resource utilization associated with the addition of idelalisib to ofatumumab.

The study was conducted at 81 sites in 11 countries (the United States, Canada, Belgium, Denmark, France, Ireland, Poland, Spain, Sweden, United Kingdom, and Australia). It commenced in December 2012 and the cut-off date for inclusion of data in the study report was

15 January 2015. The study report itself was dated 21 April 2015. At the time of writing, it appears that the study has not been published other than as a conference abstract.[7]

7.1.2. Inclusion and exclusion criteria

Inclusion criteria and exclusion criteria are listed below.

7.1.2.1. Inclusion criteria

Subjects who met all of the following criteria were eligible for participation in the study:

- Male or female ≥ 18 years of age
- Diagnosis of B cell CLL, with diagnosis established according to IWCLL criteria and documented within medical records
- CLL that warranted treatment (consistent with accepted IWCLL criteria for initiation of therapy). Any of the following conditions constitute CLL that warranted treatment:
  - Evidence of progressive marrow failure as manifested by the onset or worsening of anemia and/or thrombocytopenia, or
  - Massive (i.e. lower edge of spleen ≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly,
  - Massive (i.e. ≥ 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or
  - Progressive lymphocytosis in the absence of infection, with an increase in blood ALC ≥ 50% over a 2-month period or lymphocyte doubling time of < 6 months (as long as initial ALC was ≥ 30,000/L), or
  - Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosterioids or other standard therapy, or
  - Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
    - Unintentional weight loss of ≥ 10% within the previous 6 months, or
    - Significant fatigue (≥ Grade 2),
    - Fevers > 100.5 °F or 38.0 °C for ≥ 2 weeks, or
    - Night sweats for > 1 month
- Presence of radiographically measurable lymphadenopathy (defined as the presence of ≥ 1 nodal lesion that measures ≥ 2.0 cm in the longest diameter (LD] and ≥ 1.0 cm in the longest perpendicular diameter (LPD] as assessed by computed tomography [CT] or magnetic resonance imaging [MRI])
- Prior treatment for CLL comprising therapy with either of the following given alone or in combination:
  - A purine analog (e.g. fludarabine, pentostatin, cladribine) administered for ≥ 2 cycles of cytotoxic treatment, or
  - Bendamustine administered for ≥ 2 cycles of treatment
- Documentation of CLL progression < 24 months since the completion of the last prior therapy for CLL

[7] Jones JA, Wach M, Robak T et al. Results of a phase III randomized, controlled study evaluating the efficacy and safety of idelalisib (IDELA) in combination with ofatumumab (OFA) for previously treated chronic lymphocytic leukemia (CLL). J Clin Oncol 33, 2015 (suppl; abstr 7023).

- Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL > 6 weeks before randomisation
- All acute toxic effects of any prior anti-tumour therapy resolved to Grade ≤ 1 before randomisation (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grades 1, 2, 3 or 4 permitted])
- Karnofsky performance score of ≥ 60
- Required baseline laboratory data (within 4 weeks prior to randomisation) as shown in the table below. Subjects with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy could enrol

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert syndrome or hemolysis)
	Serum ALT Serum AST	≤ 2.5 × ULN
Renal	eCLcr[a]	> 30 mL/min
Pregnancy	β-HCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

β-HCG = beta human chorionic gonadotropin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCLcr = estimated creatinine clearance; HBc antibody = anti-hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus, HIV = human immunodeficiency virus; Ig = immunoglobulin; PCR = polymerase chain reaction; ULN = upper limit of normal

a As calculated by the Cockcroft-Gault formula

b For women of child-bearing potential only; serum β-HCG must have been negative during screening and serum β-HCG or urine dipstick pregnancy test must have been negative at randomization (Visit 2)

- For female subjects of child-bearing potential, willingness to use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and to 30 days from the last dose of study drug or 12 months from the last dose of ofatumumab (whichever is later)
- For male subjects of child-bearing potential and having intercourse with females of child-bearing potential, willingness to use a protocol-recommended method of contraception from the randomisation visit (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug and to refrain from sperm donation from randomisation (Visit 2) throughout the study treatment period and for 90 days following the last dose of study drug
- In the judgement of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current CLL disease status, medical condition, and the potential benefits and risks of alternative treatments for CLL
- Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions
- Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation

7.1.2.2. Exclusion criteria

Subjects with any of the following were not eligible for participation in the study:

- Known histological transformation from CLL to an aggressive lymphoma (i.e. Richter's transformation)
- Known presence of intermediate- or high-grade myelodysplastic syndrome (i.e. subjects are excluded who have ≥ 5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias due to myelodysplasia)
- History of a non-CLL malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to randomisation, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 2 years
- Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for either idelalisib or ofatumumab
- Evidence of ongoing systemic bacterial, fungal, or viral infections at the time of initiation of randomisation (Visit 2)
- Ongoing drug-induced liver injury, chronic active hepatitis C virus (HCV), chronic active HBV, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension
- Ongoing drug-induced pneumonitis
- Ongoing inflammatory bowel disease
- Ongoing alcohol or drug addiction
- Pregnancy or breastfeeding
- History of prior allogenic bone marrow progenitor cell or solid organ transplantation
- Ongoing immunosuppressive therapy other than corticosteroids
- In a subject with a history of prior ofatumumab therapy, the time from the last dose of ofatumumab to documented CLL progression was < 6 months
- History of prior therapy with any inhibitor of serine/threonine protein kinase (Akt), Bruton tyrosine kinase, Janus kinase, mammalian target of rapamycin, PI3K (including idelalisib), or spleen tyrosine kinase
- Prior participation in an idelalisib clinical study
- Concurrent participation in another therapeutic clinical study
- Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results

Comment: The inclusion criteria refer to various criteria promulgated by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL). These criteria come from an international consensus guideline originally developed by the National Cancer Institute

(NCI) in the United States in 1996, which was revised in 2008.[8] IWCLL criteria are currently standard for studies in CLL.

All subjects were required to have undergone prior treatment for CLL with either a purine analogue or bendamustine. However, the proposed indication includes use of the combination as first-line treatment in the presence of 17p deletion or TP53 mutation.

In Australia, ofatumumab monotherapy is only approved for use in subjects with CLL that is refractory to treatment with fludarabine and alemtuzumab. In the pivotal study of ofatumumab monotherapy, "refractory" was defined as failure to achieve at least a partial response with fludarabine or alemtuzumab treatment, or disease progression within 6 months of the last dose of fludarabine or alemtuzumab. The inclusion criteria for GS-US-312-0119 permitted enrolment of subjects with less treatment-resistant disease than this group. However, current treatment guidelines[9] recommend ofatumumab monotherapy as a treatment option for all subjects with relapsed or refractory CLL. The choice of comparator is therefore considered acceptable.

7.1.3. Study treatments

Subjects were randomised (2:1) to the following:

- Group A – Ofatumumab 1g IV for a total of 12 doses, together with idelalisib 150 mg BD orally until disease progression;
- Group B - Ofatumumab 2 g IV for a total of 12 doses.

Idelalisib could be taken with or without food. Subjects were instructed to take the drug at approximately the same times each day at approximately 12-hour intervals. The dose of idelalisib could be reduced to 100 mg BD in the event of toxicity.

Ofatumumab was administered IV in the clinic starting at a dose of 300 mg on Day 1 (Week 1) (Groups A and B) and continued with a dose of either 1g (Group A) or 2g (Group B) on Day 8 (Week 2), Day 15 (Week 3), Day 22 (Week 4), Day 29 (Week 5), Day 36 (Week 6), Day 43 (Week 7), Day 50 (Week 8), Day 78 (Week 12), Day 106 (Week 16), Day 134 (Week 20), and Day 162 (Week 24). The ofatumumab dose was diluted into 1000 mLs of normal saline. The first infusion was commenced at 12 mLs/hour and the rate increased up to 200 mLs/hr over 2 hours. Subsequent infusions were commenced at 25 mLs/hr and increased up to 400 mLs/hr over 2 hours.

All subjects received the following recommended premedication prior to ofatumumab infusions: paracetamol 1g or equivalent, an oral or IV antihistamine (cetirizine 10 mg or equivalent) and an IV corticosteroid (prednisolone 100 mg or equivalent). These were administered 30 to 60 minutes prior to the ofatumumab infusion.

Comment: The ofatumumab monotherapy regimen used in Group B is identical to that approved in Australia for refractory CLL.

7.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Survival;
- Change in tumour size (e.g. lymph nodes, spleen, liver);

[8] Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood; 2008; 111: 5446-5456.
[9] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology – Non-Hodgkin's Lymphomas – Version 1.2016.

- Changes in haematological parameters.

The primary efficacy outcome was progression-free survival (PFS) defined as the interval from randomisation to first documentation of either definitive disease progression or death from any cause (whichever occurred earlier).

Secondary efficacy outcomes were:

- Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR);
- Lymph node response (LNR) rate – defined as the proportion of subjects who achieve a ≥50% decrease in the sum of the products of the perpendicular diameters (SPD) of index lymph nodes;
- Overall survival (OS) – defined as the interval from randomisation to death from any cause;
- PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation;
- CR rate – defined as the proportion of subjects who achieve a CR.

Exploratory efficacy outcomes were:

- Time to response (TTR) – defined as the interval from randomisation to the first documentation of confirmed CR or PR;
- Duration of response (DOR) – defined as the interval from the first documentation of confirmed CR or PR to the earlier of a) the first documentation of definitive disease progression or b) death from any cause;
- Percent change in lymph node area – defined as the percent change from baseline in the SPD of index lymph nodes;
- Splenomegaly response rate – defined as the proportion of subjects with a 50% decrease from baseline (minimum decrease of 2 cm) in the enlargement of the spleen in its longest vertical dimension (LVD) or to ≤ 12 cm by imaging;
- Hepatomegaly response rate – defined as the proportion of subjects with a 50% decrease (minimum decrease of 2 cm) from baseline in the enlargement of the liver in its LVD or to ≤ 18 cm by imaging, or regression to a liver LVD of ≤ 15 cm by physical examination;
- ALC response rate – defined as the proportion of subjects with baseline lymphocytosis (absolute lymphocyte count [ALC] ≥ 4 x 109/L) who achieve an on-study ALC < 4 x 109/L or demonstrate a 50% decrease in ALC from baseline;
- Platelet response rate – defined as the proportion of subjects with baseline thrombocytopenia (platelet count < 100 x 109/L) who achieve an on-study platelet count ≥ 100 x 109/L or demonstrate a ≥ 50% increase in platelet count from baseline without need for supportive care (e.g. transfusion or growth factor). Platelet values within 4 weeks post-baseline were excluded from the platelet response rate evaluation;
- Haemoglobin response rate – defined as the proportion of subjects with baseline anaemia (haemoglobin < 110 g/L) who achieve an on-study haemoglobin ≥ 110 g/L or demonstrate a ≥ 50% increase in haemoglobin from baseline without supportive care (e.g., red blood cell transfusions or growth factor). Haemoglobin values within 4 weeks post-baseline were excluded from the haemoglobin response rate evaluation;
- Neutrophil response rate – defined as the proportion of subjects with baseline neutropenia (absolute neutrophil count [ANC] < 1.5 x 109/L) who achieve an ANC ≥ 1.5 x 109/L or demonstrate a ≥ 50% increase in ANC from baseline without the need for exogenous growth factors. ANC values within 4 weeks post-baseline were excluded from the neutrophil response rate evaluation;

- Change in health-related quality of life (HRQL) based on the Functional Assessment of Cancer Therapy: Leukaemia (FACT-Leu) questionnaire.
- Changes in Karnofsky performance status.

> *Comment: Subjects in the trial were also administered another QoL instrument (the EQ5D). The sponsor considered this to be a pharmacoeconomic endpoint rather than an efficacy endpoint and therefore the results will not be reviewed in this report.*

Tumour response and progression were defined according to IWCLL criteria. An independent review committee (IRC), which was blinded to treatment allocation, reviewed the radiographic and clinical data.

The FACT-Leu questionnaire has two parts – a general measure of quality of life (the FACT-G) containing 27 questions in four domains - Physical Well-Being (PWB - 7 items), Social/Family Well-Being (SFWB - 7 items), Emotional Well-Being (EWB - 6 items), and Functional Well-Being (FWB - 7 items) - and a section on 'additional concerns' containing 17 leukaemia-specific items (LeuS). Each of the 44 items is answered using a 5-point scale (0 = 'Not at all' to 4 = 'Very much'). The questions refer to symptoms etc. experienced in the last 7 days. Scores are summed. Hence the range of possible scores for the total FACT-Leu score (44 items) is 0 to 176. High scores indicate better quality of life. The study report focussed on results for the following three scores:

- Trial Outcome Index (TOI, score range: 0-124) = PWB + FWB + LeuS;
- FACT-G Total Score (score range: 0-108) = PWB + SFWB + EWB + FWB;
- Additional concerns (score range: 0-68) = LeuS.

Subjects attended the clinic at weekly intervals up to week 8, then at 4-weekly intervals up to week 24, then 6-weekly intervals up to week 48 and at 12-weekly intervals thereafter until disease progression. At the time of discontinuation from the study, subjects had an end-of-study (EOS) clinic visit and a further visit 30 days after EOS.

Radiological assessment (CT or MRI) of the neck, chest abdomen and pelvis was performed within 6 weeks of randomisation and then at weeks 8, 16 and 24, then at 12 weekly intervals and at EOS. Physical examination (including lymph nodes, liver and spleen) was conducted at weeks 1, 5 and 8 and then at every clinic visit thereafter. Haematology parameters were measured at each clinic visit. Bone marrow biopsy or aspirate was only performed to confirm a CR or progressive disease (PD). FACT-Leu questionnaires were administered, and Karnofsky score recorded, at each study visit.

