EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2014
EMEA/CHMP/324336/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Zydelig

International non-proprietary name: idelalisib

Procedure No.: EMEA/H/C/003843/0000

Note

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

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Administrative information

Name of the medicinal product:	Zydelig
Applicant:	Gilead Sciences International Ltd Flowers Building Granta Park Abington Cambridge CB21 6GT UNITED KINGDOM
Active substance:	IDELALISIB
International Nonproprietary Name/Common Name:	IDELALISIB
Pharmaco-therapeutic group (ATC Code):	antineoplastic agents, other antineoplastic agents L01XX47
Therapeutic indication:	Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.
Pharmaceutical form:	Film-coated tablet
Strengths:	100 mg and 150 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	60 tablets

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
Akt	serine/threonine protein kinase
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BID	twice a day
BMI	body mass index
BR	bendamustine and rituximab
CAL-101	idelalisib
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
ChR	rituximab and chlorambucil
CI	confidence interval
CIRS	cumulative illness rating scale
CL_{cr}	creatinine clearance
CLL	chronic lymphocytic leukaemia
CPT	Child-Pugh-Turcotte
CR	complete response
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
CYP	cytochrome P450 enzyme
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EC_{50}	half-maximal effective concentration
EC_{90}	90% effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOP1	End-of-Phase 1 (meeting)
ESMO	European Society for Medical Oncology
EU	European Union
F	fludarabine
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FC	fludarabine and cyclophosphamide
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	(US) Food and Drug Administration
FL	follicular lymphoma

Gilead	Gilead Sciences
GS-1101	idelalisib
HL	Hodgkin lymphoma
HRQL	health-related quality of life
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IDELA	idelalisib (GS-1101; formerly CAL-101)
Ig	immunoglobulin (A, E, G, and M)
IND	Investigational New Drug (Application)
iNHL	indolent non-Hodgkin lymphoma
IRC	independent review committee
ITT	intent-to-treat
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LPL	lymphoplasmacytic lymphoma
m	module
mAb	monoclonal antibody
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MM	multiple myeloma
MR	minor response
MRI	magnetic resonance imaging
MST	medical search term
MZL	marginal zone lymphoma
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (US)
NE	not evaluable
NHL	non-Hodgkin lymphoma
NR	not reached; not reported
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
Pgp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase p110δ isoform
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)

PR	partial response
PT	preferred term
Q1, Q2, Q3, Q4	first quartile, second quartile, third quartile, fourth quartile
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
R	rituximab (MabThera)
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CVP	rituximab, cyclophosphamide, vincristine, and prednisone
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
SAE	serious adverse event
SEM	standard error of the mean
SD	stable disease
SLL	small lymphocytic lymphoma
SOC	system organ class
SPD	sum of the products of the greatest perpendicular diameters
StD	standard deviation
TTR	time to response
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal range
US	United States
UV	ultraviolet
vs	versus
WHO	World Health Organization
WM	Waldenstrom macroglobulinemia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd submitted on 28 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for idelalisib Gilead Sciences International Ltd, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2013.

The applicant applied for the following indication: Idelalisib is indicated, alone or in combination, for the treatment of patients with relapsed chronic lymphocytic leukaemia (CLL) and for the treatment of patients with refractory indolent non-Hodgkin lymphoma(iNHL).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that idelalisib was considered to be a new active substance.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included the EMA Decision P/0278/2013 on the agreement of a paediatric investigation plan (PIP) for mature B-cell lymphoma and the EMA Decision CW/1/2011 on the granting of a class waiver for chronic lymphocytic leukaemia.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

New active Substance status

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

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

A new application was filed in the following countries: USA.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill, County Cork
Ireland

1.3. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder	Co-Rapporteur:	Pieter de Graeff

CHMP Peer reviewer: Jens Ersbøll

- The application was received by the EMA on 28 October 2013.
- The procedure started on 20 November 2013.
- Accelerated Assessment procedure was agreed-upon by CHMP on 21 November 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 February 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 March 2014.
- During the meeting on 20 March 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant and to revert to a normal timetable. The final consolidated List of Questions was sent to the applicant on 21 March 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 June 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 June 2014
- During a meeting of SAG on 10 June 2014, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 26 June 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 2 July 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 June 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 18 July 2014.

- During the meeting on 24 July 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zydelig.
- The CHMP adopted a report on similarity of Zydelig with Arzerra, Litak and Gazyvaro on 24 July 2014

2. Scientific discussion

2.1. Introduction

Problem statement

Chronic Lymphocytic Leukaemia (CLL)

Chronic lymphocytic leukaemia (CLL) is a progressive hematologic disease characterized by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs, and diagnosis requires the presence of ≥ 5000 B-lymphocytes/µL in the peripheral blood for the duration of at least 3 months. It is the most common form of adult leukaemia in the Western world, with an incidence of 4 per 100,000 persons per year. The median age of diagnosis in the EU is 72 years and only 10% of patients are less than 55 years old. The current WHO classification system recognizes and groups CLL and small lymphocytic lymphoma (SLL) as the same biological entity, with CLL clinically manifesting primarily in bone marrow and peripheral blood, and SLL primarily manifesting in the lymph nodes.

Current treatments for CLL are not curative. Fewer patients obtain responses with each subsequent regimen, and subjects become increasingly resistant to available therapy. Patients who relapse after a disease-free period of over 1 year (2-3 years for chemoimmunotherapy) are considered treatment sensitive and may be candidates for treatment reinitiation. Patients who relapse after a shorter interval, or are refractory to first-line treatment, present a more challenging group, particularly those who are older, have comorbid conditions, and/or harbour high-risk cytogenic abnormalities. A retrospective analysis of patients in the German CLL8 trial found that overall survival after the start of salvage treatment among patients whose disease had progressed within 2 years after the end of chemoimmunotherapy was about 2 years, comparable to that of truly refractory patients.

Patients with the del(17p) chromosomal abnormality represent a high risk group of CLL. According to the ESMO guidelines, there is no standard treatment for these patients, who have a median life expectancy of 2–3 years from front-line treatment. While only a small minority of CLL patients will have detectable del(17p) at the time of diagnosis, the proportion increases with successive chemotherapy treatments, so that in the relapsed setting up to 30% to 50% of patients have del(17p).

The monoclonal antibody ofatumumab, is currently approved in the EU in the treatment of CLL in the refractory setting as a single agent. The combination of the monoclonal antibody rituximab with chemotherapy (eg, fludarabine and cyclophosphamide) (FCR regimen) is approved in the EU for use in this setting. Marketing authorization for alemtuzumab, which had been indicated for the treatment of CLL in patients for whom fludarabine combination chemotherapy is not appropriate, was withdrawn in the EU in August 2012.

Indolent Non-Hodgkin Lymphoma (iNHL)

Indolent Non-Hodgkin Lymphoma (iNHL) comprises 4 clinical entities (follicular lymphoma [FL], small lymphocytic lymphoma [SLL], lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia [LPL/WM], and marginal zone lymphoma [MZL]). The current WHO classification

system recognizes and groups CLL and small lymphocytic lymphoma (SLL) as the same biological entity (see above).

While initial treatments for each of the indolent lymphomas may vary at the time of disease progression, next-line therapies largely comprises the same armamentarium of anti-CD20 antibodies and chemotherapies, but the clinical evidence supporting this approach is limited especially with respect to MZL and LPL/WM. In resistant and refractory stages the current treatment alternatives are very limited and often carry significant toxicities.

About the product

Idelalisib inhibits phosphatidylinositol 3 kinase p110δ (PI3Kδ), which is hyperactive in B cell malignancies and is central to multiple signalling pathways that drive proliferation, survival, homing, and retention of malignant cells in lymphoid tissues and bone marrow. Idelalisib is a selective inhibitor of adenosine 5'-triphosphate (ATP) binding to the catalytic domain of PI3Kδ, resulting in inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol and prevention of Akt (protein kinase B) phosphorylation (see SmPC, section 5.1).

The applicant initially claimed the approval for the following indication:

Idelalisib is indicated, alone or in combination, for the treatment of patients with relapsed chronic lymphocytic leukaemia (CLL).

Idelalisib is indicated for the treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL).

The final indication following CHMP review of this application is (see SmPC, section 4.1):

Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL):

- who have received at least one prior therapy, or
- as first line treatment in the presence of 17p deletion or *TP53* mutation in patients unsuitable for chemo-immunotherapy.

Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

Treatment with Zydelig should be conducted by a physician experienced in the use of anticancer therapies.

The recommended dose of Zydelig is 150 mg, taken orally, twice daily. Treatment should be continued until disease progression or unacceptable toxicity. Dose modifications are described in Table 63 (Summary Table of Risk Minimization Measures) and the SmPC section 4.2.

Type of application and aspects on development

- Legal basis

This application concerns a centralised procedure and is submitted in accordance with article 8(3) of Directive 2001/83/EC.

- Accelerated procedure

In October 2013 the applicant submitted to the EMA a request for Accelerated Assessment for idelalisib, pursuant to Article 14 (9) of Regulation (EC) No 726/2004. During the CHMP meeting of November 2013, the request for accelerated assessment was accepted.

In view of the Major Objections raised, and in order to allow adequate time for the assessment of the responses to the list of questions, the CHMP decided to revert the accelerated procedure to a normal timetable for review.

- Scientific advice

The applicant did not request CHMP scientific advice.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 100 mg and 150 mg of idelalisib as active substance.

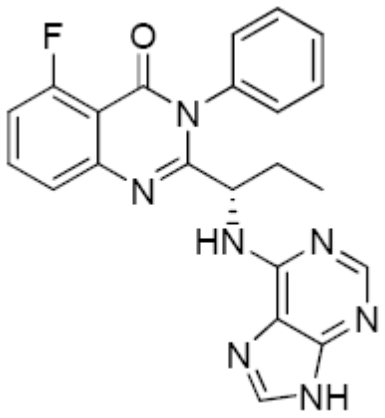
Other ingredients are: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate and magnesium stearate. The film coating consists of polyvinyl alcohol, macrogol, titanium dioxide, talc, sunset yellow FCF and iron oxide red.

The product is available in primary packaging as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of active substance is 5-Fluoro-3-phenyl-2-[(1*S*)-1-(9*H*-purin-6-ylamino)propyl]quinazolin-4(3*H*)-one and has the following chemical structure:



Idelalisib is a white to off-white solid practically insoluble in water at pH 7 and soluble in water at pH 1.2. The active substance has a chiral centre assigned as 1*S* and is manufactured as the pure enantiomer. Two polymorphic forms (Form I and II) have been identified and both have equivalent stability and solubility.

The chemical structure elucidation has been performed by infrared spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR, ^{19}F NMR, mass spectroscopy, ultraviolet absorption (UV) and x-ray diffraction. The molecular formula is confirmed by elemental analysis.

Manufacture, characterisation and process controls

The active substance is synthesised in five steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation. According to the synthetic process described the active substance is consistently obtained as the S-enantiomer. The manufacturing development of the active substance includes studies based on a Quality by Design (QbD) approach, in line with ICH Q8, Q9, Q10, Q11 and other regulatory guidance. However, no Design Space was proposed.

The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the active substance, respectively.

The information provided adequately describes the manufacturing including reactions conditions, quantities of raw materials and yields.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and adequately characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been discussed. The impurity profile of the active substance is practically identical for the different manufacturers.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented.

The active substance is packaged in in double-lined polyethylene bags closed with plastic or wire ties. The bags are held in high density polyethylene drums or other suitable secondary containers with lids of appropriate size and fitted with a tamper-evident security seal. The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specification includes tests for appearance, identification (IR and HPLC), clarity of solution, assay (HPLC), impurities (HPLC), residual solvents (GC), elemental impurities (ICP), particle size (laser light scattering) and melting point (Ph Eur).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. A detailed description and full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on 13 production batches of the active substance. All the batches were manufactured according to the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Six production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 36 months and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: appearance, impurities (HPLC), chiral impurities (chiral HPLC), water content (Ph Eur), X-ray powder diffraction (XRPD), melting point (Ph Eur), FTIR and microbiological quality (Ph Eur). The analytical methods used in the stability studies, which were not included in the specifications, have been adequately described and non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Stress studies were conducted by exposing the active substance to high and low temperatures and humidity. Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

All stability studies results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the drug development was to develop an immediate release solid dosage formulation that could support patient adherence to the treatment.

Idelalisib was first evaluated in Phase 1 clinical trials as a neat drug-in-capsule dosage form. A granulated powder-in-capsule dosage form was developed as a replacement for the neat drug presentation and evaluated in Phase 2 clinical trials. The initial formulation composition was defined through development of the granulated powder presentation. A film-coated tablet formulation containing the same ingredients was prepared as an alternative to the granulated powder-in-capsule presentation and evaluated in Phase 2 clinical trials and the subsequent Phase 3 clinical studies. The tablet formulation has the advantage of improving manufacturing efficiency and increasing active substance loading to allow for small tablets. During the pharmaceutical development the applicant took into account the properties of the active substance. All the excipients selected are pharmacopeia grade and controlled according with their relevant monographs. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The manufacturing process uses granulation and the development is adequately described and discussed in the documentation. In addition, the applicant discussed important aspects of the drug development such as the drug load, granulation, wet and dry milling, drying, blending and scale-up. During the drug development it was noted that tablets contain a mixture of both Forms I and II. The applicant has provided adequate documentation to support that Form II is biopharmaceutically, chemically and physically equivalent to Form I.

The process development is described using design of experiments (DoE) without claiming design space. The applicant states that they intend to operate within the proposed normal operating ranges (NOR) and movement outside of the proposed normal operating ranges would be considered a change to the manufacturing process and would initiate a quality investigation and regulatory post approval change

process if required. PARs for the mixing, milling, blending, lubrication, and coating processes were established based on process screening experiments and clinical manufacturing experience. Optimisation was made based on a risk assessment from knowledge gained from the development history. The granulation, drying, and compression were identified as having the greatest influence over proposed Critical Quality Attributes (CQAs).

The dissolution studies were performed in 0.1 M HCl as the solubility of the active substance is dependent on pH with superior solubility at low pH. The discriminatory power of the dissolution method has been demonstrated. The particle size distribution has been consistently observed to date in clinical and commercial active substances batches. The influence of particle size on the dissolution behaviour of the tablet has been discussed.

Bioequivalence study was performed showing bioequivalence between the clinical formulations and the proposed commercial formulation.

The primary packaging is described as stated in the SmPC. The material complies with Ph Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of nine main steps: mixing, granulation, milling, drying, drying milling, blending, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

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

Product specification

The finished product release specifications include appropriate tests for this type of dosage form: appearance, identification (HPLC and UV), water content (Ph Eur), assay (HPLC), impurities (HPLC), uniformity of dosage Units (Ph Eur), dissolution (Ph Eur) and microbiological quality (Ph Eur).

Batch analysis data of nine pilot scale batches of each strength of the finished product are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

Stability of the product

Stability data of four production scale batches of finished product stored under long term conditions for 36 months at 25 ºC / 60% RH and at 30ºC / 75% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The parameters tested are appearance, assay (HPLC), impurities (HPLC), dissolution (Ph Eur), microbiological quality (Ph Eur), water content (Ph Eur), chiral purity (chiral HPLC). The analytical methods used during the stability studies are the same as used for release testing of the finished product

with the exception of chiral purity test. A description of this method was provided, validated and it was shown to be stability indicating.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In addition stress stability studies were performed on one fully representative batch under various extreme conditions of humidity, high and low temperature. One production scale batch packed in the primary packaging proposed for marketing was stored for 60 days to -20°C, 5°C, 60°C/ambient humidity, and 25°C/80% RH, open dish exposure with 25°C/60% RH and 30°C/75%RH.

Based on the available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The main goal of the drug development was to develop an immediate release solid dosage formulation that could support patient adherence to the treatment. The development of the medicinal product includes elements of Quality by Design (QbD), but no design space has been established or claimed. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at full scale at the proposed manufacturing site and a validation protocol has been presented.

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The primary and secondary pharmacodynamics of idelalisib were investigated in a number of in vitro and in vivo studies.

Idelalisib was tested in rats, rabbits and dogs by oral gavage for the toxicology studies. In addition, safety pharmacology studies were carried out in rats and dogs (oral administration). Pivotal toxicology studies and most of the safety pharmacology studies were carried-out in compliance with GLP.

2.3.2. Pharmacology

PI3Kδ belongs to the Class I phosphatidylinositol 3-kinases (PI3Ks), part of a family of lipid kinases which mediate intracellular signalling pathways that regulate several key cellular functions, including survival, proliferation, and motility. The class I PI3Ks are composed of a regulatory subunit and a catalytic subunit which has kinase activity (designated p110α, p110β, p110γ, or p110δ). The catalytic subunit of the heterodimer defines the 4 Class I PI3K isoforms: PI3Kα, PIKβ, PI3Kγ, and PI3Kδ. Upon activation via cell surface receptor-ligand interactions, PI3Kδ phosphorylates the key lipid second messenger phosphatidylinositol to generate phosphatidylinositol 3,4,5, trisphophate (PIP3).

PI3Kδ is a key signalling molecule in normal and malignant B lymphocytes. Signalling induced by stimulation or tonic activation of the B cell receptor (BCR), CD40, B-cell activating factor receptor (BAFFR), chemokine receptors CXCR4 and CXCR5, and integrins are all PI3Kδ-dependent(Figure 1). The receptors and their associated signalling pathways are critical to normal B lymphocyte function and evidence suggests they are also critical in B cell malignancies.

Due to differences present in the ATP binding pocket between these Class I PI3K isoforms, selective inhibition of PI3Kδ can be achieved with a small molecule competitive ATP inhibitor.

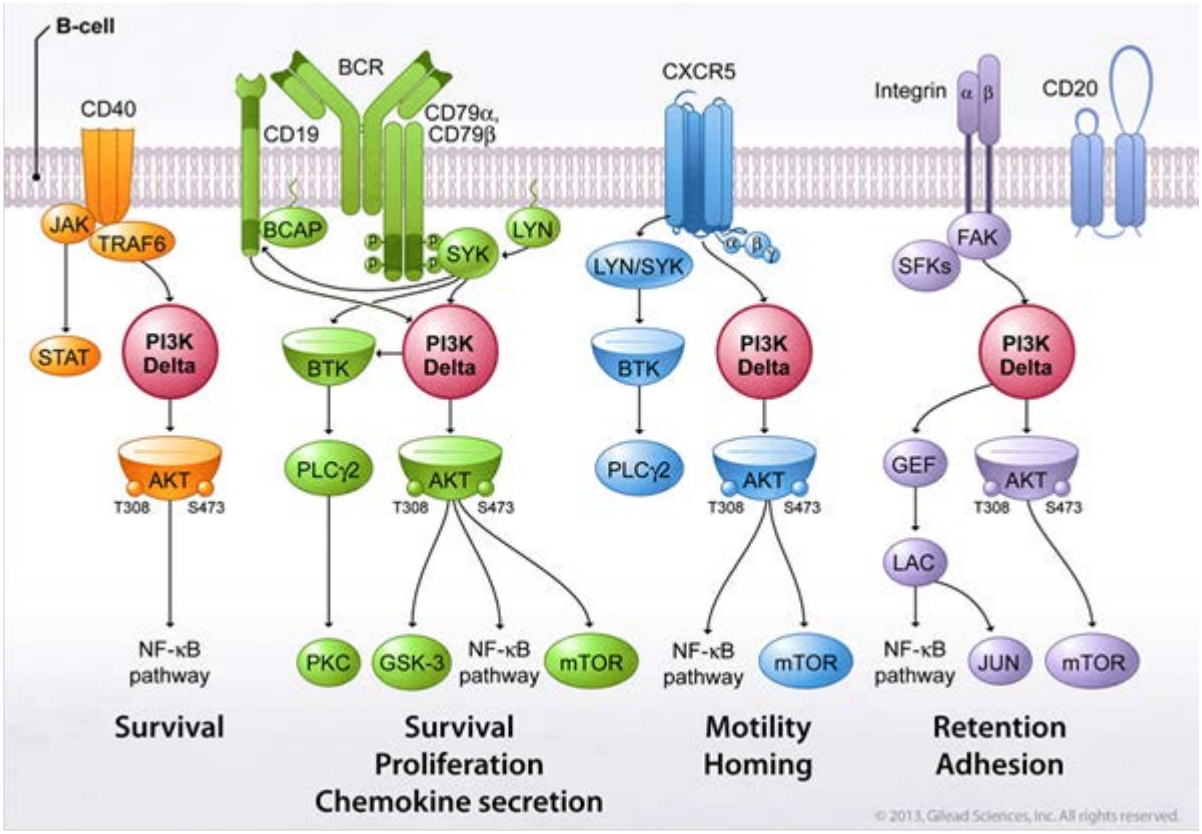


Figure 1: PI3Kδ Signalling Pathways Targeted by Idelalisib in B-Cell Malignancies Mediate Survival, Proliferation, and Homing

Primary pharmacodynamic studies

In vitro *studies*

Receptor binding and activity

The crystal structure of idelalisib bound to p110δ was determined in order to understand the structural basis for the inhibition p110δ by idelalisib. The co-crystal structure shows that idelalisib is a competitive inhibitor of the ATP binding site of the PI3K p110δ catalytic domain.

Idelalisib was evaluated for PI3Kδ potency and selectivity relative to the other class I PI3K isoforms using in vitro biochemical enzyme assays at steady-state concentrations of adenosine triphosphate (ATP). Enzymatic activity of the class I PI3K isoforms was measured using a time resolved fluorescence resonance energy transfer (TR-FRET) assay that monitors formation of the product 3,4,5-inositol triphosphate molecule, as it competes with fluorescently labelled PIP3 for binding to the GRP-1 pleckstrin homology domain protein.

PI3K Isoform	**IC_{50} (nM)**	**IC_{50}-based PI3Kδ Fold Selectivity**
PI3Kδ	19	1
PI3Kα	8,600	453
PI3Kβ	4,000	211
PI3Kγ	2,100	110

Idelalisib was screened for its potential to interact with 353 kinases including 30 mutant kinases or inhibit a panel of 131 kinases using KINOMEscan (DiscoveRx) and KinaseProfiler™ screening; at a concentration of 10 µM idelalisib did not significantly interact with any of the kinases other than the PI3K isoforms.

The major metabolite of idelalisib, GS-563117 (also called CAL-244), an oxidative metabolite, was evaluated for its potential to bind or inhibit PI3Kδ and other Class I isoforms as well as other kinases. GS-563117 did not show inhibitory activity at any of PI3K kinases and among 442 other kinases it only showed binding to Ste20-like kinase (SLK) and lymphocyte-oriented kinase (LOK) and inhibition studies with these kinases demonstrated IC_{50} values of 110 nM and 50 nM, respectively.

The cellular potency of idelalisib against all 4 of the Class I PI3K isoforms, PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ was determined using a series of PI3K isoform-specific in vitro cell-based assays using primary human basophils, lymphocytes and murine embryonic fibroblasts. To evaluate cell-based potency in the presence of human plasma, a whole blood cell-based assay using PI3Kδ- and PI3Kγ-specific stimuli was also utilised.

PI3K Isoform	**Cell-based Assay and Stimulus**	**EC_{50}[a] (nM)**	**Cell-based Delta Selectivity (fold)**
PI3Kδ	Human Basophil- and Anti- FcεRI	8.9	1
PI3Kα	Murine Embryonic Fibroblast and-PDGF	> 10,000 [a]	1,124
PI3Kβ	Murine Embryonic Fibroblast and LPA	1,419 [a]	159

PI3Kγ	Human Basophil and fMLP	2,500 [a]	281
Human Whole Blood Cell Assays			
PI3Kδ	Basophil- and Anti- FcεRI	39[a]	1
PI3Kγ	Basophil and fMLP	2833[a]	70
Human Lymphocyte Proliferation Assays			
PI3Kδ	B-lymphocyte and Anti-IgM	6	1
PI3Kδ/γ	T-lymphocyte and Anti- CD3ε	973	160

[a] geometric mean

In vitro activity on malignant B-cells

The pharmacological activity of idelalisib was evaluated in malignant B-cells cell lines that were derived from patients with indolent lymphoma, specifically follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and acute lymphocytic leukaemia (ALL). Idelalisib potently inhibited the cell viability of the FL lines WSU-FSCCL and WSU-NHL with an EC_{50} of 0.03 μM in a 72-hour assay. In the WSU-FSCCL FL cell line, idelalisib inhibited cell proliferation and caused cell cycle arrest in the G1 phase of the cell cycle as demonstrated by an increased proportion of cells in the G1 phase of the cell cycle and a corresponding decrease in cells in the S and G2/M phase. In the FL cell line WSU-NHL, idelalisib induced apoptosis at concentrations of 0.5 and 5 μM with a similar level of effect at both concentrations as demonstrated by an increase in the sub-G1 cell cycle population, increased Annexin V positivity, as determined by flow cytometry, and increased cleaved caspase 3 and cleaved poly (ADP-ribose) polymerase (PARP) expression as determined by ELISA.

The SU-DHL-5, WSU-NHL, KARPAS-422 and CCRF-SB cell lines, derived respectively from patients with DLBCL, FL, FL, and ALL, were utilized to evaluate the effect of idelalisib on inhibiting PI3Kδ-mediated intracellular signaling with the phosphorylation status of Akt and S6 ribosomal protein (S6RP) as endpoints. Serum-starved cells were incubated with idelalisib for 1 hour and evaluated by immunoblot and ELISA analyses to measure the relative levels of phosphorylated Akt (pAkt) and phosphorylated S6RP (pS6RP). Treatment with idelalisib caused a dose-dependent reduction in pAkt ($pAkt^{T308}$) and pS6RP ($pS6RP^{S235/236}$) at EC_{50} values ranging from 0.1 to 1.0 μM for the individual cell lines. Treatment with idelalisib for 24 hours at concentrations of 0.5 or 1.0 μM resulted in a 3- to 5-fold increase in apoptosis as measured by population of Annexin V-positive cells using flow cytometry.

Studies were performed with fresh isolates of primary tumor cell samples obtained from patients with FL, chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL). FL samples attained from patients (n=7) were evaluated for levels of pAkt ($p\text{-}Akt^{S473}$) by flow cytometry before and after stimulation of the BCR with anti-IgM/IgG. The effect of idelalisib on $p\text{-}Akt^{S473}$ at a concentration of 0.1μM was evaluated in un-stimulated and BCR-stimulated patient samples. In all (7/7) samples tested in absence of BCR stimulation, idelalisib reduced the basal $p\text{-}Akt^{S473}$ levels by 1% to 29%. However, in all (7/7) patient samples with BCR stimulation, idelalisib inhibited the Akt phosphorylation; the average percent inhibition of $p\text{-}Akt^{S473}$ levels was 86% and the range was 55% to 97%

In primary tumour samples attained from patients with CLL (n=5) and MCL (n=5), levels of pAkt ($p\text{-}Akt^{T308}$) were present in the samples indicating constitutive activation of a PI3K-dependent pathway in these cells. Idelalisib treatment in vitro for 1 hour at a concentration of 100 nM resulted in a 60% reduction in $pAkt^{T308}$ compared to untreated samples.

In primary CLL cells freshly isolated from patients, the expression of PI3Kδ was consistently detected at high levels by western blot in all of the samples tested (n=40). Treatment with idelalisib caused a dose-dependent induction of apoptosis in primary CLL cells (n=7); the mean percentage of apoptotic cells at 1 µM was 28% with range from 0% to 54% and at 10 µM was 60% with a range from 26% to 78%.

Nurse-like cells (NLC) present within the tumour microenvironment support malignant B-cell viability and growth. NLCs secrete the chemokines CXCL12 and CXCL13 which attract or induce homing of iNHL cells and CLL cells via the cognate chemokine receptors CXCR5 and CXCR4. NLCs also stimulate malignant B-cell proliferation by secretion of B-cell-activating factor and through stimulation of the BCR. To model some of the stimulatory interactions present in the tumour microenvironment primary CLL cells were stimulated through the BCR with anti-IgM or by co-culture with NCLs. MCL samples were stimulated through the CD40 pathway with soluble CD40 ligand (sCD40L). These stimuli caused rapid phosphorylation of Akt to $pAkt^{S473}$ in vehicle-treated cultures and pre-treatment with idelalisib at concentrations of 0.1 to 1.0 µM inhibited the generation of $pAkt^{S473}$ by 90% or more.

In primary CLL cells attained from patients (n=15), stimulation of the BCR with anti-IgM antibody caused increased CLL cell viability, while idelalisib treatment significantly reduced cell viability of BCR-stimulated CLL cells at all concentrations tested (0.5, 1, 5 and 10 µM) below the level of the un-stimulated controls. A similar effect of idelalisib on CLL cell viability was also demonstrated in primary CLL cells from patients (n=12) co-cultured with NLCs. The viability of CLL cells was increased when co-cultured with NLCs compared to cultured alone. Idelalisib caused a dose-dependent inhibition of CLL viability in NLC co-cultures at concentrations of 0.5, 1, 5, and 10 µM.

Chemokines and chemokine receptors are produced by malignant B cells in FL and CLL and have roles in homing to and maintenance of the tumour microenvironment in these malignancies. Stimulation of the BCR with anti-IgM resulted in a marked increase in secreted levels of the chemokines CCL3 and CCL4 by CLL cells. This effect was significantly inhibited by idelalisib at concentrations of 1 µM or greater. Co-culture with NLCs also similarly induced CLL cells to secrete high concentrations of CCL3 and CCL4 into the supernatants and this secretion was significantly inhibited by idelalisib at concentrations of 0.5 µM or greater.

To evaluate the effect of idelalisib on chemokine-induced signalling responses in CLL cells, primary CLL cells from patients (n= 3) were treated with the chemokines CXCL12 or CXCL13; evaluation of BCR stimulation with anti-IgM was also done. Idelalisib inhibited Akt and Erk phosphorylation in response to anti-IgM stimulation and in response to CXCL12 or CXCL13, respectively.

In vivo *studies*

The Applicant did not provide any in vivo data supporting the use of idelalisib in iNHL or CLL (see discussion on non-clinical aspects).

Secondary pharmacodynamic studies

Molecular target screening

Idelalisib was evaluated for its potential to interfere with ligand-receptor binding in a panel of 61 receptors including GPCRs, ion channels, receptor tyrosine kinases, steroid receptors, and transporters. In these radioligand displacement assays, idelalisib had no significant effect at a concentration of 10 µM.

Effect on bone marrow cells

The effect of idelalisib on rat erythroid lineage development was assessed in a study in Sprague Dawley rat-derived bone marrow cultures. Thy-1+cells were isolated and cultured in the presence of idelalisib or LY294002 (positive control) with or without erythropoietin. The cultured cells were assessed for erythroid precursors by flow cytometry and quantification of BFU-e in MethoCult cultures. Treatment with 50 µM of the positive control, LY294002 (a pan-PI3K inhibitor), in the presence or absence of erythropoietin, inhibited the increases in $CD36^+$ cells on Day 3, $CD71^+$ cells on Day 6 and 9, and $Ter\text{-}119^+$ cells as measured by flow cytometry. Idelalisib did not significantly inhibit erythroid differentiation at 0.1 or 1 µM, either in the presence or absence of erythropoietin. At 10 µM, idelalisib decreased or prevented the progression of the erythroid differentiation beyond the $CD36^+$ state. idelalisib decreased the BFU-e values at 10 and 100 µM significantly in the absence of erythropoietin. In the presence of erythropoietin there was a modest decrease in the BFU-e values with 10 and 100 µM idelalisib.

The potential effect of idelalisib on human bone marrow mononuclear cell cultures were evaluated in 14 day cultures in liquid phase in the presence of growth factors, with and without added erythropoietin (EPO), with our without positive control agents, and with or without idelalisib at concentrations of 0.1, 1, 10, and 50 µM. Cells were evaluated in soft agar colony formation assays for their ability to form colonies wherein total colony forming units (CFU), burst forming units-erythroid (BFU-e), burst forming units-granulocyte monocyte (BFU-GM) and burst forming units-megakaryocytes (BFU-mk) were evaluated. Idelalisib caused concentration-dependent decreases on erythroid differentiation (with and without EPO) and myeloid differentiation at all concentrations tested. At 0.1, 1, 10 and 50 µM, idelalisib inhibited BFU-e in the absence and presence of EPO, the latter by 67, 83, 100 and 100 %, respectively, and inhibited CFU-GM by 45, 68, 85 and 90%, respectively. Effects on CFU-mk were present only at 10 and 50 µM concentrations. The control compounds, LY294002 (pan-PI3K inhibitor), NVP-BEZ235 (pan-PI3K/mTOR inhibitor), and AG490 (Jak2 inhibitor) also influenced these processes at concentrations previously reported to affect hematopoietic progenitor cell differentiation.

Effect on human T-cells and NK-cells

The effect of idelalisib on normal T-lymphocytes and NK cell survival was assessed in a study using cells isolated from human blood. T-cell receptor (TCR)-mediated proliferation of T-cells is abolished by pan-PI3K inhibition. Isolated human peripheral blood lymphocytes were treated with either vehicle or idelalisib prior to TCR activation by adding antihuman CD3ε antibody. CD3-induced proliferation response was measured by incorporation of [^{3}H]thymidine. Proliferation of T-lymphocytes was inhibited by idelalisib with an EC_{50} of 973 nM. Cultures of $CD3^+$ T-lymphocytes and $CD56^+$ NK cells isolated from blood samples obtained from 9 healthy volunteers were each incubated with idelalisib for 48 hours at concentrations of 0.1, 1, and 10 µM; untreated isolated cells were used as controls for each sample. Viability was determined by expression of Annexin V and uptake of propidium iodide as determined by flow cytometry and was calculated relative to time-matched untreated control cells. Idelalisib exposure had no effects on the viability of normal T-lymphocytes or NK cells.

Safety pharmacology programme

Effects on central nervous system

Single doses of the vehicle (0.5% carboxymethylcellulose, 0.1% Tween® 80 in water), or idelalisib at 50, 100, or 150 mg/kg were administered orally to male and female Sprague Dawley rats via gavage at a dose volume of 10 mL/kg (7 to13 males/group, 8 to 12 females/group). The rats were evaluated in the modified Irwin functional observational battery at 2 and 24 hours after dosing. There were no adverse effects of idelalisib in the modified Irwin test of CNS general signs and behavior at doses up to 150 mg/kg.

Effects on cardiovascular and respiratory system

The effect of idelalisib on the stably expressed hERG (human ether-a-go-go-related gene) potassium channel current in HEK293 cells was assessed using a rubidium flux-based method. Idelalisib was tested at 10 concentrations ranging from 0.0977 to 50 µM. There was no dose-response trend or significant inhibition of the hERG channel up to 50 µM.

The potential for idelalisib to cause adverse cardiovascular and respiratory effects following administration of a single dose was evaluated in telemetered non-naïve male dogs. Idelalisib was orally administered via capsule to 4 conscious, telemetered beagle dogs at 0 (lactose monohydrate vehicle only), 1, 5, and 20 mg/kg in a Latin Square crossover design with an interval of approximately 3 days between doses. At single doses up to 20 mg/kg, idelalisib did not produce any adverse effects on heart rate, respiratory rate, core body temperature, arterial blood gas parameters, or ECG parameters (PR, QRS, QT, and QTc intervals) up to 24 hours after dose administration.