Subjects who permanently discontinued study drug for a reason other than progressive disease continued with scheduled efficacy assessments until disease progression or another anticancer or experimental therapy was initiated. Long-term follow-up for survival was to be conducted annually for 5 years, either at a clinic visit or via telephone.

7.1.5. Randomisation and blinding methods

Subjects were randomised 2:1 to Group A (combination of idelalisib and ofatumumab 1000 mg) or Group B (ofatumumab 2000 mg). Randomisation was performed centrally in blocks via an interactive web response system (IWRS) and was stratified according to the following factors:

- 17p deletion and/or TP53 mutation in CLL cells: either versus neither (or indeterminate);
- IGHV mutation: unmutated (or IGHV3-21) versus mutated (or indeterminate);
- Disease status: refractory (CLL progression < 6 months from completion of prior therapy) versus relapsed (CLL progression ≥ 6 months from completion of prior therapy).

Subjects and investigators were not blinded to treatment allocation. However, the IRC reviewing the efficacy data was blinded.

7.1.6. Analysis populations

The Intent-to Treat (ITT) Analysis Set included all subjects who were randomised, regardless of whether they received any study drug(s), or received a different regimen from that to which they were randomised. Treatment assignment was designated according to randomization. This population was used for most of the efficacy analyses.

The Per Protocol (PP) Analysis Set included subjects in the ITT Analysis Set who met the general criteria defining the target population for the study, were adherent to the protocol, were compliant with study drug treatment, and were evaluable for relevant efficacy endpoints. Study drug assignment was designated according to the actual treatment received. The PP Analysis Set was used for various sensitivity analyses.

A Safety Analysis Set included subjects who received ≥ 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. This population was used in the analyses of safety.

7.1.7. Sample size

Based on a phase 2 study, it was assumed that median PFS in the ofatumumab monotherapy arm would be approximately 8 months. An improvement in median PFS to 14 months with the addition of idelalisib was selected as the effect size of interest. It was calculated that a total of 129 PFS events would be required for a power of 85% using a log-rank test with a 2-sided significance level of 0.05. Assuming an accrual period of 12 months, a minimum follow-up period of 12 months and a 10% loss of subjects to follow-up, a total of 170 subjects would be required in Group A and 85 subjects in Group B. The planned sample size was therefore 225 subjects.

7.1.8. Statistical methods

For the primary endpoint, the difference in PFS between the treatment arms was tested using a stratified log-rank test, adjusted for the stratification factors. Median PFS and the proportion of subjects who were progression-free at 6 and 12 months were estimated using Kaplan-Meier methods. A hazard ratio and 95% CI were calculated using a Cox proportional hazards regression model. Four exploratory sensitivity analyses were planned to test the robustness of the primary PFS results (an analysis using an unstratified log rank test, an analysis using the Per Protocol Analysis Set, an analysis in which subjects who missed ≥ 2 tumour assessments were not censored and an analysis in which subjects in the combination arm who were lost to follow up were categorized as having had a PFS event). Subgroup analyses of PFS would be assessed using Cox regression modeling. Other PFS endpoints and OS were tested using similar methods.

The final analysis was planned to occur after 129 PFS events. One interim analysis was performed after approximately 75% of the planned 129 events had occurred, and a decision was made to continue the study to the final analysis. The significance level required to reject the null hypothesis at the final analysis was set at $p < 0.044$.

To preserve the overall type I error rate across the primary and secondary endpoints of the study at a 2-sided significance level of 0.05, a hierarchical testing procedure was implemented. Secondary efficacy endpoints would only be tested if the null hypothesis had been rejected for the primary endpoint. Secondary endpoints would be tested in the following order: ORR, LNR rate, OS, PFS in the subgroup with 17p deletion or TP53 mutation, CR rate. Each would be tested only if the null hypothesis had been rejected for the previous endpoint.

Differences between the treatment arms in response rates were compared using Cochran-Mantel-Haenszel (CMH) Chi-square tests after adjusting for stratification factors.

7.1.9. Participant flow

A total of 261 subjects were randomised in the study – 174 to the combination and 87 to ofatumumab monotherapy. At the time of data cut-off 48.3% of subjects in the combination arm were ongoing in the study compared to 6.9% of subjects in the ofatumumab arm.

7.1.10. Major protocol violations/deviations

The overall incidence was the same in the two arms (39.1%). Generally the various types of violation occurred with similar frequency in the two treatment arms. Errors in stratification were the most common violation and these were more common in the ofatumumab arm (27.6% vs. 21.8%). The most common type of stratification error related to reporting of disease status (relapsed vs. refractory) by the investigator at baseline. The primary analysis was performed based on corrected strata (corrected during database clean up but after randomisation). However, additional ad hoc sensitivity analyses were performed, based on strata reported at randomisation. According to the sponsor these ad hoc analyses gave comparable results to the primary analyses.

A total of 12 subjects had protocol violations sufficient to exclude them from the Per Protocol Set – 10 in the combination arm and 2 in the ofatumumab arm.

7.1.11. Baseline data

The incidence of cytopaenias at baseline was comparable between the two arms.

> *Comment: The two treatment arms were reasonably well balanced at baseline with respect to demographic and disease characteristics. However, advanced stage disease (Rai stages III/IV, Binet stage C) was more common in the combination arm, whereas refractory disease was more common in the ofatumumab arm. Consistent with the known natural history of CLL the population was predominantly male and elderly.*

The population was a heavily pre-treated one with a median of three prior regimens. The majority of subjects had previously been treated with rituximab, fludarabine and cyclophosphamide.

> *Comment: Prior treatment was comparable between the two arms.*

7.1.12. Results for the primary efficacy outcome

Results for PFS as assessed by the IRC in the ITT analysis set are summarised in Table 6 and Figure 3. At the time of data cut-off a PFS event had been reported in 130 of the 271 subjects. Treatment with the combination was associated with a statistically significant reduction in the risk of experiencing a PFS event (hazard ratio 0.27; 95% CI: 0.19 to 0.39; $p<0.0001$).

Table 6: Study GS-US-312-0119 – Progression-free survival (primary endpoint).

	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects with Events	76 (43.7)	54 (62.1)
Disease Progression	54 (31.0)	48 (55.2)
Death	22 (12.6)	6 (6.9)
Number (%) of Subjects Censored	98 (56.3)	33 (37.9)
Ongoing	75 (43.1)	4 (4.6)
Discontinued Study without Event	21 (12.1)	29 (33.3)
Missed ≥ 2 Consecutive Tumor Measurements	2 (1.1)	0
KM Estimate of PFS (Months)[a]		
Q1 (95% CI)	9.0 (7.5, 10.8)	3.5 (1.8, 5.3)
Median (95% CI)	16.3 (13.6, 17.8)	8.0 (5.7, 8.2)
Q3 (95% CI)	NR (17.8, NR)	9.2 (8.2, 16.4)
Adjusted HR (95% CI)[b]	0.27 (0.19, 0.39)	
P-value[c]	< 0.0001	

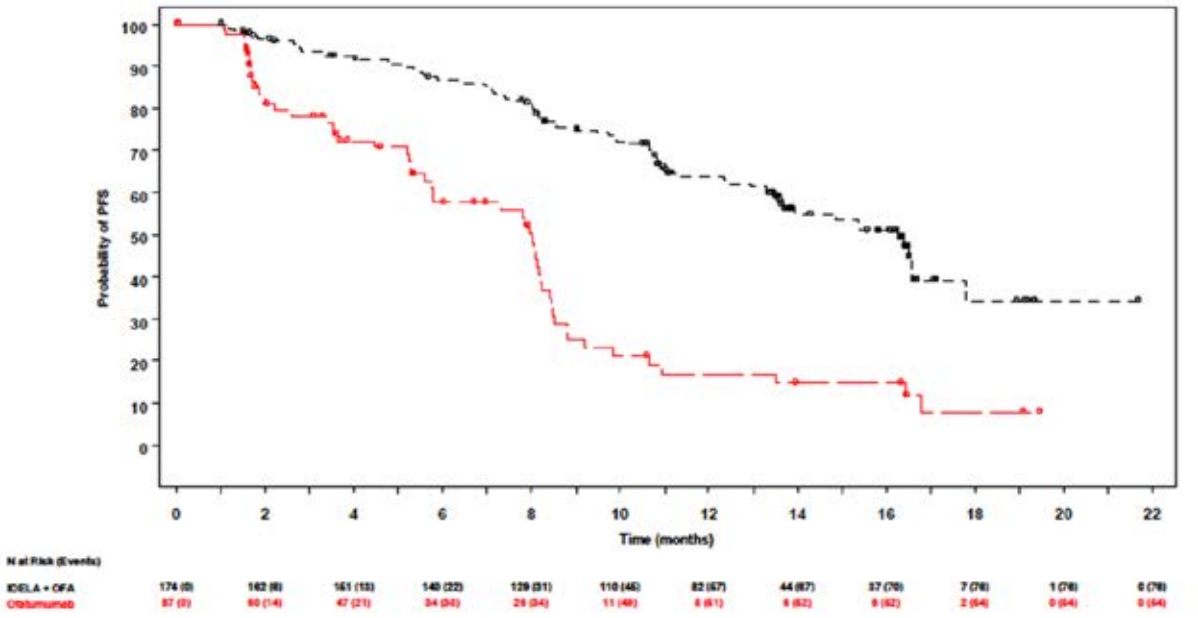
CI = confidence interval; HR = hazard ratio; Id = idelalisib; IRC = independent review committee; NR = not reached; O = ofatumumab; PFS = progression-free survival; Q1 = first quartile; Q3 = third quartile

a PFS (months) = (minimum [date of PD, date of death] – date of randomization + 1) / 30.4375.

b HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation, and disease status).

c P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation, and disease status).

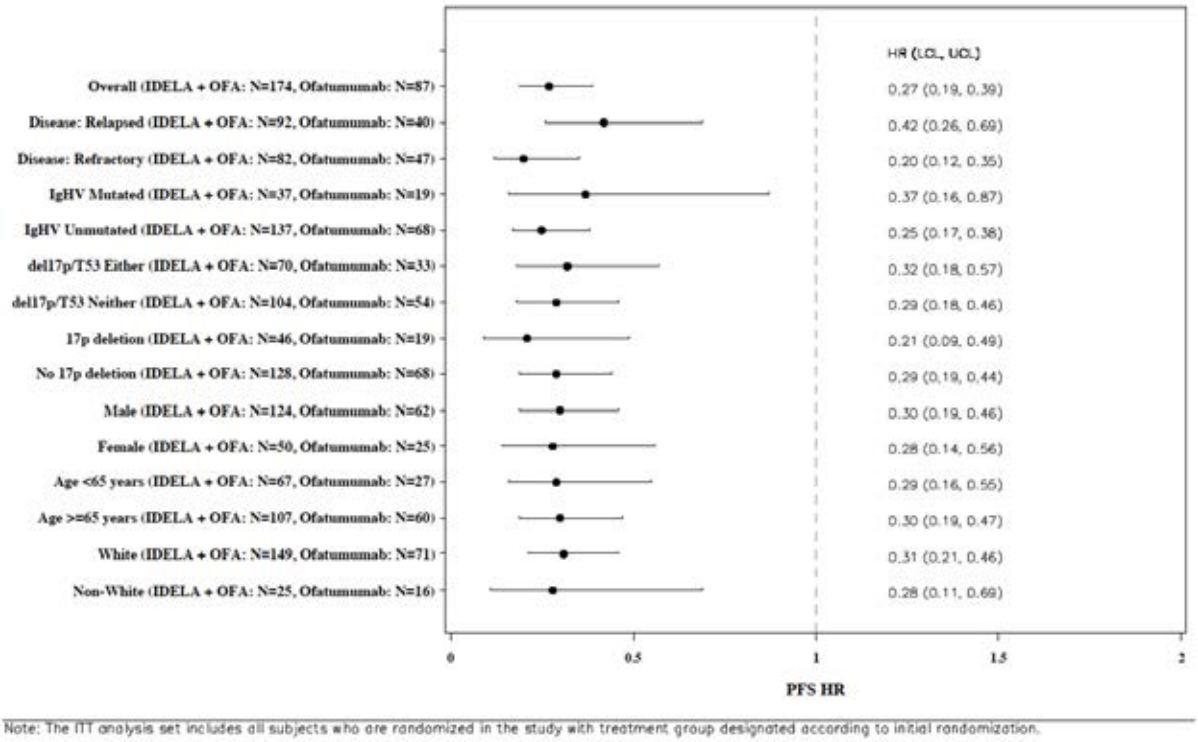
Figure 3: Study GS-US-312-0119 – Progression-free survival (primary endpoint).



Median PFS was increased from 8.0 months to 16.3 months. Estimated PFS rate at 6 months was 86.7% (95% CI: 80.5 to 91.0) for the combination and 57.6% (95% CI: 45.0 to 68.3) for ofatumumab monotherapy. Estimated PFS rate at 12 months was 63.7% (95% CI: 55.5 to 70.7) for the combination and 17.0% (95% CI: 8.3 to 28.2) for ofatumumab monotherapy.

The four planned sensitivity analyses gave comparable results to the primary analysis. Subgroup analyses indicated that the benefit in PFS was consistent across the various subgroups examined (Figure 4).

Figure 4: Study GS-US-312-0119 – Progression-free survival – Subgroup analyses.



Note: The ITT analysis set includes all subjects who are randomized in the study with treatment group designated according to initial randomization.

7.1.13. Results for secondary efficacy outcomes

7.1.13.1. Overall response rate

The ORR was **75.3%** (95% CI: 68.2 to 81.5) in the combination arm and 18.4**%** (95% CI: 10.9 to 28.1) in the ofatumumab arm (Table 7). The difference was statistically significant ($p < 0.0001$). There was only 1 complete response (in the combination arm).

Table 7: Study GS-US-312-0119 – Response rates.

	Id + O (N =174)	O (N = 87)
Best Overall Response, n (%)		
Complete Response (CR)	1 (0.6)	0
Partial Response (PR)	130 (74.7)	16 (18.4)
Stable Disease (SD)	31 (17.8)	51 (58.6)
Progressive Disease (PD)	1 (0.6)	13 (14.9)
Not Evaluable (NE)	11 (6.3)	7 (8.0)
No Disease	0	0
ORR[a]	131 (75.3)	16 (18.4)
95% CI[b]	68.2, 81.5	10.9, 28.1
Odds Ratio for Overall Response[c]	15.94	
95% CI for Odds Ratio	7.8, 32.58	
P-value	< 0.0001	

CI = confidence interval; Id = idelalisib; IRC = Independent Review Committee; O = ofatumumab; ORR = overall response rate
Subjects with CR or PR who maintain the response for at least 8 weeks (with 1 with interval) are defined to have confirmed response for CR or PR. Otherwise, response status is categorized to SD.

a ORR is the percentage of subjects that had best overall response of CR or PR.

b 95% CI for ORR is based on the exact method.

c Odds ratio, 95% CI, and p-value are calculated from the CMH Chi-square test stratified by stratification factors.

7.1.13.2. Lymph node response (LNR) rate

The LNR rate was 93.3**%** (95% CI: 88.3 to 96.6) in the combination arm and only 4.9**%** (95% CI: 1.4 to 12.2) in the ofatumumab arm (Table 8). The difference was statistically significant (p < 0.0001).

Table 8: Study GS-US-312-0119 – Lymph node response rates.

	Id + O (N = 174)	O (N = 87)
LNR Rate[a]	153/164 (93.3)	4/81 (4.9)
95% CI for LNR Rate[b]	88.3, 96.6	1.4, 12.2
Odds Ratio[c]	486.96	
95% CI for Odds Ratio	97.91, 2421.85	
P-value	< 0.0001	

CI = confidence interval; Id = idelalisib; LNR = lymph node response; O = ofatumumab

a LNR rate was defined as the percentage of subjects who achieved a ≥ 50% decreased from baseline in the SPD of index lymph nodes.

b 95% CI for response rate was based on the exact method.

c Odds ratio, 95% CI, and p-value was calculated from the Cochran-Mantel-Haenszel Chi-square test stratified by stratification factors.

7.1.13.3. Overall survival

Results for OS in the ITT analysis set are summarised in Table 9 and Figure 5. OS data were immature with only 64 of 261 subjects (24.5%) having died. There was no statistically significant difference in overall survival between the two treatment arms.

Table 9: Study GS-US-312-0119 – Overall survival.

	Id + O (N = 174)	O (N = 87)
Number (%) of Subjects with Events	42 (24.1)	22 (25.3)
Death	42 (24.1)[a]	22 (25.3)
Number (%) of Subjects Censored	132 (75.9)	65 (74.7)
Ongoing	84 (48.3)	6 (6.9)
Discontinued Study	48 (27.6)	59 (67.8)
KM Estimate of OS (Months)[b]		
Q1 (95% CI)	15.8 (11.4, 20.9)	13 (6.0, 19.4)
Median (95% CI)	20.9 (20.9, NR)	19.4 (16.9, NR)
Q3 (95% CI)	NR (20.9, NR)	NR (19.4, NR)
Adjusted HR (95% CI)	0.74 (0.44, 1.25)	
P-value[c]	0.27	

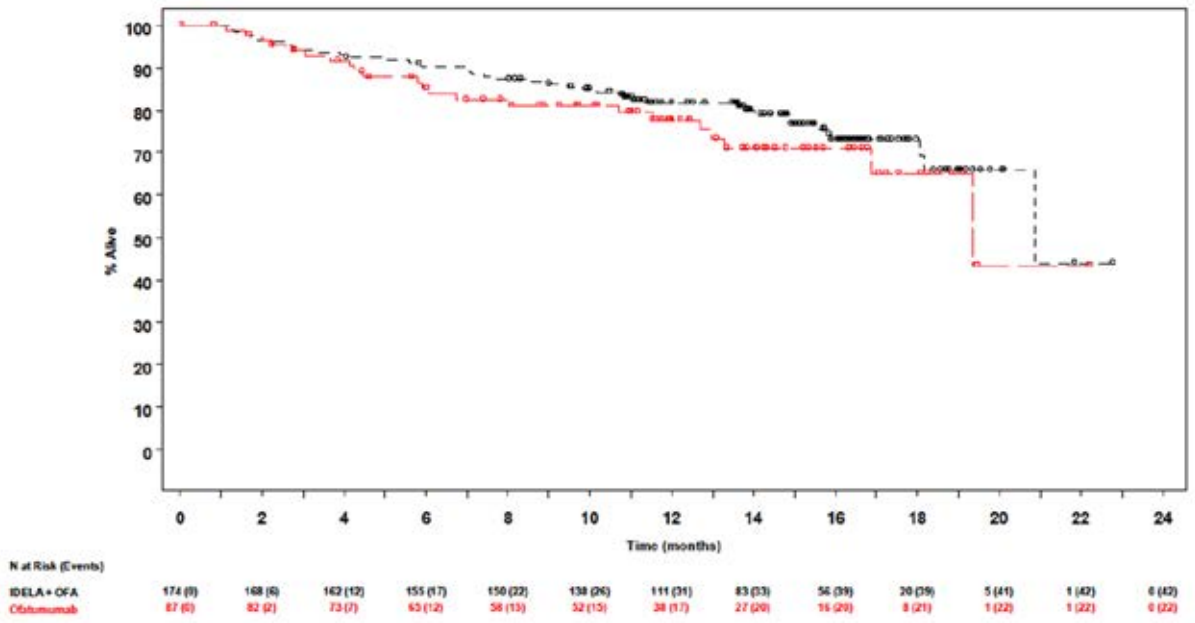
CI = confidence interval; HR = hazard ratio; Id = idelalisib; KM = Kaplan Meier; NR = not reached; O = ofatumumab; OS = overall survival; Q1 = first quartile; Q3 = third quartile

a One subject who died in the idelalisib + ofatumumab group did not receive treatment and therefore is not included in safety analyses.

b OS (months) = (date of death – date of randomization + 1) / 30.4375

c P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation, and disease status).

Figure 5: Study GS-US-312-0119 – Overall survival.



Comment: The study report did not contain any information on subsequent therapies received in subjects who experienced disease progression (e.g. whether subjects in the ofatumumab monotherapy arm with disease progression received idelalisib).

7.1.13.4. PFS in the subgroup of subjects with 17p deletion and/or TP53 mutation

Results for PFS in this subgroup of patients are summarised in Table 10. The incidence of PFS events was numerically lower in the combination arm (50.0% vs. 60.6%). As the null hypothesis for the previous secondary endpoint (OS) had not been rejected, *formal* statistical testing was

not conducted. However, informal testing suggested that the difference between treatment arms was significant (HR = 0.32; 95% CI: 0.18 to 0.57; p < 0.0001) median PFS was prolonged from 5.8 months to 13.7 months.

Table 10: Study GS-US-312-0119 – PFS in subjects with 17p deletion or TP53 mutation.

	Deletion/Mutation: Either		Deletion/Mutation: Neither	
	Id + O N = 70	O N = 33	Id + O N = 104	O N = 54
Number (%) of Subjects with Events	35 (50.0)	20 (60.6)	41 (39.4)	34 (63.0)
Disease Progression	25 (35.7)	16 (48.5)	29 (27.9)	32 (59.3)
Death	10 (14.3)	4 (12.1)	12 (11.5)	2 (3.7)
Number (%) of Subjects Censored	35 (50.0)	13 (39.4)	63 (60.6)	20 (37.0)
Ongoing	27 (38.6)	1 (3.0)	48 (46.2)	3 (5.6)
Discontinued Study without Event	6 (8.6)	12 (36.4)	15 (14.4)	17 (31.5)
Missed ≥ 2 Consecutive Tumor Measurements	2 (2.9)	0	0	0
KM Estimate of PFS (Months)[a]				
Q1 (95% CI)	8.6 (5.4, 11)	2.6 (1.7, 5.3)	9.5 (7.4, 11.4)	3.6 (1.7, 7.3)
Median (95% CI)	13.7 (11, 17.8)	5.8 (4.5, 8.4)	16.4 (13.9, NR)	8.1 (5.6, 8.5)
Q3 (95% CI)	17.8 (16.5, NR)	8.5 (8, NR)	NR (NR, NR)	9.9 (8.2, 16.4)
Unadjusted HR (95% CI)[b]	0.32 (0.18, 0.57)		0.29 (0.18, 0.46)	
P-value	< 0.0001		NA	

CI = confidence interval; HR = hazard ratio; Id = idelalisib; NR = not reached; O = ofatumumab; Q1 = first quartile; Q3 = third quartile

a PFS (months) = (mininum [date of PD, date of death] – date of randomization + 1) / 30.4375.

b HR and 95% CIs are calculated using the Cox proportional hazards model without any adjustment

7.1.13.5. CR rate

As there was only one complete response this endpoint was not analysed.

7.1.14. Results for exploratory efficacy outcomes

7.1.14.1. Time to response

Median time to response was 1.7 months in both arms.

7.1.14.2. Duration of response

Median duration of response was 14.9 months (95% CI: 12.9 to not reached) in the combination arm and 6.7 months (95% CI: 5.6 to 15.0) in the ofatumumab arm.

7.1.14.3. Percent change in lymph node area

Results for this endpoint are summarised in Table 11. At baseline, mean lymph node area was greater in the ofatumumab group (8455.6 vs. 6528.3 mm^2). After treatment, mean best percent reduction in lymph node area was greater in the combination arm (-72.1% vs. -11.2%).

Table 11: Study GS-US-312-0119 – Best percentage change in lymph node SPD.

	Id + O (N = 174)	O (N = 87)
Baseline		
N	174	87
Mean (StD)	6528.3 (6391.95)	8455.6 (7344.48)
Median	4823.0	6336.7
Q1, Q3	2532.8, 8166.1	3253.0, 11333.9
Min, Max	298.1, 44383.3	343.7. 35241.1
Best % Change		
N	164	81
Mean (StD)	-72.1 (13.63)	-11.2 (31.64)
Median	-74.6	-13.1
Q1, Q3	-82.5, -65.0	-29.3, 0.1
Min, Max	-94.5, -16.4	-73.6, 140.0

Id = idelalisib; IRC = independent review committee; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; SPD = sum of the products of greatest perpendicular diameters; StD = standard deviation
The tumor measurement from the first reader was used, unless the adjudicator picked the second reader.
Baseline was defined as the last measurement before randomization.
The best percent change from baseline was defined as the largest decrease in SPD postbaseline. For subjects who had SPD increases only, the smallest increase was considered the best change from baseline.

7.1.14.4. Splenomegaly and hepatomegaly response rates

Results are summarised in Table 12. A greater proportion of subjects in the combination arm achieved significant reductions in both spleen and liver size, compared with the ofatumumab arm.

Table 12: Study GS-US-312-0119 – Splenomegaly and hepatomegaly response rates.

	Id + O (N = 174)	O (N = 87)
Splenomegaly Response Rate[a]	100/122 (82.0%)	24/56 (42.9%)
95% CI[b]	74, 88.3	29.7, 56.8
Hepatomegaly Response Rate[c]	56/86 (65.1%)	11/44 (25.0%)
95% CI[b]	54.1, 75.1	13.2, 40.3

CI = confidence interval; Id = idelalisib; O = ofatumumab

a Analysis included only subjects in the ITT Analysis Set who had splenomegaly at baseline and had at least 1 evaluable postbaseline spleen measurement. Responders were subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the spleen in its LVD or to ≤ 12 cm by imaging.

b 95% CI for the response rate was based on the exact method.

c Analysis only included subjects who had hepatomegaly at baseline and at least 1 evaluable postbaseline liver measurement.Hepatomegaly response rate was the percentage of subjects with a 50% decrease (minimum 2 cm) from baseline in the enlargement of the liver in its LVD or to ≤ 18 cm by imaging.

LVD = longest vertical dimension

7.1.14.5. Responses in haematological parameters

Results are summarised in Table 13. For each of the four haematology parameters, a greater proportion of subjects in the combination arm achieved a response compared with the ofatumumab arm.

Table 13: Study GS-US-312-0119 – Haematology parameter response rates.