Pharmacokinetic drug interactions

In vitro data indicated that idelalisib is not an inhibitor of the metabolising enzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A, or UGT1A1, or of the transporters OAT1, OAT3, or OCT2.

GS-563117 is not an inhibitor of the metabolising enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT1A1, or of the transporters P gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

2.3.3. Pharmacokinetics

Idelalisib showed high forward permeability in Caco 2 cell monolayers. The efflux ratio decreased with increasing concentration of idelalisib, suggesting that idelalisib was a substrate for efflux transporters and that efflux transporters were saturated.

Idelalisib is primarily metabolized by aldehyde oxidase to its major circulating plasma metabolite, GS-563117. In rat, dog, and monkey, plasma levels of GS-563117 are below those of idelalisib. However, in humans GS-563117 plasma levels exceed those of idelalisib.

Idelalisib exhibits moderately high plasma protein binding in mouse, rat, dog, and human. After po administration of [^{14}C] to rats and dogs, radioactivity is widely distributed, but relatively excluded from bone, brain, spinal cord, and eye lens in rats and from brain and eyes in dogs. In rats, the radioactivity declines steadily and most tissues have undetectable levels by 72 hours post dose.

The oral bioavailability is moderate. The volume of distribution is greater than the volume of total body water in all species. Clearance of idelalisib is moderate to high in the rat and moderate in the dog and cynomolgus monkey.

2.3.4. Toxicology

Single dose toxicity

Table 1: Single dose toxicity studies conducted with idelalisib

Species / Strain Study No.	Dose (mg/kg) Method of Administration	Gender and No. / Group	Noteworthy Findings
Rat/Sprague Dawley (Crl)	300, 900, 1500 Oral Gavage	3/sex toxicology animals (3/sex TK animals)	Animals were observed for 5 days (toxicology animals) or 2 days (TK animals) post-dose. No mortality was observed. Clinical signs were ruffled haircoat and/or squinted eyes (Day 5, females given 1500 mg/kg). BW loss (≤ 20%) in mid- and high-dose animals. Histopathologic findings (Day 5) in all treated groups were depletion/necrosis of hematopoietic cells (bone marrow and spleen) and lymphocytes (lymphoid organs; thymus, spleen, lymph node, and gut-associated lymphoid tissue), and neutrophilic inflammation (intestine). Hypertrophic centrilobular hepatocytes noted in 1500 mg/kg males. Males C_{max} = 38.2, 38.9, and 2.20 µg/mL for 300, 900 and 1500 mg/kg groups, respectively. AUC_{all} = 621, 814, and 9.59 µg·h/mL for 300, 900 and 1500 mg/kg groups, respectively. Females C_{max} = 34.3, 37.8, 37.9 µg/mL for 300, 900 and 1500 mg/kg groups, respectively. AUC_{all} = 758, 828, 781 µg·h/mL for 300, 900 and 1500 mg/kg groups, respectively.
Dog/Beagle	10, 25, 50, 200 Oral Gavage	2 M 2 F	Mortality in 2 females given 200 mg/kg within a few hours following dosing. Clinical observations prior to death included yellow mucus, emesis, tremors and tonic-clonic convulsions, vasoconstriction (blanching of skin and gums, cold body), dyspnea, transient cessation of breathing following a forced inspiration, lethargy and ataxia. Surviving animals observed for 7 days post-dose. Males given 200 mg/kg survived until scheduled necropsy with clinical observations of watery/loose stool and/or emesis. Animals given 25 and 50 mg/kg noted with loose black stool containing yellow mucus, emesis, and decreased FC. BW loss (≤ 10%) in all dose groups. At 10 mg/kg, the mean $AUC_{0\text{-last}}$ was 103 and 159 µg·h/mL for males and females, respectively. At 10 mg/kg, the mean C_{max} was 8.3 and 16.4 µg/mL for males and females, respectively.

Repeat dose toxicity

Table 2: Repeat dose toxicity studies conducted with idelalisib

Species / Strain Duration of Dosing Study No.	Dose (mg/kg/day) Method of Administration	Gender and No. per Group	Noteworthy Findings
Rat/Sprague Dawley (Crl) 4 weeks + 4 weeks recovery	0, 25, 100, 150 Oral Gavage	10+4/sex toxicology animals (6/sex TK animals)	No effects on body weights, food consumption, ophthalmologic findings, coagulation parameters or urinalysis results. *Mortality* There were 9 unscheduled deaths in the 100 mg/kg/day (1 male, 3 females) and 150 mg/kg/day (1 male, 4 females) groups. Other than one female animal in the 100 mg/kg/day group that died on Day 12 of dosing, all other idelalisib-related deaths occurred after completion of the dosing period during the 4-week recovery period. Increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) in several of these animals correlated with

			hepatic necrosis and/or tongue ulceration. In general, severe bone marrow depletion with marked myeloid hyperplasia and erythroid depletion was also seen in these early deaths. Overall, the microscopic findings among animals that died or were euthanized in moribund condition reflected more severe presentations of similar, milder findings seen among animals from these dose groups that survived to the conclusion of the 4-week dosing period. *Clinical signs* ≥ 100 mg/kg/day: excessive salivation leading to wet fur and/or dry, red material on the fur due to porphyrin staining. *Clinical pathology* ≥ 100 mg/kg/day: Reversible decreases in total white blood cells (WBC) (0.46- to 0.53-fold), primarily due to decreases in absolute lymphocyte counts (0.26- to 0.51-fold). This correlated with reversible hyperplasia of myeloid and granulocytic lineage cells in the bone marrow with concurrent decreases in erythroid precursors. 150 mg/kg: Small reversible reductions in several erythrocyte parameters (ie, RBC, HGB, HCT) (0.84- to 0.96-fold). No toxicological relevant changes in serum chemistry were seen among animals that survived to the conclusion of the 4-week dosing period. *Histopathology and organ weights* ≥ 100 mg/kg/day: Decreased thymus weight correlating with lymphocyte depletion. Dose-related decrease in secondary follicles of lymph nodes and Peyer's patches. B cell reduction in spleen and thymus. Lymphocyte reductions generally more severe in females. Effects on lymphocyte numbers and subsets were reversible. Decreased testis and epididymis weights were present in all idelalisib-treated male groups and correlated with dose-dependent, minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in the epididymis. These changes were incompletely reversed following the 4-week recovery period. A reversible increase in incidence of chronic inflammatory cell infiltrates (macrophages, lymphocytes, and plasma cells) in the liver was seen in both male and female animals treated with idelalisib at all dose levels. Increased liver weight (F: ≥ 100 mg/kg; M: 150 mg/kg) without microscopic correlates. A slightly increased incidence and/or severity of generally minor chronic inflammatory cell infiltrates (macrophages, lymphocytes, and plasma cells) were seen in the myocardium of all idelalisib-treated groups of rats except 50 mg/kg/day females after 4 weeks of dosing and persisted after the 4-week recovery period.
Rat/Sprague Dawley (Crl) 13 weeks + 4 weeks recovery	0, 25, 50, 90 Oral gavage	10+5/sex toxicology animals (6/sex TK animals)	There were no idelalisib-related effects on mortality, body weight, food consumption, ophthalmic examination results, haematology, coagulation, or urinalysis parameters in males and females and no clearly idelalisib-related clinical chemistry changes. *Clinical signs* 90 mg/kg: Wet fur and discoloured material around the eyes and nose, and an unkempt appearance (2/15F). Three female rats had inflammatory changes in the skin and mucocutaneous junction, associated with changes in haematological and/or clinical chemistry parameters. No similar effects were seen in males or after the recovery period. *Histopathology and organ weights* ≥25 mg/kg: Decreases in lymphocytes in predominantly B cell-dependent areas. Following the non-dosing period, animals were observed with a hyperplastic lymphoid response, suggesting these changes were reversible. Decreases in mean testes weights (-5.2% to -23.9%) and epididymides weights (-0.7% to -15%) correlating with dose-dependent minimal to mild seminiferous tubule degeneration and partial depletion of spermatocytes and spermatids. Partially reversible. ≥50 mg/kg: Slight increase in incidence and/or severity of inflammation in pancreas (M) 90 mg/kg: Reversible increases in mean heart weights (+12.1% to +14.8%) in males and a slight increase in incidence and severity of background

			cardiomyopathy in females. Slight increase in pancreatic haemorrhage (M).
Rat/Sprague Dawley (Crl) 26 weeks + 12 weeks recovery	0, 25, 50, 90 Oral gavage	10+4/sex toxicology animals (6/sex TK animals)	There were no idelalisib-related effects on body weights, food consumption, ophthalmic findings, coagulation or urinalysis parameters, or macroscopic observations at necropsy. *Mortality* 25 mg/kg: 1M/1F; 50 mg/kg: 1F; 90 mg/kg: 2M. The cause of death of the 25 mg/kg/day male was determined to be malignant lymphoma. The cause of death in the remaining 4 animals could not be determined. *Histopathology and organ weights* ≥25 mg/kg: Lymphoid changes, including decreased mean spleen weight due to decreased lymphocytes in the splenic marginal zone. Partly reversible in males ≥50 mg/kg and fully reversible in other groups. ≥50 mg/kg: Reversible decreases in mean testes and epididymides weights lacking microscopic correlates.
Dog/Beagle 4 weeks+ 4 weeks recovery	0, 2.5, 5, 20 Oral capsule	4+3/sex	There were no idelalisib-related effects on ophthalmology or electrocardiography observations, coagulation or urinalysis parameters. *Mortality* One female dog in the 20 mg/kg/day group was found moribund on Day 29 prior to scheduled necropsy. This animal had shown clinical signs that included soft faeces, faecal blood, red discoloured eyes, shivering, thin body condition, lethargy, salivation, mouth ulceration and inappetence with loss of body weight (-21%) beginning on Day 10. Marked depletion of thymic lymphocytes with minimal haemorrhage and moderate congestion may have led to moderate to marked suppurative inflammation in the lungs with mild multifocal haemorrhage. Aspiration pneumonia could not be ruled out, however, because this animal had an episode of vomiting on Day 17. Minimal to mild congestion or haemorrhage in the large intestine was consistent with similar GI-tract changes seen in other idelalisib-treated animals *Clinical signs* 20 mg/kg: Soft faeces and apparent faecal blood. Decreased food consumption and lowered body weights in females (-8.3%). Nasal or ocular discharge more frequent. *Clinical pathology* ≥2.5 mg/kg: Decreases in absolute basophil counts (21% to 38% of control) showing recovery. Decreases in circulating lymphocyte numbers in females, in the 20 mg/kg group persisting through the recovery period. 20 mg/kg: Elevated ALT, AST, and ALP in females, showing recovery. *Histopathology and organ weights* ≥2.5 mg/kg: Dose-dependent decreases in testicular weight (45% to 69% of control) at the conclusion of the 4 week recovery period, appearing to correlate with reduced spermatogenesis microscopically at doses of 5 mg/kg/day. ≥5 mg/kg: Mild reversible lymphoid depletion in the axillary and inguinal lymph nodes. 20 mg/kg: Moderate lymphoid depletion in the Peyer's patch of the ileum, mild to marked lymphoid depletion in the axillary and inguinal lymph nodes, and moderate to marked lymphoid depletion or cortical lymphoid necrosis in the thymus. In general reversible, with the exception of persistent mild lymphoid depletion in the Peyer's patches of 2/3 females. Histologic findings in the liver included minimal to mild cytoplasmic rarefaction and necrosis of hepatocytes, and minimal to moderate hepatocellular swelling primarily in centrilobular to mid-zonal regions. Chronic inflammation (primarily macrophages and lymphocytes), often surrounded individual necrotic hepatocytes. Minimal hepatocellular necrosis was also observed in 1 of 4 males at 5 mg/kg/day idelalisib and 1 control male. Hepatic findings often correlated with 1 or more modest increases in ALT (3.9- to 136-fold), AST (2.3- to 44.3-fold), ALP (2.0- to 7.3-fold), and GGT (1.7- to 4.3-fold), and/or total bilirubin (1.5- to 6.0-fold) at the Day 29 necropsy. Although some liver findings were identified on Day 57, they were usually of lower severity than Day 29 and were unaccompanied by noteworthy elevations in serum enzyme concentrations; thus, the hepatic findings were considered

			largely reversible.
Dog/Beagle 13 weeks+ 4 weeks recovery	0, 2.5, 5, 7.5 Oral capsule	4+3/sex	There were no early mortalities; no effects on body weights, food consumption, haematology, clinical chemistry, coagulation or urinalysis parameters, or in ophthalmic and electrocardiographic examinations. Immunphenotyping was performed, showing inconsistent changes in lymphocyte subsets; these data were considered of limited or no value for characterizing the toxicity of idelalisib. *Histopathology and organ weights* ≥2.5 mg/kg: Decreases in lymphocyte numbers in predominantly B cell-dependent areas. Following recovery, there was generally a hyperplastic response, indicating reversal of the idelalisib-related reduction of lymphoid tissues. Dose-dependent decreases in testicular organ weights (5.3% to 44.9%), correlating microscopically with reduced spermatogenesis. Incompletely reversible. Non-adverse minimal to mild subacute inflammation in alveolar spaces of the lungs (M)
Dog/Beagle 39 weeks+ 12 weeks recovery	0, 2.5, 5, 7.5 Oral capsule	4+2/sex	In animals surviving until the scheduled necropsy there were no idelalisib-related effects on food consumption, serum chemistry, coagulation, urinalysis, ophthalmic and electrocardiographic examinations or organ weights. *Mortality* Two idelalisib-treated animals (a 2.5 mg/kg/day group female [Week 33] and a 7.5 mg/kg/day group male [Week 21]) were euthanized in moribund condition prior to the scheduled necropsy. The cause of death for these 2 animals was systemic inflammation (likely sepsis) which was secondary to decreased lymphocytes in multiple peripheral lymphoid tissues including spleen, thymus, Peyer's patches, and lymph nodes. *Clinical signs* Clear discharge and injected sclera in several animals across all idelalisib groups and reddened facial area in the 7.5 mg/kg/day group. These clinical findings generally resolved during the recovery period. *Body weight* 7.5 mg/kg: Decreases in mean body weight gain (males, -11.3%; females, -8.9%,) *Histopathology* ≥2.5 mg/kg: Decreased lymphocytes, primarily involving typical B-cell regions with lesser effects in typical T-cell regions, of the spleen, lymph nodes (mandibular, mesenteric, and axillary), and Peyer's patches. Minimal to slight increases in dilated crypts/glands, often accompanied by small numbers of mucosal granulocyte infiltrates (neutrophils and eosinophils) were seen in one or more segments of the GI tract (jejunum through rectum). Complete recovery of the histopathologic changes was noted at the end of the 12-week non-dosing interval with the following exceptions: minimal to mild decreases in lymphocytes persisted in the spleen and mesenteric lymph node of 1 of 2 males in the 7.5 mg/kg/day group and a slightly increased severity of granulocyte infiltrates persisted in the ileum in the 7.5 mg/kg/day males.

Genotoxicity

Table 3: Genotoxicity studies conducted with idelalisib

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Gene mutations in bacteria 961805	*Salmonella* strains TA1535, TA1537, TA98, TA100 and *E coli*	up to 5000 µg/plate +/- S9	Negative

GLP	WP2 *uvrA*		
Chromosomal aberrations in mammalian cells 961806 GLP	Human peripheral blood lymphocytes	up to 256 µg/mL +/- S9	Negative
Chromosomal aberrations in vivo 961807 GLP	Rat, micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg	A slight, but statistically significant increase in the incidence of micronucleated immature erythrocytes, with a group mean value for the 2000 mg/kg males slightly outside the laboratory historical negative control range primarily due to the results from 2 of 5 rats. There was also some evidence of a perturbation in erythropoiesis in the 2000 mg/kg group as indicated by a statistically significant reduction in the proportion of immature erythrocytes at the 48-hour sampling time point. Based on the mechanism of action of PI3Ks and their role as intracellular signalling proteins essential to migratory, proliferative, survival and differentiation pathways, idelalisib may cause small increase in micronucleated erythrocytes as a result of interference with cell division or other mechanisms unrelated to the inherent genotoxicity of the compound

A Derek analysis of the main human metabolite GS-563117 showed no structural alerts for mutagenicity.