	Id + O (N = 174)	O (N = 87)
ALC Response Rate[a]	139/143 (97.2%)	60/68 (88.2%)
95% CI[b]	93, 99.2	78.1, 94.8
Platelet Response Rate[c]	88/93 (94.6%)	34/43 (79.1%)
95% CI[b]	87.9, 98.2	64, 90
Hemoglobin Response Rate[d]	65/73 (89.0%)	21/42 (50.0%)
95% CI[b]	79.5, 95.1	34.2, 65.8
ANC Response Rate[e]	31/32 (96.9%)	14/22 (63.6%)
95% CI[b]	83.8, 99.9	40.7, 82.8

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; CI = confidence interval; Id = idelalisib; O = ofatumumab

a Analysis included subjects who had lymphocytosis (ALC $\geq 4 \times 10^9$/L) at baseline. Responders were subjects with baseline lymphocytosis who achieved on-study ALC $< 4 \times 10^9$/L or $\geq$ 50% decrease in ALC from baseline.

b 95% CI for the response rate was based on the exact method.

c Analysis included subjects who had thrombocytopenia (platelet count $< 100 \times 10^9$/L) at baseline. Responders were subjects with baseline thrombocytopenia who achieved on-study platelet count of $\geq 100 \times 10^9$/L or $\geq$ 50% increase in platelet count from baseline.

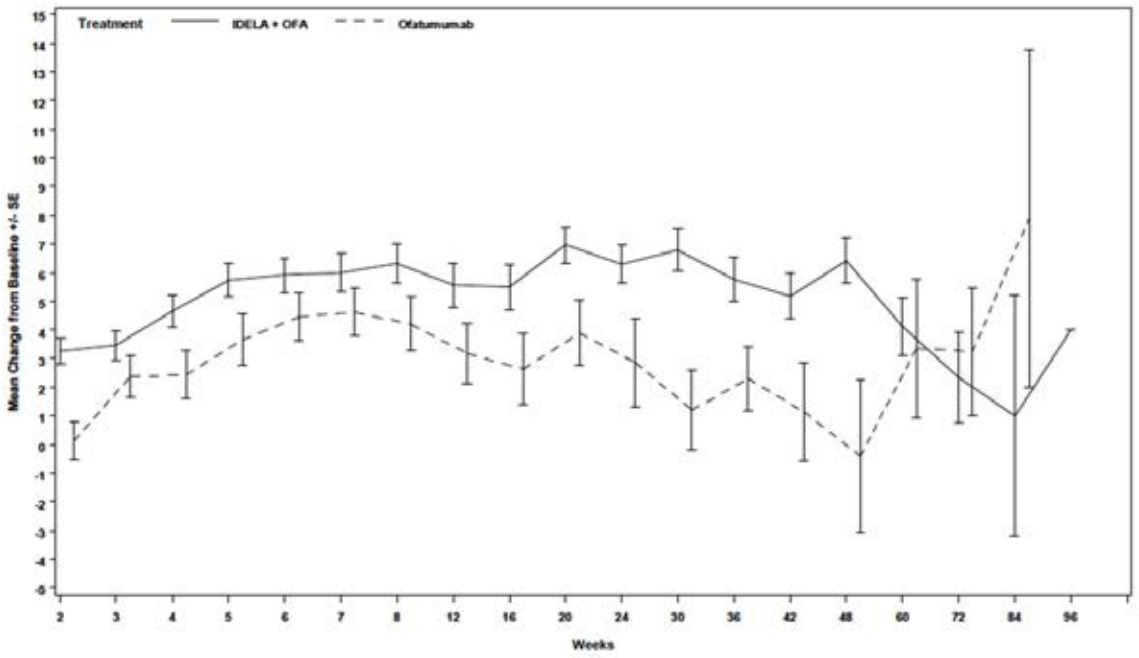
d Analysis included subjects who had anemia (hemoglobin < 110 g/L [11 g/dL]) at baseline. Responders were subjects with baseline anemia who achieved on-study hemoglobin $\geq$ 110 g/L (11 g/dL) or $\geq$ 50% increase in hemoglobin from baseline.

e Analysis included subjects in the ITT Analysis Set who had neutropenia (ANC $< 1.5 \times 10^9$/L) at baseline. Responders were subjects with baseline neutropenia who achieved on-study ANC of $\geq 1.5 \times 10^9$/L or $\geq$ 50% increase in ANC from baseline.

7.1.14.6. FACT-Leu questionnaire

The study report focussed on results for the Trial Outcome Index (TOI) composite score, the FACT-G Total Score and the Additional Concerns subscale (LeuS). For the Additional Concerns score, the percent change from baseline is illustrated in Figure 6, and the differences between the arms over time are summarised in14. The potential range of scores is 0-68. At baseline the mean score was 46.3 (± 10.9) in the combination arm and 45.7 (± 9.9) in the ofatumumab arm. Symptoms improved in both arms, with greater improvement in the combination arm. A similar pattern was seen with the TOI score and FACT-G total score.

Figure 6: Study GS-US-312-0119 – FACT-Leu questionnaire – Additional concerns (LeuS) subscale - change from baseline.



OFA = ofatumumab; SE = standard error

Table 14: Study GS-US-312-0119 – FACT-Leu questionnaire – Additional concerns (LeuS) subscale.

		Estimate (IDELA+OFA over Ofatumumab)	SE	P-value
ADDITIONAL CONCERNS				
Least Squares Means	Week 2	3.1	1.08	0.0039
	Week 3	1.4	1.09	0.1909
	Week 4	2.5	1.10	0.0224
	Week 5	2.1	1.10	0.0537
	Week 6	1.5	1.10	0.1715
	Week 7	1.4	1.11	0.2190
	Week 8	2.2	1.12	0.0510
	Week 12	2.7	1.13	0.0153
	Week 16	2.3	1.20	0.0573
	Week 20	2.7	1.20	0.0254
	Week 24	3.2	1.24	0.0094
	Week 30	5.1	1.27	0.0001
	Week 36	3.2	1.32	0.0164
	Week 42	5.4	1.38	0.0001
	Week 48	6.6	1.51	0.0000
	Week 60	1.0	1.92	0.5883
	Week 72	1.2	2.14	0.5600
Type 3 Test for Fixed Effect	Treatment			0.0016
	Weeks			0.0000
	Interaction			0.0051

Note: The ITT analysis set includes all subjects who are randomized in the study with treatment group designated according to initial randomization.
FACT-Leu Total Score = PWB + SWB + EWB + FWB + LeuS, where PWB - Physical well-being, SWB - Social well-being, EWB - Emotional well-being, FWB - Functional well-being, LeuS - additional concerns (Leukemia-Specific Subscale)
Trial Outcome Index (TOI) = PWB + FWB + LeuS, where PWB - Physical well-being, FWB - Functional well-being, LeuS - additional concerns (Leukemia-Specific Subscale)
Results are from mixed effects model with treatment arm, study weeks (week 2 to week 48), interaction of treatment by study weeks and stratification factors as covariates.

Comment: According to the sponsor the minimally important difference (MID) for the Additional Concerns score is 5 points. This cut-off was apparently based on a published study conducted in patients with chronic myeloid leukaemia. As shown in Table 14, the difference between the treatment arms was less than 5 points for most study visits.

Therefore, although improvement in symptoms was greater in the combination arm, the difference is unlikely to be clinically significant. It is noted that the sponsor is not seeking to make any claims regarding improved quality of life in the product information.

7.1.14.7. Karnofsky score

Average Karnofsky score improved in both arms, to a similar extent (Table 15).

Table 15: Study GS-US-312-0119 – Karnofsky score.

		Id + O (N = 174)		O (N = 87)	
	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline	n	173		87	
	Mean (StD)	84.2 (10.34)		82.9 (9.75)	
	95% CI	(82.6, 85.7)		(80.8, 85.0)	
	Median	80.0		80.0	
	Q1, Q3	80.0, 90.0		80.0, 90.0	
	Min. Max	60.0, 100.0		60.0, 100.0	
Best Change from Baseline[a]	n	173	173	86	86
	Mean (StD)	92.1 (8.78)	7.8 (9.57)	89.4 (9.62)	6.6 (9.02)
	95% CI	(90.8, 93.4)	(6.4, 9.2)	(87.4, 91.5)	(4.7, 8.6)
	Median	90.0	10.0	90.0	10.0
	Q1, Q3	90.0, 100.0	0.0, 10.0	90.0, 100.0	0.0, 10.0
	Min. Max	50.0, 100.0	-20.0, 40.0	60.0, 100.0	-20.0, 40.0

CI = confidence interval; Id = idelalisib; O = ofatumumab; Q1 = first quartile; Q3 = third quartile; StD = standard deviation

a Best change from baseline is defined as the highest value of change from baseline among all post-baseline visits.

7.2. Other efficacy studies

7.2.1. Study 101-07

This study is an ongoing phase 1, open-label trial. It included subjects with CLL, indolent non-Hodgkin's lymphoma (iNHL) or mantle cell lymphoma (MCL). Subjects were required to have relapsed or refractory disease. This study was reviewed in the clinical evaluation of the original submission for the registration of idelalisib. In the current submission, the sponsor provided an updated study report. The original report was dated 24 July 2013 and the updated report was dated 17 February 2015.

The study enrolled multiple separate cohorts of patients to explore the efficacy and safety of idelalisib when used in combination with a variety of other agents (rituximab, ofatumumab, bendamustine, fludarabine, everolimus, bortezomib, chlorambucil and lenalidomide) in the treatment of the three diseases. Overall, 241 subjects were enrolled. In one of the cohorts, subjects with relapsed or refractory CLL were treated with a combination of idelalisib and ofatumumab. Only the results for this cohort are reviewed in this report.

The cohort enrolled 21 subjects, 13 with relapsed disease and 8 with refractory disease. Median time since diagnosis was 6.5 years. Seven subjects (33.0%) had 17p deletion or TP53 mutation. The median number of prior treatment regimens was 2.0. Subjects were treated with idelalisib 150 mg BD. The ofatumumab dose regimen was identical to that used in the pivotal study (initial 300 mg dose, then 1000 mg per dose for a further 11 doses over 24 weeks).

Efficacy results for the cohort are summarised in Table 16.

Table 16: Study 101-07 – Efficacy results (Idelalisib + ofatumumab cohort).

N	21
Complete response, n (%)	2 (9.5)
Partial response, n (%)	13 (61.9)
Stable disease, n (%)	5 (23.8)
Progressive disease, n (%)	0
Not done, n (%)	1 (4.8)
Overall response rate, n (%)	15 (71.4)
95% CI	47.8 – 88.7
Duration of response (months), median (95% CI)	NR (3.5 – NR)
Time to response (months), median (Q1, Q3)	1.9 (1.9 – 2.3)
Progression-free survival (months), median (95% CI)	NR (8.7 – NR)
Overall survival (months), median (95% CI)	NR (NR – NR)
Lymph Node response rate n (%)	17 (81.0)
95% CI	58.1 – 94.6

CI=confidence interval; NR=not reached; Q=quartile.

Comment: The overall response rate seen in this study (71.4%) is comparable to that seen in the pivotal study (75.3%). The efficacy results for this cohort in the updated study report are essentially unchanged from those in the original study report.

7.3. Analyses performed across trials (pooled & meta analyses)

In the Summary of Clinical Efficacy of the submission, the sponsor presented analyses of efficacy endpoints for pooled data from studies GS-US-312-0116 (combination with rituximab) and GS-US-312-0119 (combination with ofatumumab). As the question raised by the current application is the efficacy of the ofatumumab combination only, these analyses are not considered directly relevant to this review.

Both studies demonstrated a highly statistically significant effect of idelalisib on the primary endpoint of PFS. The pooled analysis of PFS gave a consistent result (HR=0.21; $p < 0.0001$). When the results of the extension study GS-US-312-0117 were included in an analysis, a beneficial effect of idelalisib on overall survival was suggested (Table 17). However, the data were not yet mature.

Table 17: Pooled analysis of overall survival.

Studies GS-US-312-0116, GS-US-312-0117, and GS-US-312-0119
Pooled: OS (ITT Analysis Set)

	Id+Anti-CD20 (N = 284)	Anti-CD20 (N = 197)
Number (%) of Subjects Who Died	63 (22.2)	65 (33.0)
Number (%) of Subjects Censored	221 (77.8)	132 (67.0)
Ongoing	132 (46.5)	34 (17.3)
Completed/Discontinued Study	89 (31.3)	98 (49.7)
KM Estimate of OS (Months) [a]		
Q1 (95% CI)	18.1 (14.9, 23.5)	10.7 (8, 13.3)
Median (95% CI)	NR (23.5, NR)	21 (18.1, NR)
Q3 (95% CI)	NR (NR, NR)	NR (NR, NR)
Adjusted Hazard Ratio (95% CI) [b]	0.53 (0.37, 0.75)	
P-value From Stratified Log-Rank Test [c]	0.0004	
P-value From Unstratified Log-Rank Test	0.0008	

a Overall survival (months) = (date of death - date of randomization + 1)/ 30.4375
b Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for 17p deletion/TP53 mutation, IGHV mutation, and study.
c P-value is from stratified log-rank test, adjusted for 17p deletion/TP53 mutation, IGHV mutation, and study.

7.4. Other efficacy data included in the submission

The submission included a number of other studies that were not directly relevant to the proposed new indication. The safety data from these studies have been reviewed. One of these studies (Study 101-09) included efficacy data that was relevant to one of the currently approved indications (follicular lymphoma).

Study 101-09 was a phase 2 single-arm trial in 125 subjects with treatment-refractory indolent NHL. Subjects were treated with idelalisib monotherapy (150 mg BD). The primary efficacy variable was response rate. A full study report for this trial was reviewed in the clinical evaluation of the original submission to register idelalisib. In the current submission the sponsor provided a brief update of efficacy data from the study prepared in response to a request from the EMA as a 'post-authorisation measure (PAM)'.

The original and updated results are summarised in Table 18. With longer follow-up, there was a slight increase in response rate.

Table 18: Study 101-09 – Updated efficacy results.

	Original results	Updated results
N (all subjects)	125	125
N (follicular lymphoma)	72	72
Overall response rate, follicular lymphoma - % [95% CI]	54.2 [42.0 – 66.0]	55.6 [43.4 – 67.3]

	Original results	Updated results
Complete response, n (%)	8.3	13.9
Partial response, n (%)	45.8	41.7
Overall response rate, all subjects - % [95% CI]	56.8 [47.6 – 65.6]	57.6 [48.4 – 66.4]
Duration of response, all subjects - (months), median	12.5	12.5

7.5. Evaluator's conclusions on clinical efficacy

The pivotal efficacy study was well designed and executed. The study design was consistent with the recommendations of the relevant EMA guidelines adopted by the TGA. The study demonstrated a statistically significant improvement in efficacy when idelalisib was combined with ofatumumab, compared to ofatumumab monotherapy. The magnitude of the efficacy benefit was clinically significant with a doubling of median PFS (16.3 versus 8.0 months) and a 3.7 fold increase in the proportion of subjects alive and free of progressive disease at 12 months (63.7% versus 17.0%). A PFS benefit was observed consistently across the various subgroups examined including those subjects with an adverse prognosis due to the presence of a 17p deletion or TP53 mutation.

The sponsor is proposing that the combination of idelalisib with ofatumumab should be approved for use as first line therapy in subjects with 17p deletion or TP53 mutation. The submitted efficacy studies did not examine the efficacy of the combination in the first line setting. However, efficacy was demonstrated in this subgroup in the setting of relapsed/refractory disease. It is possible that efficacy may be superior in the first line setting where the disease would be expected to be less treatment resistant. Given that disease with 17p deletion or TP53 mutation responds poorly to conventional first line chemoimmunotherapy, it is considered reasonable to extrapolate the efficacy data into the first line setting for this subgroup. It is noted that idelalisib is already approved for use in combination with rituximab in the first line setting for these patients.

Table 19 shows a comparison of the PFS results obtained in Study GS-US-312-0119 with those obtained in Study GS-US-312-0116, the pivotal study that led to the approval of idelalisib in combination with rituximab in CLL. Although both studies were conducted in subjects with relapsed CLL, the inclusion criteria and baseline characteristics of subjects were different and as a result any conclusions regarding comparative efficacy based on cross-trial comparison are likely to be unreliable.

Table 19: Comparison of PFS results in studies GS-US-312-0119 and GS-US-312-0116.

	GS-US-312-0119		GS-US-312-0116	
	Idelalisib + Ofatumumab	Ofatumumab	Idelalisib + Rituximab	Rituximab
% of subjects with PFS event	43.7%	62.1%	22.7%	63.6%
Median PFS – months (95% CI)	16.3 (13.6, 17.8)	8.0 (5.7, 8.2)	19.4 (12.3 – NR)	6.5 (4.0, 7.3)
Adjusted HR (95% CI)	0.27 (0.19 – 0.39)		0.15 (0.09 – 0.24)	
p-value	< 0.0001		= 1.6×10^{-16}	

Study 101-07 provided some supportive evidence of efficacy with an overall response rate comparable to that seen in the pivotal study.

Updated efficacy data from study 101-09 in subjects with indolent NHL were consistent with the original data.

8. Clinical safety

Idelalisib is known to be associated with the following toxicities, as described in the current PI:

- Hepatotoxicity;
- Gastrointestinal toxicity (diarrhoea, colitis, intestinal perforation);
- Pneumonitis;
- Cutaneous reactions;
- Cytopaenias;
- Infections (possibly including reactivation of hepatitis infection and progressive multifocal leukoencephalopathy).

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data relevant to the proposed new indication (treatment of relapsed CLL with idelalisib in combination ofatumumab):

8.1.1. Pivotal efficacy study

In the pivotal efficacy study, the following safety data were collected:

- Data on general adverse events (AEs) were collected at each study visit, including the EOS visit and the 30-day follow-up visit. Subjects were asked an open-ended question regarding new health problems. An AE was defined as any untoward medical occurrence in a subject. AEs were assessed as either related or not related to study drug and were graded using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

- The following were considered AEs of particular interest: diarrhoea and/or colitis, rash, pneumonitis, pneumonia, bowel perforation, anaphylaxis, PML, Richter's transformation and second malignancies.
- Laboratory tests, including haematology and biochemistry, were performed at each study visit. Urinalysis and ECGs were not routinely monitored during the study.
- Oxygen saturation by pulse oximetry was measured at each study visit. Other vital signs such as temperature, pulse and blood pressure were not systematically monitored during the study.

8.1.2. Study 101-07

Safety monitoring similar to that in the pivotal study was undertaken in this trial.

8.2. Patient exposure

8.2.1. Pivotal efficacy study

Median duration of exposure to idelalisib was 12.3 months. A total of 134 subjects were exposed for at least 6 months and 90 subjects for at least 12 months.

The planned dosing regimen for both arms involved a total of 12 doses with the final dose being given at week 24 (i.e. a planned duration of exposure of approximately 6 months). Median duration of exposure was 5.3 months in the combination arm and 4.2 months in the ofatumumab monotherapy arm.

> *Comment: Duration of exposure to treatment was considerably longer for subjects in the combination arm, and reporting of AEs would therefore have continued for a longer period. Crude incidence figures for AEs would therefore be expected to be higher in the combination arm.*

8.2.2. Study 101-07

A total of 21 subjects were treated with the combination of idelalisib with ofatumumab. Median duration of exposure to idelalisib was 10.6 months. 15 subjects were exposed for at least 6 months and 1 subject for at least 12 months.

8.3. Adverse events

An overall summary of the incidence of AEs that occurred in the pivotal study is shown in Table 20. Exposure-adjusted incidence is summarised in Table 21.

Table 20: Study GS-US-312-0119 – Overall incidence of AEs.

Adverse Event Category, n (%)	Id + O (N = 173)	O (N = 86)
Any AE	172 (99.4)	85 (98.8)
≥ Grade 3 AE	152 (87.9)	48 (55.8)
Idelalisib-Related AE	155 (89.6)	NA
≥ Grade 3 Idelalisib-Related AE	116 (67.1)	NA
Ofatumumab-Related AE	136 (78.6)	67 (77.9)
≥ Grade 3 Ofatumumab-Related AE	82 (47.4)	29 (33.7)
AE Related to both Idelalisib and Ofatumumab	102 (59.0)	NA
Any SAE	121 (69.9)	36 (41.9)
Idelalisib-Related SAE	73 (42.2)	NA
Ofatumumab-Related AE	39 (22.5)	17 (19.8)
AE That Led to Idelalisib Dose Reduction	35 (20.2)	NA
AE That Led to Idelalisib Dose Interruption	93 (53.8)	NA
AE That Led to Idelalisib Dose Interruption/Reduction	97 (56.1)	NA
AE That Led to Idelalisib Discontinuation	53 (30.6)	NA
AE That Led to Ofatumumab Delayed	79 (45.7)	20 (23.3)
AE That Led to Ofatumumab Discontinuation	16 (9.2)	20 (23.3)
Death due to AE	18 (10.4)	6 (7.0)

AE = adverse event; Id = idelalisib; NA = not applicable; O = ofatumumab; SAE = serious adverse event
Relationship to idelalisib is determined by investigator; AEs with missing relationships are considered to be related.

Table 21: Study GS-US-312-0119 – Overall incidence of AEs (exposure-adjusted).

	Id + O (N = 173)			O (N = 86)		
	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)
Any AE	172	12.4	13.89 (11.89, 16.13)	85	3.8	22.48 (17.96, 27.80)
≥ Grade 3 AE	152	63.2	2.41 (2.04, 2.82)	48	21.9	2.19 (1.62, 2.91)
Idelalisib-Related AE	155	44.7	3.47 (2.94, 4.06)	NA	NA	NA
≥ Grade 3 Idelalisib-Related AE	116	97.8	1.19 (0.98, 1.42)	NA	NA	NA
Ofatumumab-Related AE	136	46.5	2.93 (2.45, 3.46)	67	11.1	6.03 (4.67, 7.66)
≥ Grade 3 Ofatumumab-Related AE	82	105.1	0.78 (0.62, 0.97)	29	26.1	1.11 (0.74, 1.59)
AE Related to both Idelalisib and Ofatumumab	102	81.9	1.25 (1.02, 1.51)	NA	NA	NA
Any SAE	121	105.9	1.14 (0.95, 1.37)	36	25.7	1.40 (0.98, 1.94)
Idelalisib-Related SAE	73	133.3	0.55 (0.43, 0.69)	NA	NA	NA
Ofatumumab-Related AE	39	145.4	0.27 (0.19, 0.37)	17	29.6	0.57 (0.33, 0.92)
AE That Led to Idelalisib Dose Reduction	35	150.2	0.23 (0.16, 0.32)	NA	NA	NA
AE That Led to Idelalisib Dose Interruption	93	105.8	0.88 (0.71, 1.08)	NA	NA	NA
AE That Led to Idelalisib Dose Interruption/Reduction	97	104.4	0.93 (0.75, 1.13)	NA	NA	NA
AE That Led to Idelalisib Discontinuation	53	167.9	0.32 (0.24, 0.41)	NA	NA	NA
AE That Led to Ofatumumab Delayed	79	107.7	0.73 (0.58, 0.91)	20	27.8	0.72 (0.44, 1.11)
AE That Led to Ofatumumab Discontinuation	16	170.6	0.09 (0.05, 0.15)	20	31.6	0.63 (0.39, 0.98)
Death due to AE	18	172.6	0.10 (0.06, 0.16)	6	32.5	0.18 (0.07, 0.40)

AE = adverse event; Id = idelalisib; NA = not applicable; O = ofatumumab; SAE = serious adverse event

a The total exposure time of all subjects (T) was calculated as $T = \sum t_i$ where t_i was the i^{th} subject exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

AE was classified by PT using MedDRA version 17.1.

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal study

The incidence of AEs was high in both arms – 99.4**%** in the combination arm and 98.8**%** in the ofatumumab arm. Common AEs (those with an incidence ≥ 10%) are listed in Table 22. AEs that

were notably more common in the idelalisib arm included diarrhoea, abdominal pain, cytopaenias, rash and hypokalaemia.

Table 22: Study GS-US-312-0119 – Common AEs (incidence ≥ 10%).

Adverse Events by System Organ Class and Preferred Term	Id + O (N = 173) n (%)	O (N = 86) n (%)
Infections and Infestations	132 (76.3)	51 (59.3)
Pneumonia	30 (17.3)	11 (12.8)
Upper respiratory tract infection	31 (17.9)	9 (10.5)
Urinary tract infection	23 (13.3)	6 (7.0)
Sinusitis	19 (11.0)	2 (2.3)
Bronchitis	19 (11.0)	0
Gastrointestinal Disorders	124 (71.7)	51 (59.3)
Diarrhoea	83 (48.0)	20 (23.3)
Nausea	52 (30.1)	23 (26.7)
Constipation	36 (20.8)	13 (15.1)
Vomiting	25 (14.5)	12 (14.0)
Abdominal pain	26 (15.0)	6 (7.0)
General Disorders and Administration Site Conditions	122 (70.5)	56 (65.1)
Fatigue	55 (31.8)	24 (27.9)
Pyrexia	56 (32.4)	20 (23.3)
Oedema peripheral	29 (16.8)	9 (10.5)
Chills	24 (13.9)	13 (15.1)
Asthenia	23 (13.3)	10 (11.6)
Blood and Lymphatic System Disorders	96 (55.5)	28 (32.6)
Neutropenia	61 (35.3)	14 (16.3)
Anaemia	34 (19.7)	9 (10.5)
Thrombocytopenia	22 (12.7)	6 (7.0)
Febrile neutropenia	22 (12.7)	3 (3.5)
Respiratory, Thoracic and Mediastinal Disorders	95 (54.9)	38 (44.2)
Cough	52 (30.1)	18 (20.9)
Dyspnoea	29 (16.8)	10 (11.6)
Skin and Subcutaneous Tissue Disorders	89 (51.4)	30 (34.9)
Rash	34 (19.7)	7 (8.1)
Pruritus	19 (11.0)	6 (7.0)
Night sweats	7 (4.0)	10 (11.6)
Metabolism and Nutrition Disorders	80 (46.2)	20 (23.3)
Decreased appetite	30 (17.3)	7 (8.1)
Hypokalaemia	25 (14.5)	4 (4.7)
Nervous System Disorders	77 (44.5)	30 (34.9)
Headache	33 (19.1)	9 (10.5)
Musculoskeletal and Connective Tissue Disorders	73 (42.2)	32 (37.2)
Back pain	23 (13.3)	11 (12.8)
Investigations	76 (43.9)	18 (20.9)
Weight decreased	18 (10.4)	5 (5.8)
Injury, Poisoning and Procedural Complications	53 (30.6)	32 (37.2)
Infusion related reaction	29 (16.8)	23 (26.7)
Psychiatric Disorders	50 (28.9)	19 (22.1)
Insomnia	27 (15.6)	13 (15.1)

Id = idelalisib; O = ofatumumab
AE was classified by PT using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT (or SOC) were counted once per PT (or SOC).