Carcinogenicity

No carcinogenicity studies with idelalisib have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Table 4: Reproduction toxicity studies conducted with idelalisib

Study type/ Study ID / GLP	**Doses (mg/kg/ day)**	**Dosing period**	**Major findings**
Male fertility in rats GLP	0, 25, 50, 100	10M/dose: 70 days prior to mating and throughout mating phase 10M/dose: 70 days followed by 10 week non-dosing period before mating.	Reversible decreases in epididymis, cauda epididymis, and testes weights were noted at all dose levels correlating with reversibly decreased epididymal sperm concentrations in the 25, 50, and 100 mg/kg/day groups. Visibly small testes correlated with testicular contraction in the absence of degeneration or loss of cellular stages of spermatogenesis in the testes microscopically. Cellular debris was present in the epididymis along with vacuolation of the pituitary gland at 100 mg/kg/day, the only idelalisib-treated group examined microscopically. Although idelalisib-related decreased epididymal sperm numbers were noted in all treated groups, the decreases had no effect on reproductive indices. Following a 10-week non-dosing period, no significant organ weight, epididymal sperm concentration, or histological changes were noted indicating the changes were reversible upon discontinuation of dosing.
Female fertility and early embryonic development in rats	0, 25, 50, 100	14 days prior to mating, throughout	One of 25 females in the 100 mg/kg/day group had a totally resorbed litter, resulting in a slightly higher incidence of mean post-implantation loss (early resorptions) and a

GLP		mating phase, and through gestation day 7.	correspondingly lower mean number of viable embryos in this group. The relationship of this total litter resorption to idelalisib could not be determined. No effects on intrauterine survival were noted in the 25 or 50 mg/kg/day groups. Based on the resorption of a single litter at 100 mg/kg/day which was of undetermined relationship to idelalisib administration the NOAEL for early embryonic toxicity was considered to be 50 mg/kg/day. Due to the lack of any other effects, 100 mg/kg/day, the highest dosage level evaluated, was considered the NOAEL for female systemic and reproductive toxicity of idelalisib when administered orally once-daily by gavage.
Embryo-fœtal development in rats GLP	0, 25, 75, 150	GD6 to GD17	The NOAEL for maternal toxicity was 75 mg/kg/day based on the death of 1 female, clinical findings of red vaginal discharge and/or red material on the urogenital area in several females, and lower mean body weight gains and food consumption at 150 mg/kg/day. The NOAEL for embryo-fetal developmental toxicity was 25 mg/kg/day based on a higher incidence of post-implantation loss at 150 mg/kg/day, lower mean fetal weights at 75 and 150 mg/kg/day that correlated with sites of reduced fetal skeletal ossification, and increased incidences of short tail (75 and 150 mg/kg/day), anury, vertebral agenesis, microphthalmia/anophthalmia, and hydrocephaly (150 mg/kg/day) as well as skeletal developmental variations at 75 and 150 mg/kg/day. For further details see below.

Toxicokinetic data

Toxicokinetic analyses were performed as part of the toxicology studies.

Table 5: Toxicokinetic parameters for idelalisib

Rat 4 weeks						
IDELA (mg/kg/day)	**sex**	**AUC_{last} (µg·h/mL)**		**C_{max} (µg/mL)**		**AUC Exposure margin at termination[a]**
		Day 1	**Day 28**	**Day 1**	**Day 28**	
50	Male	22.0	35.6	6.34	6.57	1.8
	Female	47.4	82.6	8.01	12.9	4.1
100	Male	58.3	157	9.24	16.2	7.8
	Female	152	300	16.1	34.8	15
150	Male	168	590	16.2	50.5	29

Rat 4 weeks						
IDELA (mg/kg/day)	sex	AUC_{last} (µg·h/mL)		C_{max} (µg/mL)		AUC Exposure margin at termination[a]
		Day 1	Day 28	Day 1	Day 28	
	Female	341	502	27.3	33.7	25
Rat 13 weeks						
IDELA (mg/kg/day)	sex	AUC_{last} (µg·h/mL)		C_{max} (µg/mL)		
		Day 1	Day 90	Day 1	Day 90	
25	Male	3.50	7.37	1.20	1.98	0.37
	Female	13.3	30.9	3.50	6.33	1.5
50	Male	12.3	45.0	2.86	5.13	2.2
	Female	27.6	73.3	5.11	10.1	3.6
90	Male	25.1	114	4.63	10.2	5.7
	Female	85.4	172	9.21	15.1	8.5
Rat 26 weeks						
IDELA (mg/kg/day)	sex	AUC_{last} (µg·h/mL)		C_{max} (µg/mL)		
		Day 1	Day 181	Day 1	Day 181	
25	Male	3.39	10.6	1.30	2.21	0.53
	Female	7.86	23.0	3.11	3.93	1.1
50	Male	7.09	43.7	2.45	4.84	2.2
	Female	18.7	55.0	5.96	8.57	2.7
90	Male	17.8	104	6.51	8.22	5.2
	Female	55.7	182	11.0	15.5	9.0
Dog 4 weeks						
IDELA (mg/kg/day)	sex	AUC_{last} (µg·h/mL)		C_{max} (µg/mL)		
		Day 1	Day 28	Day 1	Day 28	
2.5	Male	2.13	4.76	0.609	0.873	0.24
	Female	2.92	3.85	0.700	0.638	0.19
5	Male	5.39	8.49	1.40	1.31	0.42
	Female	6.42	9.28	1.28	1.54	0.46
20	Male	56.9	113	7.17	11.5	5.6
	Female	47.6	292	6.56	20.5	14
Dog 13 weeks						
IDELA (mg/kg/day)	sex	AUC_{last} (µg·h/mL)		C_{max} (µg/mL)		
		Day 1	Day 90	Day 1	Day 90	
2.5	Male	3.35	5.25	0.775	0.760	0.26
	Female	2.07	3.48	0.562	0.669	0.17
5	Male	4.32	12.4	0.855	1.44	0.62
	Female	5.35	5.86	1.23	1.03	0.29
7.5	Male	15.2	24.2	2.47	3.46	1.2
	Female	4.49	9.62	1.12	1.32	0.48
Dog 39 weeks						
IDELA (mg/kg/day)	sex	AUC_{last} (µg·h/mL)		C_{max} (µg/mL)		
		Day 1	Day 272	Day 1	Day 272	
2.5	Male	3.05	3.89	0.745	0.792	0.19
	Female	1.63	6.29	0.490	1.41	0.31
5	Male	3.58	8.55	0.660	1.37	0.42
	Female	2.71	10.7	0.667	1.69	0.53
7.5	Male	12.9	18.5	2.13	2.40	0.92
	Female	3.47	15.9	0.770	2.93	0.79

a Based on IDELA clinical AUC_{0-12} at 150 mg BID IDELA = 10.081 µg·h/mL

Table 6: Toxicokinetic parameters for the main human metabolite GS-563117

Rat 13 weeks						
IDELA (mg/kg/day)	**sex**	**AUC_{last} (µg·h/mL)**		**C_{max} (µg/mL)**		**AUC Exposure margin at termination[a]**
		Day 1	**Day 90**	**Day 1**	**Day 90**	
25	Male	0.127	0.195	0.038	0.047	0.005
	Female	0.109	0.209	0.035	0.047	0.005
50	Male	0.359	0.905	0.074	0.094	0,023
	Female	0.298	0.582	0.057	0.098	0.015
90	Male	0.640	1.84	0.130	0.180	0.047
	Female	0.545	0.843	0.066	0.090	0.022
Rat 26 weeks						
IDELA (mg/kg/day)	**sex**	**AUC_{last} (µg·h/mL)**		**C_{max} (µg/mL)**		
		Day 1	**Day 181**	**Day 1**	**Day 181**	
25	Male	0.082	0.133	0.033	0.053	0.003
	Female	0.924	0.280	0.047	0.069	0.007
50	Male	0.218	0.454	0.097	0.086	0.012
	Female	0.218	0.562	0.093	0.179	0.014
90	Male	0.585	0.980	0.161	0.155	0.025
	Female	0.378	1.02	0.152	0.167	0.026
Dog 13 weeks						
IDELA (mg/kg/day)	**sex**	**AUC_{last} (µg·h/mL)**		**C_{max} (µg/mL)**		
		Day 1	**Day 90**	**Day 1**	**Day 90**	
2.5	Male	1.82	1.48	0.291	0.164	0.038
	Female	1.37	0.970	0.258	0.126	0.025
5	Male	2.14	2.44	0.300	0.207	0.062
	Female	2.84	1.67	0.417	0.207	0.043
7.5	Male	5.06	3.80	0.710	0.432	0.098
	Female	2.32	1.81	0.391	0.190	0.047
Dog 39 weeks						
IDELA (mg/kg/day)	**sex**	**AUC_{last} (µg·h/mL)**		**C_{max} (µg/mL)**		
		Day 1	**Day 272**	**Day 1**	**Day 272**	
2.5	Male	1.15	1.10	0.201	0.151	0.028
	Female	1.02	1.98	0.180	0.268	0.051
5	Male	1.51	2.00	0.183	0.201	0.051
	Female	1.40	2.51	0.260	0.281	0.065
7.5	Male	3.82	3.47	0.528	0.292	0.089
	Female	2.19	4.02	0.324	0.509	0.103

a Based on GS-563117 clinical AUC_{tau} at 150 mg BID IDELA = 38.9 µg·h/mL

Local Tolerance

No local tolerance study has been submitted (see discussion on non-clinical aspects).

Other toxicity studies

Immunotoxicity:

Evaluation of bone marrow recovery after cyclophosphamide administration

Myelosuppression is often associated with chemotherapeutic regimens containing cyclophosphamide (CTX). This study evaluated the potential for idelalisib to induce or exacerbate CTX-induced myelosuppression in rats. Rats given a single dose of CTX at 75 mg/kg exhibited suppression of erythropoiesis and lower counts of WBCs. Rats give idelalisib at 50 mg/kg for 10 days had mildly lower WBCs and lymphocyte counts. Coadministration of idelalisib with CTX did not appear to exacerbate the myelosuppressive effects of CTX.

Effects of idelalisib on T-cell dependent antibody responses

The ability of idelalisib to alter the primary antibody-forming cell (AFC) response to sheep erythrocytes (sRBC) was assessed in rats. Female Lewis rats (5/group) were dosed twice daily via oral gavage with either the vehicle or idelalisib at doses of 1, 3, 10, 30, or 150 mg/kg/day for 10 days. CTX was used as a positive control and was administered IP (100 mg/kg) for two days. Four hours after the first dose (Day 1), animals were immunized via IP injection with sRBC. The IgM and IgG primary AFC response was evaluated by ELISA from serum collected pre-test and on Days 7 and 10. Idelalisib was able to suppress the T-dependent antibody response to sRBC at doses of 10-150 mg/kg/day BID.

Effect of idelalisib on host defense

This study was conducted to investigate the potential ability of idelalisib to inhibit the normal short-term host defense response to a staphylococcal infection in a rat groin abscess model. Idelalisib doses of 30, 60, and 120 mg/kg/dose administered once prior to infection and 12, 24 and 36 hours post infection inhibited growth of the infectious agent by between 65%, 72%, and 85% respectively relative to the vehicle control group. The positive control group (dexamethasone) demonstrated reduced host defense, leading to an increase in colony counts (+351%). Idelalisib did not inhibit the ability of the test system to tolerate the infectious challenge.

Studies on impurities:

Three potential in silico genotoxic positive process impurities (GS-567201, GS-606709, and GS-606710) were qualified in a GLP compliant bacterial reverse mutation test at a range of concentrations up to 5000 µg/plate in the presence and absence of a S9 mix using the plate incorporation and preincubation method of the bacterial mutation test. None of the 3 potential impurities showed any evidence of genotoxic activity.

Potential idelalisib related process impurities (GS-563116, GS-563118, GS-563120, GS-563973, and GS-575510) were qualified in a 28 day oral gavage toxicity study in rats (GLP). Sprague Dawley rats were assigned to 4 groups (10/sex/group) and received either the vehicle, 90 mg/kg/day idelalisib, or 25 or 90 mg/kg/day of a lot of idelalisib spiked with these impurities. There were no differences in toxicity findings between the two lots.

Phototoxicity:

Idelalisib and the primary metabolite, GS-563117, were evaluated for the potential to induce phototoxicity in the embryonic murine fibroblast cell line BALB/c 3T3 using Neutral Red uptake as a marker of cellular viability in the presence and absence of UVA light exposure (non-GLP). Concentrations from 0 to 100 µg/mL of idelalisib and GS-563117 were evaluated twice, with and without UVA exposure, at a light dosage of 5 J/cm^2. Phototoxicity results for idelalisib were inconclusive due to cytotoxicity. The primary oxidative metabolite, GS-563117, was phototoxic in this assay.

Mechanistic studies:

Two studies were performed in dogs to study transaminase elevation and the potential of beclomethasone diproprionate (BDP) or budesonide to alter the magnitude or time course of any observed effects.

Female dogs administered idelalisib at 15 mg/kg/day without concomitant BDP administration exhibited a pattern of multifocal, primarily centrilobular hepatocellular degenerative and/or necrotic changes that were associated with expected secondary inflammatory changes as a result of tissue repair responses commonly seen following the administration of a number of different chemically diverse xenobiotic agents. These changes were variably associated with modest, transient serum transaminase elevations, typically occurring between Days 13 and 27 that spontaneously resolved during continued dosing. Dogs

pretreated with BDP for 14 days prior to idelalisib administration had evidence of expected steroid histopathologic responses and did not show transient transaminase elevations at examined time points.

Female dogs administered idelalisib at 15 mg/kg/day without concomitant budesonide (BUD) administration exhibited variable, transient transaminase elevations between Days 21 and 42 that generally resolved spontaneously with continued idelalisib administration. Concomitant and pretreatment with BUD appeared to limit the magnitude and delayed the emergence of these transient transaminase elevations.

2.3.5. Ecotoxicity / environmental risk assessment

Table 7: Summary of main study results

Substance (INN / Invented Name): Idelalisib			
CAS-number (if available): 870281-82-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	Potentiometric titration (PDM-1632.03, non-GLP)	1.95	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.95	not B
	BCF	Not assessed	B/not B
Persistence	DT50 or ready biodegradability	Not assessed	P/not P
Toxicity	NOEC or CMR	Not assessed	T/not T
PBT-statement	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.5 (default) 0.0089 (refined)	µg/L	> 0.01 threshold (Yes for default)
O.C.s (e.g. chemical class)			None

Idelalisib is not PBT as log Kow does not exceed 4.5. As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of idelalisib to the environment. A Phase II assessment will be performed and submitted by the end of 2015.

2.3.6. Discussion on non-clinical aspects

Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B cells and in primary tumour cells. Through inhibition of chemokine receptors CXCR4 and CXCR5 signalling induced by the chemokines CXCL12 and CXCL13, respectively, idelalisib inhibits homing and retention of malignant B cells in the tumour microenvironment including lymphoid tissues and the bone marrow (see section 5.1 of the SmPC).

The mechanistic in vitro studies performed by the applicant with tumour cell lines and primary tumour cells demonstrate a direct anti-tumour effect on CLL and MCL. These studies show that most of the anti-tumour response is due to inhibition of signalling from cytokines and/or interaction with other cells. The data from the applicant shows an involvement of chemokines and the B cell receptors but also other stimuli may be involved (IL-6, CD40, integrins). This inhibition may act in two directions: by reducing tumour cell proliferation and survival and by disturbing the tumour microenvironment.

Idelalisib reduced viability in primary CLL cells. It is noted that reduced viability was not seen in all patient samples. Of the patient samples shown, a fraction (~25%) responded to idelalisib. In Study DR-4002 data of only 7 patient samples was shown.

An important property of idelalisib is the high degree of selectivity for the PI3Kδ kinase versus the other PI3K (α, β, γ).

Idelalisib shows a high selectivity in the screens with other kinases and a broader panel of receptors and ion channels. But even if off-target activity is absent or minimal, secondary pharmacological events are likely to occur through the inhibition of PI3Kδ. The studies on haematopoiesis showed a possible interference by idelalisib however, toxicological data do not suggest haematological toxicity. Effects on lymphocyte populations, primarily B-cells, are observed but these effects are most likely due to inhibition of PI3Kδ in mature lymphocytes.

No inhibition of T-cell proliferation was observed in in vitro studies. However, PI3Kδ is active in T cells and likely to be of functional importance. The effects of a PI3Kδ inhibitor are most likely not limited to inhibition of growth and survival of B cells and B cell malignancies. In particular, there may be consequences for immune regulation, and such effects may be important for the safety profile of idelalisib (see RMP).

The Applicant did not submit any in vivo data supporting the use of idelalisib in iNHL or CLL. In the literature several murine B-cell lymphoma models can be found, these include spontaneous models of B-cell lymphoma as well as induced models. While data from animal models may have been supportive for this application, it is noted that there is ample data with patients samples. Given the in vitro data and the clinical experience, no further in vivo pharmacodynamic studies in animal models are required.

According to the CHMP Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr.*), the need for pharmacodynamics drug interaction studies should be determined on a case-by-case basis and should be considered for drugs which compete with each other at the pharmacological target and/or have similar or opposing pharmacodynamic (therapeutic or adverse) effects. In subjects with iNHL or CLL, idelalisib has been evaluated clinically in combination with anti-CD20 antibodies (rituximab or ofatumumab) and/or chemotherapeutic agents (bendamustine, fludarabine, or chlorambucil). Based on the mechanism of action of idelalisib and the different mechanisms of actions of each of these individual agents, no pharmacodynamic drug interaction studies were considered necessary.

Toxicokinetics data from repeat-dose toxicity studies allow for extrapoplation. In rats, a dose of 150 mg/kg resulted in a Cmax of 21.8 µg/ml (mean of values from male and female rats). In dogs, a dose of 20 mg/kg resulted in a Cmax of 6.86 µg/ml (mean of values from male and female dogs). In patients at the recommended dose of 150 mg, Cmax was 1.9 µg/ml. Thus, the performed studies would reach sufficient exposure to conclude on the absence of a non-clinical concern about acute adverse effects on CNS, cardiovascular and respiratory systems.

Pharmacokinetics

Analytical methods used in the GLP safety studies are appropriate and validated for their purpose.

Protein binding is low to moderate, and there are no important species differences. Tissue distribution studies showed no signs of tissue retention. The metabolism of idelalisib seems to be well characterised.

Toxicology

In the repeat dose toxicity studies idelalisib induced lymphoid depletion in spleen, thymus, lymph nodes and gut associated lymphoid tissue. In general, B lymphocyte dependent areas were more affected than

T lymphocyte dependent areas. In rats, idelalisib has the potential to inhibit T dependent antibody responses. However, idelalisib did not inhibit the normal host response to *Staphylococcus aureus* and did not exacerbate the myelosuppressive effect of cyclophosphamide. Idelalisib is not considered to have broad immunosuppressive activity.

Idelalisib induced inflammatory changes in both rats and dogs. In studies up to 4 weeks in rats and dogs, hepatic necrosis was observed at 5 and 7 times the human exposure based on AUC, respectively. Serum transaminase elevations correlated with hepatic necrosis in dogs, but were not observed in rats. No hepatic impairment or chronic transaminase elevations were observed in rats or dogs in studies of 13 weeks and longer duration (see section 5.3 of the SmPC).

There are examples where it has been demonstrated that genetic defects in certain immunological signalling pathways may lead to a deregulated immune system, resulting in inflammation due to autoimmune reactions or exaggerated immune reactivity to environmental non-pathogens. The possibility that inhibition of PI3Kδ in B and T lymphocytes could have such consequences should be considered. This could be a possible explanation for non-clinical adverse events, gastrointestinal toxicity, systemic inflammation and hepatic toxicity. This possibility is supported by the demonstration of chronic colitis in mice with a knockout mutation in PI3Kδ (Uno et al 2010). Further characterisation of the immune consequences of idelalisib treatment will be performed as part of the RMP. The applicant has outlined a study program including in vitro evaluation of the effect of idealisib on T-cell proliferation, cytokine production and specific studies with regulatory T-cells. The effect of idealisib in autoimmune disease models will be studied in rats (collagen-induced arthritis) and mice (MRL/Lpr model of lupus). These studies will be reported as part of the RMP by the end of Q1 2015.

A standard genotoxicity package was performed with negative outcome. Idelalisib did not induce mutations in the microbial mutagenesis (Ames) assay, was not clastogenic in the in vitro chromosome aberration assay using human peripheral blood lymphocytes, and was not genotoxic in the in vivo rat micronucleus study. The minor chromosomal effects at the high dose in the rat study are most likely due to the pharmacological effect on PI3K kinases, with all isotypes affected at this high dose.

No carcinogenicity studies with idelalisib have been conducted. Carcinogenicity studies are in general not required to support marketing for therapeutics intended to treat patients with advanced cancer. However, considering that life expectancy may be relatively long in some of these patients, in this particular case, there is a further need for carcinogenicty studies for idelalisib as well as for the major metabolite GS-563117. The applicant will conduct carcinogenity studies to address this concern (see RMP).

In an embryo foetal development study in rats, increased post implantation loss, malformations (absence of caudal vertebrae and in some cases also of sacral vertebrae), skeletal variations and lower foetal body weights were observed. Malformations were observed at exposures from 12 times the human exposure based on AUC. Effects on embryo foetal development were not investigated in a second species (see sections 4.6 and 5.3 of the SmPC). Based on these findings, idelalisib may cause foetal harm. Women should avoid becoming pregnant while taking idelalisib, and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraception while taking idelalisib and for 1 month after stopping treatment. It is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method as a second form of contraception.

Degeneration of the seminiferous tubules in the testes was observed in 2 to 13 week repeated dose studies in dogs and rats, but not in studies of 26 weeks and longer duration. In a rat male fertility study, decreases in epididymides and testes weight were observed but no adverse effects on mating or fertility

parameters, and no degeneration or loss in spermatogenesis were observed. As a consequence, restriction to father a child was not required for idelalisib.

Female fertility was not affected in rats (see section 5.3 of the SmPC). Although there are no human data available on the effect of idelalisib on fertility, animal studies indicate the potential for harmful effects of idelalisib on fertility and foetal development (see section 4.6). Similarly, there are no or limited amount of data from the use of idelalisib in pregnant women. However since studies in animals have shown reproductive toxicity, idelalisib is not recommended during pregnancy and in women of childbearing potential not using contraception.

No studies on metabolites were performed. For the major human metabolite GS-563117, exposure in animal studies did not reach above 1/10 of the clinical exposure. GS-563117 lacks activity at PI3K and showed a low oral bioavailability in nonclinical species. In ICH S9, it is stated that a separate evaluation of human metabolites that have not been qualified in other studies is generally not warranted for patients with advanced cancer. However, for these indications, life expectancy may be considered sufficiently long to warrant further carcinogenicity investigation. Since human exposure to the metabolite exceeds the exposure to the parent compound, and exposure in animal studies is less than 1/10 of the clinical exposure, further safety data related to the metabolite could be of value. The applicant has presented data showing poor bioavailability in the rat, and i.v. dosing was associated with short half-life. An i.v. repeat dose toxicity study in rat was not considered feasible. However, a dose-range finding (DRF) study including toxicokinetic analysis has now been conducted in mice showing a 2-fold exposure to the metabolite in terms of C_{max} as compared to humans, and an AUC which is 73% of the steady state AUC in humans. Although clinical AUC values are not reached in mice, it is considered that the study in mice will provide sufficient data to base a risk assessment with regard to the metabolite. The data from the 4 week repeat-dose toxicity study in mice will be reported in Q4 2014 (see RMP).

During the procedure, the applicant has submitted an in silico analysis using DEREK revealing no genotoxic potential of metabolite GS-563117. The negative in silico outcome and the fact that the metabolite is structurally similar to the parent idelalisib were considered sufficient to conclude that GS-563117 is unlikely to be genotoxic. Preliminary data suggest that in mice dosing with idelalisib leads to exposure to the metabolite allowing for qualification. The data from a 4 week repeat-dose toxicity study will be reported as part of the RMP in Q4 2014. To further identify potential safety concerns for the metabolite an extended (non-kinase) receptor binding study will be performed and reported in Q4 2014. The SAG-oncology was consulted on whether data on mutagenicity and carcinogenicity would be required prior to authorisation and the SAG-O concluded that such data could be provide post-authorisation (see additional expert consultation, below).

A number of dedicated studies addressed certain aspects of immunotoxicity. These studies did not show any important effects of idelalisib. The antibody response was clearly inhibited, but the conclusions from this study are weakened by the fact that the immune response in the control group was weak, and no convincing quantification of the antibody response was shown. The possibility that idelalisib treatment results in immune deregulation, resulting in autoimmune responses and exaggerated immune reactivity to environmental non-pathogens will be further investigated by the applicant (see RMP).

Evaluation of the potential for phototoxicity in the embryonic murine fibroblast cell line BALB/c 3T3 was inconclusive for idelalisib due to cytotoxicity in the in vitro assay. The major metabolite, GS-563117, may enhance phototoxicity when cells are simultaneously exposed to UVA light. There is a potential risk that idelalisib, via its major metabolite, GS-563117, may cause photosensitivity in treated patients (see section 5.3 of the SmPC).

Idelalisib is not a PBT substance. The applicant was recommended to conduct a Phase II assessment.

Local tolerance studies have not been submitted. As the intended clinical route of administration is oral, and this route of administration has been employed in the toxicity studies, dedicated stand-alone local tolerance studies are not necessary. The local tolerance of idelalisib has been assessed in the general toxicity studies.

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 10 June 2014 to provide advice on the following question:

The mutagenicity and carcinogenicity data of the parent substance and main human metabolite (GS-563117) were not complete in the initial application. What data would be required before and/or after registration to address this deficiency taking prior and alternative treatment options as well as prognosis with respect to survival into account? In addition, would absence of such data influence your willingness to prescribe idelalisib?

The feedback was that despite interspecies differences in metabolites, especially the main metabolite, there are no signals at the moment that would warrant limiting prescription according to proposed indication. Thus, further data to address this issue pre-authorisation are not required on clinical grounds.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 4.6, 5.1, 5.3). The applicant will conduct non-clinical studies to further evaluate the role of aldehyde oxidase in the metabolism of idelalisib, DDI of idelalisib with transport substrates, the safety of the main human metabolite GS-563117 and the carcinogenicity of idelalisib.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 8: Clinical Studies supporting the marketing authorisation application of idelalisib

Study Identifier	Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects by Treatment	Healthy Subjects or Patient Population	Duration of Treatment	Study Status; Type of Report
Comparative Bioavailability and Bioequivalence							
101-06	Evaluate the PK of single 100 mg dose of IDELA administered as a capsule (unmicronized granulation formulation), a capsule (micronized API powder), or a tablet in normal healthy male subjects	Phase 1, open-label, randomized, 3-period crossover study in subjects administered a single tablet, single capsule with unmicronized granulation formulation, or single capsule with micronized API powder	IDELA 100 mg SD as single tablet, single capsule with unmicronized granulation formulation, or single capsule with micronized API powder	Planned: 15; Enrolled: 15	Healthy male subjects	1 day with 4-day washout	Study Complete, Final CSR
Healthy Subject PK and Initial Tolerability Study Reports							
101-01	Evaluate and determine the safety and PK of single-dose and multiple-dose oral administration of IDELA in healthy males	Phase 1, randomized, double-blind, placebo-controlled, sequential dose escalation study of IDELA in healthy male subjects	IDELA SD: 17, 50, 125, 250, and 400 mg IDELA MD (7 days) 50, 100, and 200 mg BID	Planned: 64; Enrolled: 64	Healthy male subjects	7 days	Study Complete, Final CSR
101-05	Evaluate the PK of IDELA administered in a fasting or fed state and administered concomitantly with ketoconazole	Phase 1, 3-period crossover study of food and ketoconazole on PK of IDELA and AME of a microdose of ^{14}C-labeled IDELA in healthy males	IDELA 400 mg SD IDELA 10 µg + 100 nCi [^{14}C] IDELA SD (fasting), oral or IV Ketoconazole 400 mg (4 days)	Planned: 12; Enrolled: 12	Healthy male subjects	1-4 days	Study Complete, Final CSR
GS-US-313-0111	Determine the mass balance of IDELA after administration of single, oral dose of radiolabeled [^{14}C] IDELA	Phase 1 study of metabolism and excretion as well as PK of IDELA in healthy volunteers	IDELA 150 mg SD consisting of 100 µCi [^{14}C] IDELA and 149.25 mg of nonradiolabeled IDELA	Planned: 8; Enrolled: 8	Healthy male subjects	1 day	Study Complete, Final CSR
GS-US-313-0126	Investigate the PK, safety, and tolerability of IDELA after SD administration in healthy Japanese and Caucasian subjects	Phase 1 open-label study of PK, safety, and tolerability of IDELA in healthy Japanese and Caucasian subjects	IDELA 150 mg SD	Planned: 20; Enrolled: 20	Healthy Japanese and Caucasian subjects	1 day	Study Complete, Final CSR
GS-US-339-0101	Evaluate the safety, tolerability, and PK of GS-9973 and IDELA, each administered alone and in combination, in healthy female subjects	Phase 1, open-label, dose escalation study of safety, tolerability, and PK/PD of GS-9973 and IDELA administered alone or combined in healthy subjects	IDELA 100 and 150 mg BID GS-9973 200 and 600 mg BID	Planned: 24; Enrolled: 24	Healthy female subjects	12 days	Study Complete, Final CSR

Study Identifier	Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects by Treatment	Healthy Subjects or Patient Population	Duration of Treatment	Study Status; Type of Report
Patient PK and Initial Tolerability Study Reports							
101-02	Investigate the safety of IDELA in subjects with select, relapsed, or refractory hematologic malignancies by determining the MTD and DLT and determine the PK	Phase 1, sequential, dose escalation study of IDELA in subjects with select, relapsed, or refractory hematologic malignancies	IDELA × 28 days 50, 75, 100, 150, 200, 350 mg BID; 150, 300 mg once daily IDELA × 21 days/7 days off: 150 mg BID	Planned: 180; Enrolled: 191	Relapsed or refractory CLL, NHL, AML, and MM	21 or 28 days	Study Complete, Final CSR
101-04	Evaluate the safety of MD, oral administration of IDELA in allergic rhinitis subjects and determine effects on total nasal symptom scores after environmental chamber allergen challenge	Phase 1, randomized, double-blind, placebo-controlled, 2-period crossover study of IDELA in allergic rhinitis subjects and effects on response to environmental chamber allergen challenge	IDELA 100 mg BID over 7 days (no PM dose on last day)	Planned: 45; Enrolled: 41	Subjects with allergic rhinititis	7 days	Study Complete, Final CSR
Intrinsic Factor PK Reports							
GS-US-313-0112	Evaluate the PK of IDELA and GS-563117 in hepatically impaired subjects compared to matched healthy subjects	Phase 1 open-label PK study of IDELA in subjects with impaired hepatic function	IDELA 150 mg (single dose)	Planned: 60; Enrolled: 32	Subjects with normal and impaired hepatic function	1 day	Study Complete, Final CSR
GS-US-313-0118	Evaluate the PK of IDELA and GS-563117 in renally impaired subjects and matched healthy subjects	Phase 1 open-label PK study of IDELA in subjects with impaired renal function	IDELA 150 mg (single dose)	Planned: 60; Enrolled: 12	Subjects with normal and impaired renal function	1 day	Study Complete, Final CSR
Extrinsic Factor PK Reports							
GS-US-313-0130	Evaluate the effects of IDELA on CYP3A and the drug transporters Pgp, OATP1B1, and OATP1B3 using phenotyping probes and evaluate the effect of rifampin on PK of IDELA	Phase 1 study on effects of IDELA on probe substrates of CYP3A enzymes or drug transporters Pgp, OATP1B1, and OATP1B3, and the effect of rifampin on PK and safety of IDELA	IDELA 150 mg plus midazolam 5 mg IDELA 150 mg plus digoxin 0.5 mg IDELA 150 mg plus rosuvastatin 10 mg IDELA 150 mg plus rifampin 600 mg	Planned: 24 Enrolled: 24	Healthy female and male subjects	14 and 18 days	Study Complete, Final CSR
Healthy Subject PD and PK/PD Study							
GS-US-313-0117	Evaluate the effects of IDELA and metabolite GS-563117 on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, partially-blinded, randomized, placebo- and positive-controlled study of effect of IDELA on the QT/QTc interval in healthy subjects	IDELA 400 mg SD and IDELA 400 mg (150 mg IDELA + 250 mg placebo)	Planned: 48; Enrolled: 48	Healthy subjects	31 days	Study Complete, Final CSR

Study Identifier	Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects by Treatment	Healthy Subjects or Patient Population	Duration of Treatment	Study Status; Type of Report
Uncontrolled Safety and Efficacy Studies							
101-07	Investigate the safety of IDELA with an anti-CD20 mAb, chemotherapeutic agents, an mTOR inhibitor, and/or a proteasome inhibitor in subjects with relapsed or refractory CLL, iNHL, or MCL	Phase 1, open-label study of IDELA in combination with an anti-CD20 mAb, chemotherapeutic agents, an mTOR inhibitor, and/or a proteasome inhibitor in subjects with relapsed or refractory CLL, iNHL, or MCL	IDELA: 100 or 150 mg BID (oral) continuously in combination with: Rituximab 375 mg/m^2 IV weekly, Cycles 1 and 2 Bendamustine 70 or 90 mg/m^2 IV Days 1 and 2, Cycles 1-6 Rituximab+bendamustine Rituximab 375 mg/m^2 IV every 4 weeks , Cycles 1-6 and Bendamustine 70 mg/m^2 Days 1 and 2, Cycles 1-6 Ofatumumab 300 mg IV Day 1 or 2, then 1000 mg weekly for Weeks 2-8, followed by 1000 mg every 4 weeks for 4 doses during Weeks 9-12 Fludarabine 40 mg/m^2 (oral) Days 1-5, Cycles 1-6 Everolimus 10 mg (oral) Days 1-28 of every 4-week cycle Bortezomib 1.3 mg/m^2 SC Days 1, 8, and 15 for 3 weeks followed by 13-day rest period Chlorambucil 10 mg/m^2 (oral) Days 1-7, Cycles 1-12 Rituximab+chlorambucil Rituximab 375 mg/m^2 IV Day 1, Cycles 1-6 Chlorambucil 10 mg/m^2 (oral) once daily Days 1-7, Cycles 1-6	Planned: Maximum: 210; minimum: 184 Enrolled: 226	Subjects with histologically or cytologically confirmed select types of B-cell CLL, iNHL, or MCL	Up to a maximum of twelve 28-day cycles	Study Ongoing, Interim CSR and Addendum No. 1 to Interim CSR (provides additional data for Cohorts 5 and 6)
101-08	Evaluate the overall response rate of IDELA when combined with rituximab in elderly subjects with previously untreated CLL or SLL	Phase 2 single-arm study of IDELA in combination with rituximab in elderly subjects with previously untreated CLL or SLL	IDELA: 150 mg (or reduced to 75/100 mg) BID (oral) × 48 weeks Rituximab: 375 mg/m^2 IV weekly × 8 weeks	Planned: 59; Enrolled: 64	Subjects with histologically or cytologically confirmed CLL or SLL (and no prior therapy for CLL or SLL) and World Health Organization performance status ≤ 2	Up to 48 weeks	Study Ongoing, Interim CSR