The sponsor also presented data on the incidence rate of AEs adjusted for exposure time. According to this analysis the incidence rates for individual AE terms were generally comparable for the two treatment arms. Events that were more common in the combination arm (by a margin of at least 0.05 events per year) were:

- Bronchitis (0.12 events/year vs. 0.00 events/year);
- Dehydration (0.09 vs. 0.00);
- Colitis (0.08 vs. 0.00);
- Oral candidiasis (0.07 vs. 0.00);
- Productive cough (0.07 vs. 0.00);
- Maculo-papular rash (0.07 vs. 0.00);
- Sinusitis (0.12 vs. 0.06); and
- Pneumonitis (0.06 vs. 0.00).

8.3.1.2. Study 101-07

All 21 subjects (100%) treated with the combination of idelalisib and ofatumumab experienced an adverse event. The most common AEs were diarrhoea (52.4%), cough (42.9%), dyspnoea (33.3%), pyrexia (33.3%), nausea (28.6%), neutropaenia (28.6%) and decreased appetite (23.8%).

8.3.2. Grade ≥ 3 adverse events

8.3.2.1. Pivotal study

The incidence of grade 3 or higher AEs was increased in the combination arm - **87.9%** vs. **55.8%**. Grade 3 or higher AEs occurring in > 2% of subjects are shown in Table 23.

Table 23: Study GS-US-312-0119 – Grade ≥ 3 AEs (incidence > 2%).

System Organ Class Preferred Term	Id + O (N = 173)	O (N = 86)
Subjects with ≥ Grade 3 AE	152 (87.9%)	48 (55.8%)
Blood and lymphatic system disorders	87 (50.3%)	22 (25.6%)
Neutropenia	59 (34.1%)	13 (15.1%)
Anaemia	20 (11.6%)	5 (5.8%)
Febrile neutropenia	20 (11.6%)	3 (3.5%)
Thrombocytopenia	16 (9.2%)	6 (7.0%)
Granulocytopenia	5 (2.9%)	1 (1.2%)
Infections and infestations	60 (34.7%)	24 (27.9%)
Pneumonia	22 (12.7%)	7 (8.1%)
Sepsis	12 (6.9%)	1 (1.2%)
Pneumocystis jirovecii pneumonia	8 (4.6%)	0
Lower respiratory tract infection	4 (2.3%)	2 (2.3%)
Neutropenic sepsis	4 (2.3%)	2 (2.3%)
Urinary tract infection	6 (3.5%)	0
Bronchitis	5 (2.9%)	0
Lung infection	4 (2.3%)	1 (1.2%)
Septic shock	4 (2.3%)	1 (1.2%)
Respiratory tract infection	2 (1.2%)	2 (2.3%)
Progressive multifocal leukoencephalopathy	0	2 (2.3%)
Gastrointestinal disorders	49 (28.3%)	5 (5.8%)
Diarrhoea	30 (17.3%)	1 (1.2%)
Colitis	10 (5.8%)	0
Abdominal pain	5 (2.9%)	0
Investigations	40 (23.1%)	4 (4.7%)
Alanine aminotransferase increased	14 (8.1%)	0
Neutrophil count decreased	11 (6.4%)	2 (2.3%)
Aspartate aminotransferase increased	6 (3.5%)	0
Platelet count decreased	4 (2.3%)	1 (1.2%)
White blood cell count decreased	4 (2.3%)	0

Table 23: Study GS-US-312-0119 – Grade ≥ 3 AEs (incidence > 2%).

System Organ Class Preferred Term	Id + O (N = 173)	O (N = 86)
Metabolism and nutrition disorders	36 (20.8%)	5 (5.8%)
Hypokalaemia	11 (6.4%)	1 (1.2%)
Hyponatraemia	7 (4.0%)	0
Dehydration	6 (3.5%)	0
Hyperglycaemia	5 (2.9%)	0
Respiratory, thoracic and mediastinal disorders	33 (19.1%)	4 (4.7%)
Dyspnoea	7 (4.0%)	1 (1.2%)
Pneumonitis	8 (4.6%)	0
Respiratory failure	4 (2.3%)	1 (1.2%)
General disorders and administration site conditions	26 (15.0%)	8 (9.3%)
Pyrexia	12 (6.9%)	2 (2.3%)
Fatigue	6 (3.5%)	4 (4.7%)
Asthenia	5 (2.9%)	1 (1.2%)
Vascular disorders	11 (6.4%)	2 (2.3%)
Hypotension	7 (4.0%)	1 (1.2%)
Musculoskeletal and connective tissue disorders	10 (5.8%)	1 (1.2%)
Pain in extremity	4 (2.3%)	0
Skin and subcutaneous tissue disorders	9 (5.2%)	2 (2.3%)
Rash maculo-papular	4 (2.3%)	0
Renal and urinary disorders	9 (5.2%)	1 (1.2%)
Renal failure acute	4 (2.3%)	0
Injury, poisoning and procedural complications	6 (3.5%)	4 (4.7%)
Infusion related reaction	4 (2.3%)	1 (1.2%)

Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT (or SOC) are counted once per PT (or SOC) in the highest severity grade.
Severity of AEs is graded according to the CTCAE, Version 4.03.

Comment: Grade 3 or higher diarrhoea and cytopaenias were again more common in the combination arm. Other notable Grade 3 or higher events that were more common in the combination arm included transaminase elevations (ALT: 8.1% vs. 0%; AST: 3.5% vs. 0%), pneumonitis (4.6% vs. 0%) and pneumocystis pneumonia (4.6% vs. 0%).

8.3.2.2. Study 101-07

16 of 21 subjects (76.2%) treated with the combination of idelalisib and ofatumumab experienced a grade 3 or higher AE. Individual Grade ≥ 3 AEs that occurred in more than one subject were neutropaenia (23.8%), pneumonia (14.3%), ALT increase (9.5%) and hyperglycaemia (9.5%)

8.3.3. Treatment-related adverse events (adverse drug reactions)

8.3.3.1. Pivotal study

A total of 89.6**%** of subjects in the combination arm experienced AEs that were assessed as being related to idelalisib. Those occurring in ≥ 5% of subjects are listed in Table 24. The most common events were diarrhoea, neutropaenia and fatigue. 67.1% of subjects experienced grade 3 or higher AEs that were assessed as being related to idelalisib.

Table 24: Study GS-US-312-0119 – AEs related to idelalisib (incidence ≥ 5%).

System Organ Class Preferred Term	Id + O (N = 173)
Number of Subjects with any AE Reported by the Investigator as Related to Idelalisib	155 (89.6)
Gastrointestinal disorders	92 (53.2)
Diarrhoea	57 (32.9)
Nausea	25 (14.5)
Constipation	14 (8.1)
Abdominal pain	13 (7.5)
Colitis	12 (6.9)
General disorders and administration site conditions	54 (31.2)
Fatigue	30 (17.3)
Pyrexia	18 (10.4)
Blood and lymphatic system disorders	53 (30.6)
Neutropenia	31 (17.9)
Febrile neutropenia	12 (6.9)
Thrombocytopenia	10 (5.8)
Anaemia	9 (5.2)
Infections and infestations	50 (28.9)
Pneumonia	12 (6.9)
Skin and subcutaneous tissue disorders	43 (24.9)
Rash	15 (8.7)
Rash maculo-papular	9 (5.2)
Investigations	42 (24.3)
Alanine aminotransferase increased	16 (9.2)
Aspartate aminotransferase increased	11 (6.4)
Neutrophil count decreased	10 (5.8)
Nervous system disorders	38 (22.0)
Headache	13 (7.5)
Dysgeusia	9 (5.2)
Metabolism and nutrition disorders	32 (18.5)
Decreased appetite	12 (6.9)
Respiratory, thoracic and mediastinal disorders	27 (15.6)
Cough	10 (5.8)
Pneumonitis	10 (5.8)[a]

Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT (or SOC) are counted once per PT (or SOC).

a Includes 1 event (in Subject 7570-15440) with the verbatim term "interstitial pneumonitis" that was coded to the preferred term "interstitial lung disease.

The overall incidence of AEs that were assessed as being related to ofatumumab was comparable in the two treatment arms – 78.6**%** in the combination arm and 77.9**%** in the ofatumumab arm. Those occurring in ≥ 5% of subjects are listed in Table 25. Grade 3 or higher events related to ofatumumab were more common in the combination arm (47.4% vs. 33.7%).

Table 25: Study GS-US-312-0119 – AEs related to ofatumumab (incidence ≥ 5%).

System Organ Class Preferred Term	Id + O (N = 173)	O (N = 86)
Number of Subjects with any AE Reported by the Investigator as Related to Ofatumumab	136 (78.6)	67 (77.9)
General Disorders and Administration Site Conditions	57 (32.9)	29 (33.7)
Fatigue	26 (15.0)	11 (12.8)
Pyrexia	17 (9.8)	6 (7.0)
Asthenia	10 (5.8)	7 (8.1)
Chills	8 (4.6)	7 (8.1)
Blood and Lymphatic System Disorders	57 (32.9)	17 (19.8)
Neutropenia	44 (25.4)	11 (12.8)
Febrile neutropenia	11 (6.4)	1 (1.2)
Anemia	6 (3.5)	5 (5.8)
Gastrointestinal Disorders	46 (26.6)	17 (19.8)
Nausea	16 (9.2)	7 (8.1)
Diarrhea	15 (8.7)	6 (7.0)
Constipation	9 (5.2)	2 (2.3)
Skin and Subcutaneous Tissue Disorders	39 (22.5)	13 (15.1)
Rash	13 (7.5)	3 (3.5)
Pruritus	10 (5.8)	4 (4.7)
Injury, Poisoning, and Procedural Complications	27 (15.6)	23 (26.7)
Infusion related reaction	24 (13.9)	23 (26.7)
Nervous System Disorders	29 (16.8)	13 (15.1)
Headache	11 (6.4)	1 (1.2)
Neuropathy peripheral	4 (2.3)	7 (7.0)
Investigations	22 (12.7)	7 (8.1)
Neutrophil count decreased	9 (5.2)	1 (1.2)

AE = adverse event; Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT (or SOC) are counted once per PT (or SOC) in the highest severity grade.
Severity of AEs is graded according to the CTCAE, Version 4.03.

Comment: Although the overall incidence was comparable, there were some differences with respect to individual AE terms. Infusion reactions related to ofatumumab arm were less common in the combination arm (13.9% vs. 26.7%) whereas neutropaenia related to ofatumumab was more common in the combination arm (25.4% vs. 12.8%).

8.3.3.2. Study 101-07

13 of 21 subjects (61.9%) treated with the combination of idelalisib and ofatumumab experienced an AE that was considered related to idelalisib. Individual related AEs that occurred in more than one subject were neutropaenia (14.3%) and pneumonia (9.5%).

8.3.4. Deaths and other serious adverse events

8.3.4.1. Deaths

Pivotal study

A total of 63 treated subjects had died by the time of data cut-off – 41 (23.7%) in the combination arm and 22 (25.6%) in the ofatumumab arm. There were 37 deaths that occurred during study treatment (or within the first 30 days after the last dose). Of these, 29 occurred in the combination arm and 8 in the ofatumumab arm. In 24 of these 37 cases, AEs led to the death. There were 18 subjects with AEs that led to death in the combination arm and 6 subjects in the ofatumumab arm. These adverse events are listed in Table 26.

Table 26: Study GS-US-312-0119 – AEs leading to death.

	IDELA + OFA (N=173)	Ofatumumab (N=86)
Number of Subjects with TEAEs Leading to Death by PT	18 (10.4%)	6 (7.0%)
Preferred Term		
Septic shock	3 (1.7%)	1 (1.2%)
Pneumonia	1 (0.6%)	2 (2.3%)
Sepsis	3 (1.7%)	0
Cardiogenic shock	2 (1.2%)	0
Progressive multifocal leukoencephalopathy	0	2 (2.3%)
Acute myocardial infarction	1 (0.6%)	0
Arrhythmia	1 (0.6%)	0
Atrial fibrillation	1 (0.6%)	0
Candida sepsis	1 (0.6%)	0
Cardiac failure	1 (0.6%)	0
Central nervous system leukaemia	0	1 (1.2%)
Chronic obstructive pulmonary disease	1 (0.6%)	0
Cytomegalovirus viraemia	1 (0.6%)	0
Myocardial infarction	1 (0.6%)	0
Pneumonitis	1 (0.6%)	0
Pulmonary fibrosis	1 (0.6%)	0
Respiratory failure	0	1 (1.2%)
Respiratory tract infection	1 (0.6%)	0
Thrombocytopenia	1 (0.6%)	0

For 9 of the 18 deaths in the combination arm, the AEs leading to death were assessed as being related to idelalisib or the combination of idelalisib and ofatumumab. Most of these deaths were infection-related (pneumonia or sepsis). In two subjects cause of death included pneumonitis or fibrotic lung disease. For 2 of the 6 deaths in the ofatumumab arm the AEs leading to death were assessed as being related to ofatumumab (1 PML and 1 pneumonia).

Study 101-07

Four of the 21 subjects (19.0%) treated with the combination of idelalisib and ofatumumab died while on treatment or within 30 days of their last dose. None of these deaths were assessed as being related to idelalisib.

8.3.4.2. Serious adverse events

Pivotal study

An SAE was defined as an event that resulted in any of the following outcomes:

- Death
- Life-threatening situation (subject was at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Other medically significant events that, based upon appropriate medical judgment may have jeopardized the subject or may have required medical or surgical intervention to prevent one of the outcomes listed above.

The incidence of SAEs was higher in the combination arm - 69.9**%** vs. 41.9**%**. SAEs occurring in > 2% of subjects are shown in Table 27.

Table 27: Study GS-US-312-0119 – Serious AEs (incidence ≥ 2%).