Study Identifier	Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects by Treatment	Healthy Subjects or Patient Population	Duration of Treatment	Study Status; Type of Report
101-09	Evaluate tumor regression as determined by overall response rate in subjects receiving IDELA to treat iNHL refractory to rituximab and alkylating agents	Phase 2, open-label, single-arm, 2-stage study of IDELA in subjects with previously treated iNHL refractory to both rituximab and alkylating agents	IDELA 150 mg (or reduced to 75/100 mg) BID continuously	Planned: 100; Enrolled: 125	Subjects with histologically confirmed diagnosis of B-cell iNHL (FL, SLL, LPL with or without WM, or MZL)	Until occurrence of events requiring treatment discontinuation	Study Ongoing, Primary Analysis CSR
101-10	Investigate the safety and efficacy of IDELA in subjects with previously treated iNHL and efficacy of 300-mg BID IDELA in those tolerating therapy but experiencing disease progression with ≤ 150 mg BID	Phase 1/2, single-agent, uncontrolled study of IDELA in subjects with previously treated low-grade iNHL	IDELA 150 mg BID for 28-day cycles up to 12 cycles	Planned: 15; Enrolled: 11	Subjects with histologically confirmed diagnosis of low-grade B-cell iNHL and at least 1 prior systemic therapy for iNHL	Up to 12 treatment cycles of 28 days each	Study Ongoing, Interim Synoptic CSR
101-11	Evaluate tumor regression as determined by overall response rate in subjects receiving IDELA to treat relapsed or refractory HL	Phase 2, open-label, single-arm, 2-stage study of IDELA in subjects with relapsed or refractory HL	IDELA 150 mg BID continuously (with dose reduction or escalation)	Planned: 21; Enrolled: 25	Subjects with histologically confirmed diagnosis of classic HL, nodal HL with measurable fluorodeoxyglucose avidity, relapsed or refractory HL	Until occurrence of events requiring treatment discontinuation	Study Ongoing, Interim Synoptic CSR
101-99	Investigate the long-term safety of IDELA in subjects with hematologic malignancies and determine its duration of clinical benefit	Phase 1/2 extension study of safety and durability of IDELA in hematologic malignancies	50, 100, 150, 200, or 350 mg BID; 150 or 300 mg once daily	Planned: No limit Analyzed: 183	Subjects with hematologic malignancies who completed a prior study of IDELA with clinical benefit	As long as the subject derives clinical benefit	Study Ongoing, Interim CSR
Controlled Safety and Efficacy Studies							
GS-US-312-0116	Evaluate the effect of the addition of IDELA to rituximab on safety and efficacy in subjects with previously treated CLL	Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of IDELA in combination with rituximab in subjects with previously treated CLL	IDELA 150 mg BID	Planned: 200; Enrolled: 220	Subjects with relapsed CLL who were unable to tolerate chemoimmunotherapy	Until tumor progression or unacceptable toxicity	Study Ongoing, Interim CSR
GS-US-312-0115	Evaluate the effect of the addition of IDELA to BR on safety and efficacy in subjects with previously treated CLL	Phase 3, double-blind, randomized, placebo-controlled safety and efficacy study of IDELA in combination with BR for previously treated CLL	IDELA 150 mg BID	Planned: 390; Enrolled: 34	Subjects with confirmed CLL	Until tumor progression or unacceptable toxicity	Study Ongoing, Blinded DMC Tables

Study Identifier	Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects by Treatment	Healthy Subjects or Patient Population	Duration of Treatment	Study Status; Type of Report
GS-US-312-0117	Companion trial to Study GS-US-312-0116 to evaluate the safety and efficacy of 2 different doses of single-agent IDELA in subjects with previously treated CLL	Phase 3, 2-arm, double-blind, parallel-group extension study of IDELA in subjects with previously treated CLL	IDELA 150 mg or 300 mg BID	Planned: up to 160; Enrolled: 11	Subjects with confirmed CLL	Until tumor progression or unacceptable toxicity	Study Ongoing, Blinded DMC Tables
GS-US-312-0119	Evaluate the effect of the addition of IDELA to ofatumumab on safety and efficacy in subjects with previously treated CLL	Phase 3, 2-arm, randomized, controlled, parallel-group study of IDELA in subjects with previously treated CLL	IDELA 150 mg BID	Planned: 210; Enrolled: 18	Subjects with confirmed CLL	Until tumor progression or unacceptable toxicity	Study Ongoing, Blinded DMC Tables
GS-US-313-0124	Evaluate the effect of the addition of IDELA to rituximab on safety and efficacy in subjects with previously treated iNHL	Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of IDELA in combination with rituximab in subjects with previously treated iNHL	IDELA 150 mg BID	Planned: 375; Enrolled: 1	Subjects with histologically confirmed iNHL (FL, SLL, LPL with or without WM, or MZL)	Until tumor progression or unacceptable toxicity	Study Ongoing, Blinded DMC Tables
GS-US-313-0125	Evaluate the effect of the addition of IDELA to BR on safety and efficacy in subjects with previously treated iNHL	Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of IDELA in combination with BR in subjects with previously treated iNHL	IDELA 150 mg BID	Planned: 450; Enrolled: 1	Subjects with histologically confirmed iNHL (FL, SLL, LPL with or without WM, or MZL)	Until tumor progression or unacceptable toxicity	Study Ongoing, Blinded DMC Tables

2.4.2. Pharmacokinetics

Absorption

Following oral administration of a single dose of idelalisib, peak plasma concentrations were observed 2 to 4 hours post-dose under fed conditions and after 0.5 to 1.5 hours under fasted conditions.

Following 150 mg twice daily administration of idelalisib, average (range) Cmax and AUC at steady state were 1,953 (272; 3,905) ng/mL and 10,439 (2,349; 29,315) ng•h/mL for idelalisib and 4,039 (669; 10,897) ng/mL and 39,744 (6,002; 119,770) ng•h/mL for GS-563117, respectively. The plasma exposures (Cmax and AUC) of idelalisib are approximately dose proportional between 50 mg and 100 mg and less than dose proportional above 100 mg (see section 5.2 of the SmPC).

Absolute bioavailability was not determined, but an oral/iv microdose study suggests that a high fraction of the dose is absorbed. The passive in vitro permeability in Caco-2 cells was high and idelalisib was an in vitro substrate for the efflux transporters Pgp and BCRP.

Effects of food

Relative to fasting conditions, administration of an early capsule formulation of idelalisib with a high-fat meal resulted in no change in Cmax and a 36% increase in mean AUCinf. Idelalisib can be administered without regard to food. (see section 5.2 of the SmPC).

Distribution

In the population pharmacokinetic model, idelalisib PK data was best described by a two-compartment model and the typical central and peripheral volume of distribution was 23 and 73 L, respectively. Idelalisib is 93% to 94% bound to human plasma proteins at concentrations observed clinically. The mean blood-to-plasma concentration ratio was approximately 0.5. The apparent volume of distribution for idelalisib (mean) was approximately 96 L (see section 5.2 of the SmPC).

Elimination

Idelalisib is metabolised primarily via aldehyde oxidase, and to a lesser extent via CYP3A and UGT1A4. The main metabolite both in plasma, faeces and urine was the oxidative metabolite GS-563117. The metabolite has no pharmacological activity on PI3Kð.

Maximum plasma concentrations are observed after 1-2 hours. The terminal elimination half-life of idelalisib was 8.2 (range: 1.9; 37.2) hours and the apparent clearance of idelalisib was 14.9 (range: 5.1; 63.8) L/h following idelalisib 150 mg twice daily oral administration.

A mass-balance study was performed, with drug dissolved in ethanol. Following a single 150 mg oral dose of [14C] labelled idelalisib, approximately 78% and 15% was excreted in faeces and urine, respectively. Unchanged idelalisib accounted for 23% of total radioactivity recovered in urine over 48 hours and 12% of total radioactivity recovered in faeces over 144 hours (see section 5.2 of the SmPC).

Dose proportionality and time dependencies

A tendency to less than proportional increase in exposure with dose was seen in ascending dose studies in both healthy subjects (17-400 mg) and patients with haematological malignancies (50-350 mg), especially on day 28. According to the PPK model, however, the relative bioavailability is essentially constant at doses in excess of 100 mg. No obvious time dependency was seen in the data, but time dependency has not been evaluated in the popPK analysis.

Special populations

A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with severe renal impairment (estimated CrCl 15 to 29 mL/min). Following a single 150 mg dose, no clinically relevant changes in exposures to idelalisib or GS-563117 were observed in subjects with severe renal impairment compared to healthy subjects (see section 5.2 of the SmPC).

A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Following a single 150 mg dose, idelalisib AUC (total, i.e., bound plus unbound) was ~60% higher in moderate and severe impairment compared to matched controls. The idelalisib AUC (unbound), after accounting for differences in protein binding, was ~80% (1.8 fold) higher in moderate and ~152% (2.5 fold) higher in severe impairment compared to matched controls. In samples from subjects with severe hepatic impairment, the plasma protein binding was lower than in matched controls (fraction unbound 11% compared with 6.7%) (see section 5.2 of the SmPC).

Gender, race or age were not found to be clinically relevant covariates in the population PK analysis on the exposures to idelalisib or GS-563117, including elderly subjects (65 years of age and older), compared to younger subjects (see SmPC section 5.2). There was a statistically significant association between exposure and body weight.

The pharmacokinetics of idelalisib in paediatric subjects have not been established.

The table below summarises the number of older people included in PK studies.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	10/218	0/218	0/218

Pharmacokinetic interaction studies

Idelalisib is metabolised primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117, which is not pharmacologically active. Idelalisib and GS-563117 are substrates of P-gp and BCRP.

Effect of other medicinal products on idelalisib pharmacokinetics

CYP3A inducers

A clinical drug interaction study found that co-administration of a single dose of 150 mg idelalisib with rifampicin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib AUC_{inf}. Co-administration of idelalisib with moderate or strong CYP3A inducers such as rifampicin, phenytoin, St. John's wort, or carbamazepine should be avoided as this may result in decreased efficacy (see sections 4.4 and 4.5 of the SmPC).

CYP3A/P-gp inhibitors

A clinical drug interaction study found that co-administration of a single dose of 400 mg idelalisib with 400 mg once daily ketoconazole (a strong CYP3A, P-gp and BCRP inhibitor) resulted in a 26% increase in C_{max} and a 79% increase in AUC_{inf} of idelalisib. No initial dose adjustment of idelalisib is considered necessary when administered with CYP3A/P-gp inhibitors, but an intensified monitoring of adverse reactions is recommended.

Effect of idelalisib on the pharmacokinetics of other medicinal products

CYP3A substrates

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A inhibitor. A clinical drug interaction study found that co-administration of idelalisib with midazolam (a sensitive CYP3A substrate) resulted in a ~140% increase in C_{max} and a ~440% increase in AUC_{inf} of midazolam due to the CYP3A inhibition by GS-563117. Co-administration of idelalisib with CYP3A substrates may increase their systemic exposures and increase or prolong their therapeutic activity and adverse reactions. *In vitro*, the CYP3A4 inhibition was irreversible, and return to normal enzyme activity is therefore expected to take several days after stopping idelalisib administration.

Potential interactions between idelalisib and co-administered medicinal products that are CYP3A substrates are listed in Table 9 (increase is indicated as "↑"). This list is not exhaustive and is intended to serve as guidance only. In general, the SmPC for the other product must be consulted for the

recommendations regarding co-administration with CYP3A4 inhibitors (see sections 4.4 and 4.5 of the SmPC).

Table 9: Interactions between idelalisib and other medicinal products that are CYP3A substrates

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
Alpha-1 adrenoreceptor antagonists		
Alfuzosin	↑ serum concentrations	Idelalisib should not be co-administered with alfuzosin.
Analgesics		
Fentanyl, alfentanil, methadone, buprenorphine/naloxone	↑ serum concentrations	Careful monitoring of adverse effects (e.g., respiratory depression, sedation) is recommended.
Antiarrhythmics		
Amiodarone, quinidine	↑ serum concentrations	Idelalisib should not be co-administered with amiodarone or quinidine.
Bepridil, disopyramide, lidocaine	↑ serum concentrations	Clinical monitoring is recommended.
Anti-cancer agents		
Tyrosine kinase inhibitors such as dasatinib and nilotinib, also vincristine and vinblastine	↑ serum concentrations	Careful monitoring of the tolerance of these anticancer agents is recommended.
Anticoagulants		
Dabigatran, rivaroxaban, warfarin	↑ serum concentrations	It is recommended that the international normalised ratio (INR) be monitored upon co-administration and following ceasing treatment with idelalisib.
Anticonvulsivants		
Carbamazepine	↑ serum concentrations	Anticonvulsant drug levels should be monitored.
Antidepressants		
Trazodone	↑ serum concentrations	Careful dose titration of the antidepressant and monitoring for antidepressant response is recommended.
Anti-Gout		
Colchicine	↑ serum concentrations	Dose reductions of colchicine may be required. Idelalisib should not be co-administered with colchicine to patients with renal or hepatic impairment.
Anti-Hypertensives		
Amlodipine, diltiazem, felodipine, nifedipine, nicardipine	↑ serum concentrations	Clinical monitoring of therapeutic effect and adverse reactions is recommended.
Anti-Infectives		
Antifungals		
Ketoconazole, itraconazole, posaconazole, voriconazole	↑ serum concentrations	Clinical monitoring is recommended.
Antimycobacterials		
Rifabutin	↑ serum concentrations	Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is recommended.
HCV protease inhibitors		
Boceprevir, telaprevir	↑ serum concentrations	Clinical monitoring is recommended.
Macrolide antibiotics		
Clarithromycin, telithromycin	↑ serum concentrations	No dose adjustment of clarithromycin is required for patients with normal renal function or mild renal impairment (creatinine clearance [CrCl] 60-90 mL/min). Clinical monitoring is recommended for patients with CrCl < 90 mL/min. For patients with CrCl < 60 mL/min, alternative antibacterials should be considered. Clinical monitoring is recommended for telithromycin.

Medicinal product	Expected effect of idelalisib on drug levels	Clinical recommendation upon co-administration with idelalisib
Anti-psychotics/neuroleptics		
Quetiapine, pimozide	↑ serum concentrations	Idelalisib should not be co-administered with quetiapine or pimozide. Alternative medicinal products, such as olanzapine, may be considered.
Endothelin Receptor Antagonists		
Bosentan	↑ serum concentrations	Caution should be exercised and patients closely observed for bosentan-related toxicity.
Ergot alkaloids		
Ergotamine, dihydroergotamine	↑ serum concentrations	Idelalisib should not be co-administered with ergotamine or dihydroergotamine.
Gastrointestinal motility agents		
Cisapride	↑ serum concentrations	Idelalisib should not be co-administered with cisapride.
Glucocorticoids		
Inhaled/nasal corticosteroids: Budesonide, fluticasone	↑ serum concentrations	Clinical monitoring is recommended.
Oral budesonide	↑ serum concentrations	Clinical monitoring is recommended for increased signs/symptoms of corticosteroid effects.
Hmg Co-A Reductase Inhibitors		
Lovastatin, simvastatin	↑ serum concentrations	Idelalisib should not be co-administered with lovastatin or simvastatin.
Atorvastatin	↑ serum concentrations	Clinical monitoring is recommended and a lower starting dose of atorvastatin may be considered. Alternatively, switching to pravastatin, rosuvastatin, or pitavastatin may be considered.
Immunosuppressants		
Ciclosporin, sirolimus, tacrolimus	↑ serum concentrations	Therapeutic monitoring is recommended.
Inhaled Beta Agonist		
Salmeterol	↑ serum concentrations	Concurrent administration of salmeterol and idelalisib is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Phosphodiesterase Inhibitors		
		For pulmonary arterial hypertension:
Sildenafil	↑ serum concentrations	Idelalisib should not be co-administered with sildenafil.
Tadalafil	↑ serum concentrations	Caution should be exercised, including consideration of dose reduction, when co-administering tadalafil with idelalisib.
		For erectile dysfunction:
Sildenafil, tadalafil	↑ serum concentrations	Particular caution must be used and dose reduction may be considered when prescribing sildenafil or tadalafil with idelalisib with increased monitoring for adverse events.
Sedatives/Hypnotics		
Midazolam (oral), triazolam	↑ serum concentrations	Idelalisib should not be co-administered with midazolam (oral) or triazolam.
Buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ serum concentrations	Concentration monitoring of sedatives/hypnotics is recommended and dose reduction may be considered.

CY2C8 substrates

In vitro, idelalisib both inhibited and induced CYP2C8, but it is not known whether this translates to an *in vivo* effect on CYP2C8 substrates. Caution is advised if idelalisib is used together with narrow therapeutic index drugs that are substrates of CYP2C8 (paclitaxel).

Substrates of inducible enzymes (e.g., CYP2C9, CYP2C19, CYP2B6 and UGT)

In vitro, idelalisib was an inducer of several enzymes, and a risk for decreased exposure and thereby decreased efficacy of substrates of inducible enzymes such as CYP2C9, CYP2C19, CYP2B6 and UGT cannot be excluded. Caution is advised if idelalisib is used together with narrow therapeutic index drugs that are substrates of these enzymes (warfarin, phenytoin, S-mephenytoin).

BCRP, OATP1B1, OATP1B3 and P-gp substrates

Co-administration of multiple doses of idelalisib 150 mg twice daily to healthy subjects resulted in comparable exposures for rosuvastatin (AUC 90% CI: 87, 121) and digoxin (AUC 90% CI: 98,111), suggesting no clinically relevant inhibition of BCRP, OATP1B1/1B3 or systemic P-gp by idelalisib. A risk for P-gp inhibition in the gastrointestinal tract, that could result in increased exposure of sensitive substrates for intestinal P-gp such as dabigatran etexilate, cannot be excluded (see section 4.5 of the SmPC).

Paediatric population

Interaction studies have only been performed in adults.

Pharmacokinetics using human biomaterials

Plasma protein binding of idelalisib was assessed at substrate concentrations of 0.5 and 2 µM in mouse and rat and 0.5 to 20 µM in dog and human by equilibrium dialysis. Idelalisib exhibited moderately high plasma protein binding in all species with the free fraction ranging from 9.3 to 25.1%. The lowest average free fraction was observed in human plasma (~16% free). In mouse, rat, and dog the average plasma protein binding was comparable, ranging from 18.7% free (rat) to 20.8% free (dog). Plasma protein binding in dog and human was drug concentration-independent between 1 and 20 µM. Plasma protein binding of GS-563117, the oxidative metabolite of idelalisib, was assessed in human plasma at a substrate concentration of 10 µM by equilibrium dialysis. GS-563117 was highly protein bound with a free fraction of ~12%. In human plasma, GS-563117 was slightly more protein bound than its parent compound idelalisib (data not shown).

For reports of hepatic metabolism and interaction studies, see above (special populations and pharmacokinetic interaction studies).

In Vitro Assessment of Blood Distribution of Idelalisib and GS-563117 was submitted (data not shown). The purpose of this study was to assess the distribution of idelalisib and its metabolite GS-563117 between the cellular and soluble fractions of blood. After incubation of whole blood from rat, dog, and human with idelalisib and GS-563117 (initial concentration 0.5 µM), the cell to plasma concentration ratios for idelalisib and GS-563117 were < 1.5 in all species, indicating that the compounds are not preferentially associated with blood cells. For idelalisib, the human blood to plasma ratio was the lowest ($\lambda = 0.68$) with the Sprague-Dawley rat and beagle dog showing more homogeneous distribution within blood ($\lambda = 0.87$ and 1.11, respectively). For GS-563117, the human blood to plasma ratio was also the

lowest (λ = 0.60) with the Sprague-Dawley rat and beagle dog showing more homogeneous distribution within blood (λ = 1.28 and 1.10, respectively).

2.4.3. Pharmacodynamics

Mechanism of action

See non-clinical aspects.

Primary and Secondary pharmacology

The principal source of information regarding the shape of the exposure response relationship (PK/PD) for idelalisib is a sequential dose escalation study (101-02), evaluating idelalisib doses of 50, 100, 150, 200, or 350 mg BID, or 150 or 300 mg once daily administered as monotherapy to subjects with relapsed or refractory hematologic malignancies. The PK/PD was evaluated visually using box plots of changes in tumour size (SPD) from baseline stratified by quartile of idelalisib Ctau for subjects with iNHL and CLL respectively. These box-plots suggested that the median SPD response reached a plateau at/above the second Ctau quartile for patients with iNHL and third Ctau quartile for patients with CLL and that the average exposure provided by 150 mg BID would be sufficient in both groups of patients (for further details see section 2.5.1)

A single-dose PK/PD study placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in 40 healthy subjects to evaluate the effects of idelalisib (at therapeutic [150 mg] and supratherapeutic [400 mg] doses) and metabolite GS-563117 on time-matched, baseline-adjusted, placebo-corrected QTcF (GS-US-313-0117). There were no relationships between time-matched, baseline-adjusted, placebo-corrected QTcF and idelalisib or GS-563117 plasma concentrations and idelalisib did not prolong the QT/QTc interval (i.e.,< 10 ms).

2.4.4. Discussion on clinical pharmacology

Idelalisib is extensively absorbed, and in vitro as well as in vivo data suggest a moderate to high permeability. The terminal elimination half-life of idelalisib was 8.2 (range: 1.9; 37.2) hours and the apparent clearance of idelalisib was 14.9 (range: 5.1; 63.8) L/h following idelalisib 150 mg twice daily oral administration. If the patient misses a dose of idelalisib within 6 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 6 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

The effect of concomitant food intake on an early formulation was limited (t_{max} increased from 0.75 to 3 hours, 40% increase in AUC). The applicability of these data to the final formulation was discussed within the procedure. As the pivotal study was performed regardless of food, with at least one of the two daily administrations probably taken fed or semi-fed, a better estimate of the food effect on the final formulation was not expected to change the recommendations in the SmPC and thus a new food effect study is not required. No DDI study with acid reducing agents was provided despite the pH dependent solubility. It was however accepted that the clinical data provided did not suggest a major impact of concomitant use of acid reducing drugs, and this together with the relatively flat exposure-response relationship led to the conclusion that a specific study is not necessary.

Idelalisib is 93% to 94% bound to human plasma proteins at concentrations observed clinically. The apparent volume of distribution for idelalisib (mean) was approximately 96 L (see section 5.2 of the SmPC). The terminal elimination half-life of idelalisib was 8.2 (range: 1.9; 37.2) hours and idelalisib is mainly excreted in faeces.

At 10 µM, idelalisib did not appear to be a substrate for the hepatic uptake transporters OATP1B1 and OATP1B3. This concentration was however substantially higher than the unbound Cmax (≈0.8 µM) and it cannot be ruled out that the transporters are saturated under experimental conditions. The applicant will investigate the substrate characteristics of idelalisib towards OATP1B1 and OATP1B3 at clinically relevant concentrations (see RMP).

No dose adjustment is required for patients with mild, moderate, or severe renal impairment or elderly patients (see sections 4.2 and 5.2 of the SmPC).

From the hepatic impairment study, unbound AUC increased 1.8 times to 2.5 times in moderate and severe hepatic impairment, respectively in agreement with the average unbound concentrations presented for these groups. It is agreed that initial dose adjustment in patients with mild or moderate hepatic impairment is not necessary, but the SmPC describes the need for intensified toxicity monitoring of adverse reactions in these patients. There is insufficient data to make dose recommendations for patients with severe hepatic impairment and special caution should be taken when treating these patients (see section 4.2 and 4.4 of the SmPC).

Considering the large effect (≥ 5-fold increase in AUC) seen on midazolam, which could be underestimated with the design used in the drug-interaction study, idelalisib is classified as a strong inhibitor of CYP3A4 (due to the CYP3A inhibition by GS-563117). Thus, idelalisib has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product (see section and 4.5 of the SmPC). When idelalisib is co administered with other medicinal products, the SmPC for the other product must be consulted for the recommendations regarding co administration with CYP3A4 inhibitors. Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life threatening adverse reactions (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.

Idelalisib showed a strong inducing effect in in vitro studies. Induction in vivo is not evident from the clinical data available. However, since the metabolite GS-563117 is a strong CYP3A4 inhibitor, CYP3A4 substrates such as midazolam cannot be used to study induction in vivo. In addition, in vivo data on digoxin cannot be used since idelalisib is a Pgp inhibitor in vitro. Thus, the risk for idelalisib being an enzyme inducer of PXR regulated enzymes other than CYP3A4 in the clinical setting cannot be excluded. The applicant is recommended to conduct an in vivo DDI study with a sensitive substrate to a PXR /CAR regulated enzyme other than CYP3A4, e g CYP2C9. In addition, a weaker CAR mediated induction was seen in vitro, and the potential clinical relevance of this could probably also be elucidated with data on a CYP2C9 substrate.

Given the induction signal in vitro and the potential teratogenicity based on the developmental toxicity seen in animals, the applicant will conduct an in vivo study of the effect of idelalisib on oral contraceptive steroids (see RMP). A steroid with as small contribution of CYP3A4 as possible should be chosen, to avoid effects of CYP3A4 inhibition. Until these data are available, the risk for decreased efficacy of oral contraceptives and the need for women using hormonal contraceptives to add a barrier method as a second form of contraception have been addressed in sections 4.4 and 4.6 of the SmPC.

An inhibitory effect of idelalisib on CYP2C8 could not be excluded based on in vitro data. GS-563117 was found to be a time dependent CYP3A4 inhibitor. The applicant will submit in vitro data on the time dependent inhibition of other CYP enzymes (IC50 shift with pre-incubation) (see RMP).

No effect of idelalisib was observed on digoxin or rosuvastatin in vivo. Since digoxin is not a very sensitive substrate for Pgp inhibition in the gut, the risk for inhibition of a more sensitive substrate such as dabigatran etexilate has been reflected in section 4.5 of the SmPC.

Ketoconazole had a moderate effect (79% increase in AUC) on idelalisib pharmacokinetics in the DDI study performed. The design may not be fully worst case, and it cannot be excluded that the maximum effect of a strong CYP3A4/Pgp inhibitor on idelalisib exposure may be somewhat underestimated. Terminal half-life appears unaffected in the study, maybe because ketoconazole levels at later time points were too low to fully inhibit CYP3A4, but comparisons of the half-lives 4-12 hours revealed an increase in idelalisib half-life in the combination phase. A less pronounced increase in metabolite (31%) than parent (79%) exposure was seen, with no effect on metabolite half-life. This indicates that CYP3A4 is not involved in formation of GS-563117 in vivo; aldehyde oxidase is most likely the enzyme responsible for GS-563117. As the exposure-response relationship appears relatively flat, it is accepted not to adjust the starting dose when idelalisib is combined with strong CYP3A4/Pgp inhibitors, however section 4.5 of the SmPC was updated to include instructions that intensified monitoring of side effects should be given.

Rifampicin had a large effect (75% decrease in AUC) on idelalisib exposure. Idelalisib exposure may therefore be reduced when co administered with strong CYP3A inducers such as rifampicin, phenytoin, St. John's wort (Hypericum perforatum), or carbamazepine. Since a reduction in idelalisib plasma concentrations may result in decreased efficacy, co administration of idelalisib with moderate or strong CYP3A inducers should be avoided (see sections 4.4 and 4.5 of the SmPC).

The applicant did not discuss potential interactions with other co-administered drugs in the clinical efficacy study 101-07 (bendamustine, ofatumumab, fludarabine, everolimus, bortezomib, and chlorambucil). By inhibition of CYP3A4, idelalisib could potentially increase the exposure of everolimus and bortezomib. If the applicant intends to apply for combination therapy with one of these drugs, the effect of idelalisib on the pharmacokinetics of the combined drug and vice versa should be investigated.

Gender, race or age were not found to be clinically relevant covariates in the population PK analysis on the exposures to idelalisib or GS-563117. Although a statistically significant association between exposure and body weight was observed, it was found to have a relatively minor impact on the variability in idelalisib exposure.

It is not known whether idelalisib and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast feeding should be discontinued during treatment with Zydelig. (see section 4.6 of the SmPC).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic data in support of the approval of idelalisib is considered sufficient. The Applicant will conduct a number of post-authorisation measures (PAMs) to further clarify the interaction potential:

- In vitro study of the effects of selective aldehyde oxidase inhibitors on the conversion of idelalisib to GS-563117
- In vitro study of the substrate characteristics of idelalisib towards OATP1B1 and OATP1B3
- In vivo interaction (induction) study with an oral contraceptive

- To conduct further studies on the human enzymology of idelalisib oxidation

The applicant is recommended to perform an in vivo interaction study with a sensitive substrate to a PXR/CAR regulated enzyme other than CYP3A4, e.g. CYP2C9, address the potential of idelalisib to induce drug metabolising enzymes through interaction with PXR and/or CAR.

Awaiting data from the planned studies, the lack of information has been reflected in the SmPC.

2.5. Clinical efficacy

Overview of studies

Table 10: Study Populations for Key idelalisib Studies Contributing Efficacy Data for the Treatment of CLL and SLL

Parameter	Study 101-02/99 (N = 191; CLL N = 54; SLL N = 11)	Study 101-07/99 (N = 221; CLL N = 114; SLL N = 16)	Study 101-08/99 (N = 64; CLL N = 59, SLL N = 5)	Study 101-09 (N = 125 SLL N = 28)	Study 312-0116 (N = 220) Pivotal study
Disease	iNHL (including SLL), MCL, DLBCL, CLL, MM, AML	iNHL (including SLL), CLL, MCL	CLL, SLL	iNHL (including SLL)	CLL
Prior Treatment Requirement	• Refractory to or relapsed after at least 1 prior chemotherapy regimen and having received rituximab as a single agent or in combination with other therapies • Subjects should not have been eligible for high-dose chemotherapy and transplantation (subjects who were candidates for transplantation and had declined transplantation were eligible for this study).	• Previously treated with relapsed or refractory disease (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen)	• No prior therapy, with the exception of corticosteroids for symptoms relief	• Refractory to rituximab and to an alkylating agent (defined as lack of CR or PR during treatment, or occurrence of progressive disease (PD) within 6 months of completion of treatment, or occurrence of PD during or within 6 months of completion of rituximab maintenance therapy, with an adequate course of these agents)	• Relapsed within 24 months of previous treatment, • Subjects were unfit for cytotoxic therapy based on cytopenias or renal dysfunction, or other significant comorbidities.
Treatment	**Dose escalation trial** IDELA × 28 days 50, 75, 100, 150, 200, 350 mg BID; 150, 300 mg once daily IDELA × 21 days/7 days off: • 150 mg BID	• IDELA 100 or 150 mg BID combined with (Rituximab (R), Bendamustine (B), BR, Ofatumomab, Fludarabine, Chlorambucil (Ch), or ChR.	IDELA: 150 mg (or reduced to 75/100 mg) BID (oral) × 48 weeks Rituximab: 375 mg/m2 IV weekly • × 8 weeks	• IDELA 150 mg (or reduced to 75/100 mg) BID continuously	Phase 3, 2-arm, randomized, double-blind, placebo controlled: Rituximab combined with placebo or IDELA 150 mg BID
Disease Status	• Measurable disease by CT scan defined as at least 1 lesion that measured > 2 cm in a single dimension • Subjects with WM were exempted from this requirement if they	• Measurable disease by CT scan defined as at least 1 lesion that measured > 2 cm in a single dimension	• Histologically or cytologically confirmed CLL or SLL • CLL: Binet Stage C or Rai Stage III or IV or active disease • SLL: active	• Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that	• Advanced poor prognosis disease, relapsed within 24 months of previous treatment, and not fit for cytotoxic therapy. Poor

Parameter	Study 101-02/99 (N = 191; CLL N = 54; SLL N = 11)	Study 101-07/99 (N = 221; CLL N = 114; SLL N = 16)	Study 101-08/99 (N = 64; CLL N = 59, SLL N = 5)	Study 101-09 (N = 125 SLL N = 28)	Study 312-0116 (N = 220) Pivotal study
	had symptomatic hyperviscosity or clinically relevant cytopenias and measurable serum monoclonal IgM		disease	measures ≥ 2 cm in LD and ≥ 1 cm in LPD as assessed by CT or MRI)	prognosis cytogenetic profile (ie, 17p deletion, *TP53* mutations, or unmutated *IGHV*) were allowed to enroll. • Measureable lymphadenopathy was required

Table 11: Study Populations for Key idelalisib Studies Contributing Efficacy Data for the Treatment of iNHL

Parameter	Study 101-09 (N = 125) Pivotal study	Study 101-02/99 (N = 191; iNHL N = 64)	Study 101-07/99 (N = 221; iNHL N = 79)
Disease	iNHL	iNHL, MCL, DLBCL, CLL, MM, AML	iNHL, CLL, MCL
Prior Treatment Requirement (iNHL only)	• Refractory to rituximab and to an alkylating agent (defined as lack of CR or PR during treatment, or occurrence of PD within 6 months of completion of treatment, or occurrence of PD during or within 6 months of completion of rituximab maintenance therapy, with an adequate course of these agents)	• Refractory to or relapsed after at least 1 prior chemotherapy regimen and having received rituximab as a single agent or in combination with other therapies • Subjects should not have been eligible for high dose chemotherapy and transplantation (subjects who were candidates for transplantation and had declined transplantation were eligible for this study).	• Previously treated with relapsed or refractory disease (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen)
Therapy	idelalisib 150 mg (or reduced to 75/100 mg) BID continuously	**Dose escalation trial** idelalisib × 28 days 50, 75, 100, 150, 200, 350 mg BID; 150, 300 mg once daily idelalisib × 21 days/7 days off: • 150 mg BID	• idelalisib combined with (Rituximab (R), Bendamustine (B), BR, Ofatumomab, Fludarabine, Chlorambucil (Ch), or ChR.
Disease Status (iNHL only)	• Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2 cm in LD and ≥ 1 cm in LPD as assessed by CT or MRI)	• Measurable disease by CT scan defined as at least 1 lesion that measured > 2 cm in a single dimension • Subjects with WM were exempted from this requirement if they had symptomatic hyperviscosity or clinically relevant cytopenias and measurable serum monoclonal IgM	• Measurable disease by CT scan defined as at least 1 lesion that measured > 2 cm in a single dimension

2.5.1. Dose response study(ies)

Study 101-02: A Phase 1 Sequential Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of CAL-101 (GS-1101 [Idelalisib]) in Patients with Selected, Relapsed or Refractory Hematologic Malignancies (final report).

This was a conventionally designed MTD study conducted in patients with resistant/refractory haematological malignancies.

Eligible subjects were administered idelalisib orally once daily or BID for 28 days (1 cycle, repeating continuously) or for 21 of 28 days (1 cycle, repeating continuously). Subjects were evaluated for response after 1 full cycle of therapy. Responding subjects or those with stable disease (SD) received additional cycles up to a maximum of 12 cycles (48 weeks).

An extension study, Protocol 101-99, was initiated to enrol subjects who completed Protocol 101-02.

According to the MAA, exposure to idelalisib reached a plateau at a dose of 150 mg BID and conventionally defined DLT/MTD was not reached (see the Pharmacodynamics).

Table 12: Dose escalation cohorts in 101-02

Study population	50 mg BID	150 mg once daily	100 mg BID	150 mg BID x 21 Days	300 mg once daily	150 mg BID	200 mg BID	350 mg BID	N
Total	17	16	25	17	19	45	35	17	191
CLL	5	0	11	0	10	11	10	7	54
iNHL	7	9	7	12	5	10	10	4	64

Dose modification

A total of 41 subjects (21.5%) had dose changes during the study, 10 subjects (5.2%) had increases in dosage and 31 subjects (16.2%) had decreases in dosage.