System Organ Class Preferred Term	Id + O (N = 173)	O (N = 86)
Number of Subjects (%) with any SAE	121 (69.9)	36 (41.9)
Pneumonia	20 (11.6)	9 (10.5)
Febrile neutropenia	20 (11.6)	3 (3.5)
Pyrexia	19 (11.0)	1 (1.2)
Diarrhoea	17 (9.8)	0
Neutropenia	13 (7.5)	2 (2.3)
Sepsis	11 (6.4)	1 (1.2)
Anaemia	7 (4.0)	2 (2.3)
Colitis	9 (5.2)	0
Pneumonitis	8 (4.6)[a]	0
Thrombocytopenia	5 (2.9)	2 (2.3)
Urinary tract infection	7 (4.0)	0
Hypotension	5 (2.9)	1 (1.2)
Neutropenic sepsis	4 (2.3)	2 (2.3)
Neutrophil count decreased	6 (3.5)	0
Pneumocystis jirovecii pneumonia	6 (3.5)	0
Abdominal pain	4 (2.3)	1 (1.2)
Atrial fibrillation	3 (1.7)	2 (2.3)
Lower respiratory tract infection	3 (1.7)	2 (2.3)
Respiratory tract infection	3 (1.7)	2 (2.3)
Septic shock	4 (2.3)	1 (1.2)
Bronchitis	4 (2.3)	0
Dehydration	4 (2.3)	0
Dyspnoea	4 (2.3)	0
Lung infection	4 (2.3)	0
Nausea	4 (2.3)	0
Vomiting	4 (2.3)	0
Progressive multifocal leukoencephalopathy	0	2 (2.3)

Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT were counted once per PT.

a. Includes 1 event (in Subject [information redacted]) with the verbatim term "interstitial pneumonitis" that was coded to the preferred term "interstitial lung disease".

Comment: The pattern of SAEs was consistent with that observed for AEs overall, with an increased incidence of GIT toxicity (diarrhoea, colitis), cytopaenias, pneumonitis and some infections (sepsis, UTI, pneumocystis pneumonia) in the combination arm.

Study 101-07

12 of the 21 subjects (57.1%) treated with the combination of idelalisib and ofatumumab experienced an SAE. Individual related SAEs that occurred in more than one subject were pneumonia (9.5%) and pyrexia (9.5%).

8.3.5. Discontinuation due to adverse events

8.3.5.1. Pivotal study

A total of 53 subjects in the combination arm (30.6**%**) discontinued idelalisib due to an AE. AEs leading to discontinuation in at least 2% of subjects are listed in Table 28.

Table 28: Study GS-US-312-0119 –AEs leading to discontinuation of idelalisib (incidence > 2%).

System Organ Class Preferred Term	Id + O (N = 173)
Number of Subjects (%) with AEs Leading to Idelalisib Discontinuation[a]	53 (30.6)
Gastrointestinal Disorders	15 (8.7%)
Diarrhea	11 (6.4%)
Infections and Infestations	12 (6.9%)
Pneumonia	5 (2.9)
Respiratory, thoracic, and mediastinal disorders	7 (4.0)
Pneumonitis	5 (2.9)[b]
Investigations	6 (3.5)
Alanine aminotransferase increased	4 (2.3)

AE = adverse event; Id = idelalisib; O = ofatumumab
AEs are classified using MedDRA version 17.1.
Subjects who experienced multiple events within the same PT were counted once per PT.

a Four subjects had AEs with a study drug action taken of "drug withdrawn," but had other reasons given by the physician for idelalisib withdrawal on the drug discontinuation eCRF (physician decision, withdrawal by subject, progressive disease, and death, respectively).

b Includes 1 event with the verbatim term "interstitial pneumonitis" that was coded to the preferred term "interstitial lung disease."

AEs leading to discontinuation of ofatumumab occurred in 9.2**%** of subjects in the combination arm and 23.3**%** of subjects in the ofatumumab monotherapy arm. The only AE that led to discontinuation in more than 2% of subjects was pneumonia, which occurred in 1.7% of subjects in the combination arm and 3.5% of subjects in the ofatumumab monotherapy arm.

8.3.5.2. Study 101-07

5 of the 21 subjects (23.8%) treated with the combination of idelalisib and ofatumumab discontinued idelalisib treatment due to an AE. These events were colitis, pneumonia, elevated transaminases, acute myeloid leukaemia and neutropaenic sepsis with endocrine disorder.

8.3.6. Adverse events of special interest (pivotal study)

Analyses of exposure-adjusted incidence rates for AEs of special interest are shown in Tables 29-30. Combination treatment was associated with increased incidences of grade ≥ 3 diarrhoea/colitis and pneumonitis (any grade).

Table 29: Study GS-US-312-0119 – AEs of special interest – Exposure-adjusted incidence rate (1).

GS-US-312-0119: Adverse Events of Interest Adjusted for Exposure[a] (Safety Analysis Set)

	Id + O (N = 173)			O (N = 86)		
Preferred Term	# of Subjects with Events	Total Exposure Time in Years[b]	Adjusted Incidence Rate (95% CI)	# of Subjects with Events	Total Exposure Time in Years[b]	Adjusted Incidence Rate (95% CI)
Diarrhoea/Colitis (≥ Grade 3)	35	158.2	0.22 (0.15, 0.31)	1	32.4	0.03 (0.00, 0.17)
Pneumonia (≥ Grade 3)	31	161.9	0.19 (0.13, 0.27)	9	31.1	0.29 (0.13, 0.55)
Pneumonitis (any grade)[c]	10	168.6	0.06 (0.03, 0.11)	0	32.7	0.00 (NEst, 0.11)
Rash MST (≥ Grade 3)	7	167.8	0.04 (0.02, 0.09)	2	32.0	0.06 (0.01, 0.23)

CI = confidence interval; Id = idelalisib; MST = medical search term; O = ofatumumab
AEs were classified by PTs using MedDRA version 17.1.
Prevalence of TEAE is defined as the proportion of subjects experiencing a TEAE in the interval among those at risk at the beginning of the interval.
Pneumonia includes the terms: pneumonia, lung infection, lung infiltration, pneumocystis jiroveci pneumonia, pneumonia legionella, lung infection pseudomonal, pneumonia fungal, respiratory tract infection, lower respiratory tract infection, lower respiratory tract infection bacterial.
Rash is defined per Gilead Medical Search Term (MST) which includes exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo papular, rash papular, rash pruritic, rash morbiliform, and exfoliative rash.

a The total exposure time of all subjects (T) was calculated as $T = \sum t_i$ where t_i was the i^{th} subject exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

b Total exposure-time among the subjects at risk of an initial occurrence of the event in each treatment group

Table 30: Study GS-US-312-0119 – AEs of special interest – Exposure-adjusted incidence rate (2).

GS-US-312-0119: Richter's Transformation and Second Malignancies Adjusted for Exposure[a] (Safety Analysis Set)

	Id + O (N = 173)			O (N = 86)		
Preferred Term	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)
Richter's transformation	5	172.8	0.03 (0.0094, 0.0675)	4	32.8	0.12 (0.0333, 0.3125)
Second malignancies	24	159.4	0.15 (0.0964, 0.2240)	8	30.4	0.26 (0.1136, 0.5183)

CI = confidence interval; Id = idelalisib; O = ofatumumab
AEs were classified by PTs using MedDRA version 17.1.

a The total exposure time of all subjects (T) was calculated as $T = \sum t_i$ where t_i was the i^{th} subject exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

There was one case of bowel perforation in the combination arm and none in the ofatumumab arm. Anaphylaxis was reported in one subject in the ofatumumab arm only, and PML in two subjects in the ofatumumab arm only.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal study

LFT abnormalities occurred with increased frequency in the combination arm (Table 31). After adjustment for duration of exposure, only the incidence of ALT elevations remained increased in the combination arm (Table 32).

Table 31: Study GS-US-312-0119 – LFT abnormalities.

Parameter[a]	Id + O (N = 173)	O (N = 86)
Albumin decreased		
Any Grade	52 (30.1)	17 (19.8)
≥ Grade 3	3 (1.7)	1 (1.2)
Alkaline phosphatase increased		
Any Grade	43 (24.9)	13 (15.1)
≥ Grade 3	3 (1.7)	1 (1.2)
ALT increased		
Any Grade	90 (52.0)	18 (20.9)
≥ Grade 3	20 (11.6)	1 (1.2)
AST increased		
Any Grade	61 (35.3)	17 (19.8)
≥ Grade 3	14 (8.1)	1 (1.2)
Bilirubin increased		
Any Grade	26 (15.0)	7 (8.1)
≥ Grade 3	2 (1.2)	0
GGT increased		
Any Grade	69 (39.9)	17 (19.8)
≥ Grade 3	7 (4.0)	0

Id = idelalisib; O = ofatumumab
The Safety Analysis Set included all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
Grades were obtained per CTCAE version 4.03.
a Worst grade at post baseline

Table 32: Study GS-US-312-0119 – Abnormalities in biochemistry – Exposure-adjusted incidence rate.

GS-US-312-0119: Chemistry: Incidence Rate of Treatment-Emergent Laboratory Abnormalities (Any Grade) Adjusted for Exposure[a] (Safety Analysis Set)

	Id + O (N = 173)			O (N = 86)		
Abnormality	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)
ALP increase	43	142.5	0.30 (0.22, 0.41)	13	29.6	0.44 (0.23, 0.75)
ALT increase	90	105.5	0.85 (0.69, 1.05)	18	27.8	0.65 (0.38, 1.02)
AST increase	61	125.9	0.48 (0.37, 0.62)	17	28.4	0.60 (0.35, 0.96)
Bilirubin increase	26	158.0	0.16 (0.11, 0.24)	7	30.9	0.23 (0.09, 0.47)
Cholesterol high	18	154.9	0.12 (0.07, 0.18)	2	31.9	0.06 (0.01, 0.23)
Creatinine clearance	33	151.6	0.22 (0.15, 0.31)	12	29.2	0.41 (0.21, 0.72)
GGT increase	69	128.8	0.54 (0.42, 0.68)	17	27.3	0.62 (0.36, 1.00)
Hypertriglyceridemia	102	81.5	1.25 (1.02, 1.52)	45	19.6	2.29 (1.67, 3.07)
Hypoalbuminemia	52	139.4	0.37 (0.28, 0.49)	17	28.5	0.60 (0.35, 0.95)
Hypoglycemia	26	151.9	0.17 (0.11, 0.25)	5	31.7	0.16 (0.05, 0.37)
Hypokalemia	36	151.8	0.24 (0.17, 0.33)	8	31.6	0.25 (0.11, 0.50)
Hypophosphatemia	29	149.4	0.19 (0.13, 0.28)	3	31.7	0.09 (0.02, 0.28)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; GGT = gamma glutamyl transferase; Id = idelalisib; O = ofatumumab
The adjusted incidence rate of AEs are shown for AEs with at least 5% difference in frequency between the groups.
a The total exposure time of all subjects (T) was calculated as $T = \sum t_i$ where t_i was the i^{th} subject exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

One subject in the combination arm developed abnormal LFTs that met the criteria for Hy's law (AST or ALT > 3 × ULN with concurrent elevation of bilirubin > 2 × ULN and normal alkaline phosphatase). However, this subject had had abnormal transaminases for the previous 2

months with a concurrent intermittent grade 1 elevation of alkaline phosphatase, and at the time the bilirubin levels became elevated the subject had sepsis.

8.4.1.2. Study 101-07

For the 21 subjects treated with the combination of idelalisib and ofatumumab, the incidence of grade 3 or 4 transaminase elevations was 14.3%.

8.4.2. Kidney function

8.4.2.1. Pivotal study

Abnormalities in renal function tests occurred with comparable frequency in the two treatment arms (Table 33).

Table 33: Study GS-US-312-0119 – Renal function test abnormalities.

Parameter[a]	Id + O (N = 173)	O (N = 86)
Creatinine increased		
Any Grade	22 (12.7)	13 (15.1)
≥ Grade 3	2 (1.2)	0
Creatinine clearance decreased		
Any Grade	33 (19.1)	12 (14.0)
≥ Grade 3	5 (2.9)	3 (3.5)

Id = idelalisib; O = ofatumumab
The Safety Analysis Set included all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
Grades were obtained per CTCAE version 4.03.
a Worst grade at post baseline

8.4.2.2. Study 101-07

There were no grades 3 or higher elevations in creatinine for the 21 subjects treated with the combination of idelalisib and ofatumumab.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal study

Decreased potassium and decreased phosphate occurred with greater frequency in the combination arm (Table 34). After adjustment for duration of exposure, only the incidence of decreased phosphate remained increased (Table 35).

Table 34: Study GS-US-312-0119 – Abnormalities in other biochemistry tests.

Parameter[a]	Id + O (N = 173)	O (N = 86)
Albumin-corrected calcium increased		
Any Grade	21 (12.1)	8 (9.3)
≥ Grade 3	3 (1.7)	1 (1.2)
Glucose increased		
Any Grade	104 (60.1)	48 (55.8)
≥ Grade 3	21 (12.1)	4 (4.7)
Potassium increased		
Any Grade	4 (2.3)	3 (3.5)
≥ Grade 3	2 (1.2)	1 (1.2)
Potassium decreased		
Any Grade	36 (20.8)	8 (9.3)
≥ Grade 3	10 (5.8)	2 (2.3)
Phosphate decreased		
Any Grade	29 (16.8)	3 (3.5)
≥ Grade 3	14 (8.1)	1 (1.2)
Sodium decreased		
Any Grade	43 (24.9)	19 (22.1)
≥ Grade 3	12 (6.9)	3 (3.5)
Triglycerides increased		
Any Grade	102 (59.0)	45 (52.3)
≥ Grade 3	12 (6.9)	2 (2.3)
Urate increased		
Any Grade	19 (11.0)	6 (7.0)
≥ Grade 3	3 (1.7)	0

Id = idelalisib; O = ofatumumab
The Safety Analysis Set included all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
Grades were obtained per CTCAE version 4.03.

a Worst grade at post baseline

Table 35: Study GS-US-312-0119 – Abnormalities in biochemistry – Exposure-adjusted incidence rate.

GS-US-312-0119: Chemistry: Incidence Rate of Treatment-Emergent Laboratory Abnormalities (Any Grade) Adjusted for Exposure[a] (Safety Analysis Set)

	Id + O (N = 173)			O (N = 86)		
Abnormality	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)
ALP increase	43	142.5	0.30 (0.22, 0.41)	13	29.6	0.44 (0.23, 0.75)
ALT increase	90	105.5	0.85 (0.69, 1.05)	18	27.8	0.65 (0.38, 1.02)
AST increase	61	125.9	0.48 (0.37, 0.62)	17	28.4	0.60 (0.35, 0.96)
Bilirubin increase	26	158.0	0.16 (0.11, 0.24)	7	30.9	0.23 (0.09, 0.47)
Cholesterol high	18	154.9	0.12 (0.07, 0.18)	2	31.9	0.06 (0.01, 0.23)
Creatinine clearance	33	151.6	0.22 (0.15, 0.31)	12	29.2	0.41 (0.21, 0.72)
GGT increase	69	128.8	0.54 (0.42, 0.68)	17	27.3	0.62 (0.36, 1.00)
Hypertriglyceridemia	102	81.5	1.25 (1.02, 1.52)	45	19.6	2.29 (1.67, 3.07)
Hypoalbuminemia	52	139.4	0.37 (0.28, 0.49)	17	28.5	0.60 (0.35, 0.95)
Hypoglycemia	26	151.9	0.17 (0.11, 0.25)	5	31.7	0.16 (0.05, 0.37)
Hypokalemia	36	151.8	0.24 (0.17, 0.33)	8	31.6	0.25 (0.11, 0.50)
Hypophosphatemia	29	149.4	0.19 (0.13, 0.28)	3	31.7	0.09 (0.02, 0.28)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; GGT = gamma glutamyl transferase; Id = idelalisib; O = ofatumumab

The adjusted incidence rate of AEs are shown for AEs with at least 5% difference in frequency between the groups.

a The total exposure time of all subjects (T) was calculated as $T = \sum t_i$ where t_i was the i^{th} subject exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

8.4.3.2. Study 101-07

There were no notable findings for other biochemistry parameters for the 21 subjects treated with the combination of idelalisib and ofatumumab.

8.4.4. Haematology

8.4.4.1. Pivotal study

The combination arm was associated with a greater frequency of the following haematology abnormalities – increased lymphocyte count, neutropaenia and thrombocytopaenia (Table 36). After correction for duration of exposure only the incidence of increased lymphocyte count remained higher in the combination arm (Table 37).

Table 36: Study GS-US-312-0119 – Abnormalities in haematology tests.

GS-US-312-0119: Summary of Treatment-Emergent Hematology Abnormalities[a] (Safety Analysis Set)

Parameter[a]	Id + O (N = 173)	O (N = 86)
Hemoglobin decreased		
Any Grade	74 (42.8)	34 (39.5)
≥ Grade 3	30 (17.3)	10 (11.6)
Lymphocyte count increased		
Any Grade	31 (17.9)	5 (5.8)
≥ Grade 3	18 (10.4)	3 (3.5)
Lymphocyte count decreased		
Any Grade	35 (20.2)	19 (22.1)
≥ Grade 3	18 (10.4)	9 (10.5)
Neutrophil count decreased		
Any Grade	122 (70.5)	50 (58.1)
≥ Grade 3	82 (47.4)	28 (32.6)
Platelet count decreased		
Any Grade	58 (33.5)	21 (24.4)
≥ Grade 3	23 (13.3)	10 (11.6)
Leukocytes (white blood cell decreased)		
Any Grade	69 (39.9)	32 (37.2)
≥ Grade 3	24 (13.9)	10 (11.6)

Id = idelalisib; O = ofatumumab
The Safety Analysis Set included all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
Grades were obtained per CTCAE version 4.03.
a Worst grade at post baseline

Table 37: Study GS-US-312-0119 – Abnormalities in haematology – Exposure-adjusted incidence rate.

GS-US-312-0119: Hematology: Incidence Rate of Treatment-Emergent Laboratory Abnormalities Adjusted for Exposure[a] (Safety Analysis Set)

	Id + O (N = 173)			O (N = 86)		
Abnormality	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)	# of Subjects with Events	Total Exposure Time in Years	Adjusted Incidence Rate (95% CI)
ALC increase	31	144.0	0.22 (0.15, 0.31)	5	31.2	0.16 (0.05, 0.37)
Neutropenia	122	60.0	2.03 (1.69, 2.43)	50	18.0	2.77 (2.06, 3.65)
Thrombocytopenia	58	133.9	0.43 (0.33, 0.56)	21	26.1	0.80 (0.50, 1.23)

ALC = absolute lymphocyte count; Id = idelalisib; O = ofatumumab
a The total exposure time of all subjects (T) was calculated as $T = \sum t_i$ where t_i was the i^{th} subject exposure time in weeks. If a subject had multiple events, t_i was the time of the first event. For a subject with no events, t_i was censored at the time of data cutoff date if the subject was still on study drug, and was censored at the time of last dose date plus 30 days or the data cutoff date (whichever is shorter) if the subject discontinued study drug.

8.4.4.2. Study 101-07

For the 21 subjects treated with the combination of idelalisib and ofatumumab, incidences of grade 3 or 4 cytopaenias were 33.3% for neutropaenia, 4.8% for thrombocytopaenia and 4.8% for anaemia.

8.4.5. Vital signs

8.4.5.1. Pivotal study

There were no clinically significant differences between the study arms in average oxygen saturation measurements. The incidence of abnormally low oxygen saturation readings was comparable in the two arms.

8.4.5.2. Study 101-07

There were no clinically significant changes in temperature, blood pressure, or heart rate during this study.

8.5. Other safety data included

The submission included data from the following additional studies, which were not directly relevant to the proposed new indication:

8.5.1. Study GS-US-312-0116

This was the pivotal phase 3 study for the approval of idelalisib in combination with rituximab in relapsed CLL. In the current submission the sponsor provided an updated study report. This report was to be reviewed as part of a separate TGA submission and therefore has not been reviewed in this evaluation.

8.5.2. Study GS-US-312-0117

This trial was originally an extension study for subjects who had developed disease progression in study GS-US-312-0116. In addition, Study GS-US-312-0116 was stopped early due to overwhelming evidence efficacy following an interim analysis and all subjects still in the trial were transitioned to GS-US-312-0117. All subjects in GS-US-312-0117 were treated with idelalisib *monotherapy*. A total of 161 subjects were enrolled. Most subjects were treated with 150 mg BD. Four subjects were treated with 300 mg BD. Median duration of treatment with idelalisib was 5.7 months in subjects who had disease progression on placebo in study GS-US-312-0116, 9.9 months in subjects who did not have disease progression on placebo, and 15.9 months who were treated with idelalisib in study GS-US-312-0116.

8.5.3. Study 101-08

This was a phase 2 study in subjects with *previously untreated* CLL. The original submission to register idelalisib included a report of a cohort of 64 patients (Cohort 1) who were treated with idelalisib in combination with rituximab. In the current submission the sponsor provided a report on a separate cohort of 41 subjects (Cohort 2) who were treated with idelalisib *monotherapy* (150 mg BD). Median duration of treatment was 6.0 months.

8.5.4. Study 101-09

This was a phase 2 single-arm study in 125 subjects with treatment-refractory *indolent NHL*. Subjects were treated with idelalisib *monotherapy* (150 mg BD). A full study report for this trial was reviewed in the clinical evaluation of the original submission to register idelalisib. The trial provided the main evidence to support the TGA approval of idelalisib for refractory follicular lymphoma. In the current submission the sponsor provided a brief update of efficacy and safety data from the study. The update was prepared in response to a request from the EMA as a 'post-authorisation measure (PAM)'. The updated efficacy data have been summarised. Median duration of treatment in the updated report was 6.6 months.

8.5.5. Study 101-99

This was open open-label extension study for subjects who had completed one of the following four early phase studies:

- Study 101-02 – a phase 1 dose-escalation trial in subjects with relapsed or refractory haematologic malignancies;
- Study 101-07 (as described above);
- Study 101-08 – Cohort 1 (as described above)
- Study 101-10 – a phase 1/2 study in subjects with previously treated low-grade lymphoma.

These four studies were reviewed during the evaluation of the original submission to register idelalisib. In 101-99 subjects were treated with idelalisib *monotherapy* at the last dose they received during their parent study. Doses ranged from 100 mg OD (or 50 mg BD) to 350 mg BD. A total of 198 subjects enrolled in the extension study. Median duration of exposure varied from 3.7 to 22.4 months for the four parent study groups. Only grade ≥ 3 AEs were recorded in the extension study.

8.5.6. Study GS-US-339-0103

This is an ongoing phase 2 study of idelalisib in combination with GS-9973 (an investigational oral inhibitor of spleen tyrosine kinase) in subjects with relapsed or refractory haematological malignancies. The only data supplied from this study were listings of serious AEs, AEs leading to discontinuations and deaths. No information was supplied on the study design or other study outcomes.

The safety data from these studies (except GS-US-312-0116) have been reviewed. The incidence and patterns of AEs and laboratory abnormalities observed in these studies were consistent with those observed in the pivotal study GS-US-312-0119, and with the toxicity profile of the drug as described in the currently approved product information. No new safety issues were identified.

8.6. Post-marketing experience

No post-marketing data were included in the submission.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

Idelalisib is known to be associated with hepatotoxicity and this was confirmed in the pivotal study where subjects randomised to combination treatment had an increased incidence of transaminase elevation. There were no cases of severe drug induced liver injury (DILI) in any of the submitted studies. In addition there were no cases that clearly met 'Hy's law' criteria (predictive of DILI).

8.7.2. Haematological toxicity

Cytopaenias are a known complication of CLL, especially in advanced disease and are a known adverse effect of idelalisib. They are also a complication of many agents used in the initial treatment of CLL. Cytopaenias occurred frequently in the submitted studies. However, in the pivotal study in this submission, the incidence of cytopaenias was not increased in the combination arm after incidence was adjusted for duration of exposure.

8.7.3. Serious skin reactions

Idelalisib is known to be associated with dermatological toxicity. In the pivotal study the incidence dermatological SAEs was 1.2% in the combination arm and 0% in the ofatumumab arm.

8.7.4. Cardiovascular safety

The submitted studies did not produce evidence to suggest that idelalisib is associated with significant cardiovascular toxicity.

8.7.5. Unwanted immunological events

Idelalisib was not associated with serious immunological reactions (e.g. anaphylaxis) in the submitted studies.

8.8. Evaluator's overall conclusions on clinical safety

The safety profile of idelalisib in the submitted studies was consistent with that previously observed. No new safety issues were identified.

The addition of idelalisib to ofatumumab in the treatment of CLL results in some increase in the incidence of AEs. Combination treatment was associated with an increase in the incidence of grade ≥ 3 AEs (87.9% vs. 55.8%) and serious AEs (69.9% vs. 41.9%). This increased toxicity may be due in part to the longer observation period for subjects in the combination arm. 30% of subjects in the combination arm had an AE that led to discontinuation of idelalisib. Combination treatment was not associated with any increase in overall mortality.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of the combination of idelalisib and ofatumumab in the proposed usage are:

· A significant reduction in the risk of experiencing a PFS event (mainly events of disease progression) in patients with relapsed/refractory CLL

9.2. First round assessment of risks

The risks of idelalisib in the proposed usage are:

· An increase in the incidence of a number of adverse events such as diarrhoea, colitis, LFT abnormalities, pneumonitis and skin toxicity.

No new safety issues have been identified with the proposed new indication.

The efficacy and safety of the idelalisib-ofatumumab combination has not been presented for patients with 17p deletion who are treatment-naïve. Use in this group is consequently considered unfavourable.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of idelalisib used in combination with ofatumumab is considered favourable in patients with relapsed/refractory CLL without 17p deletion. Other studies included in the submission do not alter the benefit-risk balance for the currently approved indications.

10. First round recommendation

Satisfactory responses to the clinical questions are required before authorisation and approval of the proposed indication can be recommended.

11. Clinical questions

(Q1) Please provide an assurance that the tablet formulations used in the pivotal study (GS-US-312-0119) were identical to those registered in Australia.

(Q2) The sponsor is requested to provide a justification for the use of a non-registered regimen of ofatumumab for use in combination with idelalisib in the studies presented for evaluation.

(Q3) Given that the studies presented in this submission only recruited patients with CLL that were relapsed or refractory, the sponsor is requested to provide a justification for the extrapolation of use of the idelalisib-ofatumumab combination as first-line in patients with 17p deletion – as per the proposed indication.

12. Second round evaluation of clinical data

Not applicable

13. Second round benefit-risk assessment

Not applicable

14. Second round recommendation

Not applicable

15. References

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