Efficacy

Table 13: Study 101-02: Clinical Response Rates by Disease (Safety Analysis Set)

			NHL									
			iNHL									
	CLL[a] (N=54)	CLL[b] (N=54)	FL (N=38)	SLL (N=11)	LPL/WM (N=9)	MZL (N=6)	Total iNHL (N=64)	MCL (N=40)	DLBCL (N=9)	Total NHL (N=113)	AML (N=12)	MM (N=12)
Complete Response	0	0	1 (2.6%)	0	0	0	1 (1.6%)	2 (5.0%)	0	3 (2.7%)	-	0
Partial Response	29 (53.7%)	39 (72.2%)	15 (39.5%)	6 (54.5%)	1 (11.1%)	2 (33.3%)	24 (37.5%)	14 (35.0%)	1 (11.1%)	39 (34.5%)	-	0
Minor Response[c]	-	-	0	0	4 (44.4%)	0	4 (6.3%)	0	0	4 (3.5%)	-	-
Stable Disease	22 (40.7%)	12 (22.2%)	18 (47.4%)	3 (27.3%)	3 (33.3%)	3 (50.0%)	27 (42.2%)	19 (47.5%)	3 (33.3%)	49 (43.4%)	-	3 (25.5%)
Progressive Disease	0	0	1 (2.6%)	1 (9.1%)	0	1 (16.7%)	3 (4.7%)	4 (10.0%)	3 (33.3%)	10 (8.8%)	-	8 (66.7%)
Treatment Failure	-	-	-	-	-	-	-	-	-	-	9 (75.0%)	-
Not Evaluable	3 (5.6%)	3 (5.6%)	3 (7.9%)	1 (9.1%)	1 (11.1%)	0	5 (7.8%)	1 (2.5%)	2 (22.2%)	8 (7.1%)	3 (25.0%)	1 (8.3%)
Overall Response	29 (53.7%)	39 (72.2%)	16 (42.1%)	6 (54.5%)	5 (55.6%)	2 (33.3%)	29 (45.3%)	16 (40.0%)	1 (11.1%)	46 (40.7%)	0.0%	0.0%
95% CI for Response	39.6 – 67.4	58.4 – 83.5	26.3 – 59.2	23.4 – 83.3	21.2 – 86.3	4.3 – 77.7	32.8 – 58.3	24.9 – 56.7	0.3 – 48.2	31.6 – 50.4	0.0 – 26.5	0.0 – 26.5

The two columns for CLL show ORR according the old and new NCCN CLL response criteria, respectively.

A total of 191 subjects were enrolled in the study; 50 subjects (26.2%) completed the study (12 cycles of 28 days each for a total of 48 weeks) and of those, 48 subjects (96.0%) continued into Study 101-99. Disease progression was the predominant reason for withdrawal from the study, reported for 88 subjects (46.1%).

Study completion rates, i.e. 48 weeks of treatment without progression and without withdrawal due to AE etc., may be used as outcome measure together with ORR.

The highest rate of study completion was among subjects with CLL (46 %, N = 54). Among subjects with iNHL (FL, SLL, LPL/WM, and MZL), 30% (N = 64) completed the study. Disease progression was the predominant reason for withdrawal from the study.

Among subjects with CLL across all dose cohorts, the percentage of subjects remaining progression-free at 48 weeks was estimated to be 54%. The KM estimate of median PFS among subjects with CLL receiving 150 mg BID (N = 11) was 9 months.

The median PFS among subjects with iNHL across all dose cohorts was 7.6 months. The percentage of subjects remaining progression-free at 48 weeks was estimated to be 46.3%. The KM estimate of median PFS among subjects with iNHL receiving idelalisib 150 mg BID (N = 10) was not reached.

Data in patients with 17p deletion and/or TP53 mutation included in study 101-02 are presented in the table below.

Table 14: Efficacy of idelalisib in CLL Subjects with 17p deletion and/or TP53 Mutation in study 101-02 (ITT Analysis Set).

		PFS[a]				OS[a]	
N	ORR[a]	25%	Median (months)	At 6 months	At 1 year	At 6 months	At 1 year
13	53.8% (25.1%, 80.8%)	1.8 (0.6, 3.2)	3.2 (1.8, 11.1)	34.6% (10.9%, 60.2%)	17.3% (2.8%, 42.4%)	67.7% (34.9%, 86.5%)	50.8% (15.5%, 78.1%)

a 95% CI results presented parenthetically

2.5.2. Efficacy in chronic lymphatic leukaemia (CLL)

2.5.2.1. Main study(ies)

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study (GS-US-312-0116) Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia (Interim analysis)

Methods

Study Participants

Main inclusion criteria:

1. Diagnosis of B-cell CLL, IWCLL criteria.
2. CLL that warrants treatment (IWCLL criteria for initiation of therapy).
3. Presence of measurable lymphadenopathy (≥1 nodal lesion ≥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]).
4. Prior treatment for CLL comprising either of the following:
    a. Prior treatment with ≥1 regimen containing a therapeutic anti-CD20 antibody administered for ≥2 doses of antibody treatment
    b. Prior treatment with ≥2 regimens containing ≥ 1 cytotoxic reagent administered for ≥2 cycles
5. In a subject whose last prior therapy contained an anti-CD20 antibody (eg, rituximab, ofatumumab, GA-101), evidence of disease improvement during that therapy **or** documentation of CLL progression ≥6 months after completion of that therapy
6. Documentation of CLL progression < 24 months since the completion of the last prior therapy for CLL.

7. Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of CLL ≥ 3 weeks before randomization.
8. All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before randomization (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]).
9. Karnofsky performance score of ≥40 (sic.).
10. Appropriate for non-cytotoxic-containing therapy based on the presence of any of the following factors:
    a. Grade ≥ 3 neutropenia or thrombocytopenia attributable to cumulative myelotoxicity from prior administration of cytotoxic agents (as documented by bone marrow biopsy obtained since last prior therapy), or
    b. Estimated creatinine clearance (eCCr) < 60 mL/min (as determined by the Cockcroft-Gault method, or
    c. A Cumulative Illness Rating Scale (CIRS) score of > 6

Main exclusion criteria

1. Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation).
2. Presence of intermediate- or high-grade myelodysplastic syndrome (ie, subjects were excluded who had ≥ 5% bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias due to myelodysplasia)
3. History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
4. Ongoing immunosuppressive therapy other than corticosteroids.
5. Prior therapy with any inhibitor of AKT, Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3 kinase (PI3K: including IDELALISIB), or spleen tyrosine kinase (SYK).
6. History of anaphylaxis in association with previous administration of monoclonal antibodies.
7. Prior or ongoing clinically significant illness or medical condition in the investigator's opinion, could adversely affect the safety of the subject or the assessment of study results

Treatments

Subjects were randomized with a 1:1 ratio:

Arm A: idelalisib + rituximab

Arm B: placebo + rituximab.

Rituximab: 8 infusions of (every 2 weeks for 4 infusions and every 4 weeks for a further 4 infusions) at a dose of 375 mg/m2 on Day 1 (Week 0) and continued with a dose of 500 mg/m2 from Day 15 (dose 2 to 8; maximum 8 infusions).

Idelalisib or placebo: 150 mg tablets for initiation of treatment and 100 mg tablets for patients requiring dose reduction (oral route), twice per day continuously until disease progression (or intolerability, etc.)

Objectives

Primary objective:

- To evaluate the effect of the addition of idelalisib to rituximab on progression-free survival (PFS) in subjects with previously treated CLL

Secondary objectives:

- To evaluate the effect of the addition of idelalisib to rituximab on the onset, magnitude, and duration of tumour control
- To assess the effect of the addition of idelalisib to rituximab on measures of subject well-being, including overall survival (OS), health-related quality of life (HRQL), and performance status
- To assess the effects of the addition of idelalisib to rituximab on disease-associated biomarkers and to evaluate potential mechanisms of resistance to idelalisib
- To characterize the effect of rituximab on idelalisib exposure through evaluations of idelalisib plasma concentrations over time
- To describe the safety profile observed with the addition of idelalisib to rituximab
- To estimate health resource utilization associated with the addition of idelalisib to rituximab

Outcomes/endpoints

Primary endpoint:

- Progression-free survival (PFS) – defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is CLL progression based on standard criteria [Hallek, 2008] and occurring for any reason (ie, increasing lymphadenopathy, organomegaly or bone marrow involvement; decreasing platelet count, haemoglobin, or neutrophil count; or worsening of disease-related symptoms) other than lymphocytosis

Secondary efficacy endpoints:

- Overall response rate (ORR)
- Lymph node response rate
- Overall survival (OS)

Tertiary efficacy endpoints:

- Time to response (TTR) – defined as the interval from randomization to the first documentation of CR or PR
- Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause
- Best Percent Change in SPD of Index Lesions

- Other categorical endpoints: Splenomegaly response rate, Platelet response rate, Hemoglobin response rate, Neutrophil response rate

Other endpoints:

- Exposure
    - Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
    - Trough (pre-dose) and peak (2-hour samples) of GS-1101 plasma concentrations
- Safety

Sample size

Based on data from prior studies with rituximab, it was assumed that administration of rituximab to subjects with previously treated CLL in Arm B of this trial would result in a median PFS of ~6 months. An improvement in median PFS from 6 months to 10.5 months due to the addition of idelalisib to rituximab in Arm A of the study would correspond to a benefit ratio of 1.75 (hazard ratio 0.57). This treatment effect seemed achievable in view of the fact that the Phase 1-2 multicenter experience with single-agent idelalisib in heavily pretreated patients resulted in a median PFS of > 12 months.

Randomisation

Subjects were stratified to receive study treatment via IWRS based on the following stratification factors:

- 17p deletion and/or *TP53* mutation in CLL cells: either versus neither
- Immunoglobulin heavy chain variable region (*IGHV*) mutation: unmutated (or *IGHV*3-21) versus mutated
- Any prior therapy with an anti-CD20 therapeutic antibody: yes versus no

Blinding (masking)

The identity of the treatments was concealed by central blinding of study drug assignments. Blinding was accomplished through use of a placebo that was well-matched to the active drug in appearance, packaging, labeling, and schedule of administration.

Statistical methods

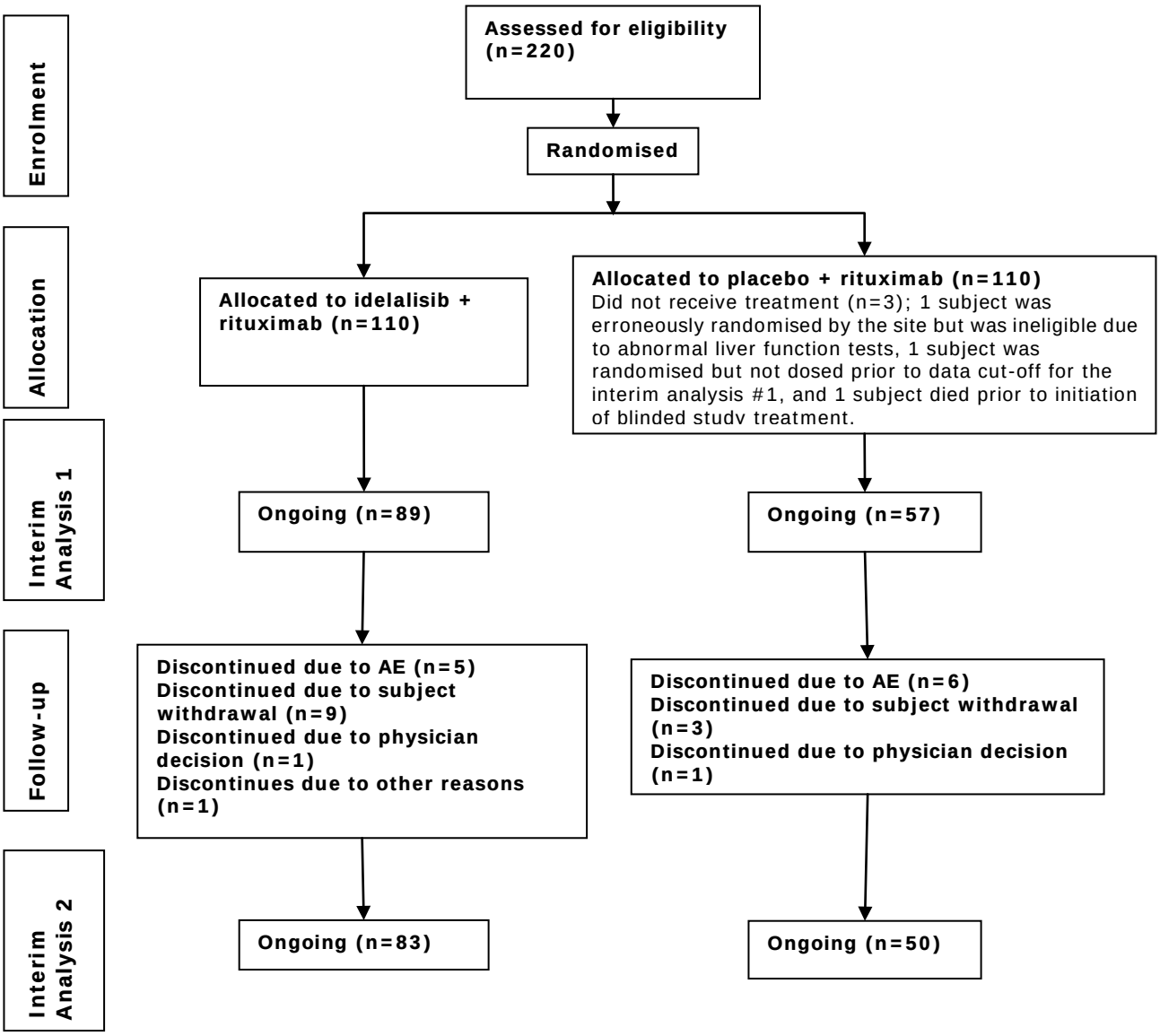
According to Amendment No 3, two interim efficacy analyses were to be conducted after approximately the 60th and 90th PFS events had occurred in 220 subjects. The significance level for the 1st interim analysis was to be 0.001.

The intent-to-treat (ITT) analysis set included all subjects who were randomized regardless of whether subjects received any study drug(s), or received a different regimen from the regimen they were randomized to. This analysis set was used in the analyses of subject characteristics, PFS, ORR, OS, and CR rate. The analysis of PFS based on the ITT analysis set was considered primary. Subjects in the ITT analysis set who did not have sufficient baseline or on-study tumor status information to be adequately assessed for response status were included in the denominators in the calculation of ORR and CR rate.

The per-protocol (PP) analysis set included subjects in the ITT analysis set who met the general criteria defining the target population for this study, were adherent to the protocol, were compliant with study drug treatment, and were evaluable for relevant efficacy endpoints. The PP analysis set was used in sensitivity analyses of the primary and secondary efficacy endpoints: PFS, ORR, and lymphadenopathy node response rate.

Results

Participant flow



Recruitment

Table 15: Key dates for the second interim analysis of study GS-US-312-0116

Event	Date
First Subject Screened	03 April 2012
First Subject Randomized	01 May 2012
Last Subject Randomized	28 August 2013
Last Subject Observation for This Interim Analysis	09 October 2013
Database Finalization for This Interim Analysis	08 November 2013

Conduct of the study

Significant Amendments to the protocol:

No 1: 23 January 2012 with revisions of eligibility and assessment criteria.

No 2: 19 December 2012 with revisions of secondary endpoints, eligibility criteria, efficacy assessments, and update on study drug information

No 3: 21 June 2013 with the addition of 2 formal ['pre-specified'] interim analyses after ~50% and ~75% of the expected number of 119 PFS events (PD or deaths) had occurred, increase of sample size (from 160 to 200), and update of idelalisib non-clinical and clinical results.

No 4: 10 September 2013 with update on extension study enrolment, revisions of endpoints, response criteria and information on CYP3A4-dependent metabolism.

Protocol deviations

Out of 65 major deviations, 4 subjects were considered to have medically important deviations that could have potentially affected the results of the study and were therefore excluded from the PP analysis. Two subjects in the idelalisib + R group were excluded from the PP analysis (1 due to history of Richter's transformation and 1 who had progressed longer than 24 months from the date of the last therapy). Two subjects in the placebo + R group were also excluded from the PP analysis (1 due to history of Richter's transformation and 1 did not fulfill inclusion criterion #5).

Baseline data

Table 16: Key demographics and baseline characteristics of study GS-US-312-0116 (ITT analysis set)

	IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
Gender, n (%)			
Male	76 (69.1)	68 (61.8)	144 (65.5)
Female	34 (30.9)	42 (38.2)	76 (34.5)
Race, n (%)			
White	100 (90.9)	98 (89.1)	198 (90.0)
Black or African American	3 (2.7)	3 (2.7)	6 (2.7)
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Other	2 (1.8)	2 (1.8)	4 (1.8)
Not Permitted	5 (4.5)	7 (6.4)	12 (5.5)
Age (years)[a]			
N	110	110	220
Mean (StD)	71 (7.7)	70 (8.1)	71 (7.9)
95% CI	(70, 72)	(69, 72)	(69, 72)
Median	71	71	71
Q1, Q3	66, 76	65, 76	66, 76
Min, Max	48, 90	47, 92	47, 92
Age Group (years)			
< 65	21 (19.1)	27 (24.5)	48 (21.8)
≥ 65	89 (80.9)	83 (75.5)	172 (78.2)
≥ 70	57 (51.8)	58 (52.7)	115 (52.3)
BMI (kg/m^2)[b]			
N	110	109	219
Mean (StD)	26.8 (5.64)	25.9 (4.76)	26.4 (5.23)
95% CI	(25.7, 27.9)	(25.0, 26.8)	(25.7, 27.1)
Median	25.5	25.0	25.4
Q1, Q3	22.7, 29.5	23.1, 28.3	23.0, 29.0
Min, Max	19.4, 49.5	11.7, 42.2	11.7, 49.5
Splenomegaly, n (%)	80 (72.7)	70 (64.2)	150 (68.5)
Hepatomegaly, n (%)	55 (50.0)	61 (56.0)	116 (53.0)
Karnofsky Performance Status, n (%)			
40	1 (0.9)	1 (0.9)	2 (0.9)
50	3 (2.7)	4 (3.6)	7 (3.2)
60	6 (5.5)	5 (4.5)	11 (5.0)
70	20 (18.2)	13 (11.8)	33 (15.0)
80	42 (38.2)	46 (41.8)	88 (40.0)
90	23 (20.9)	28 (25.5)	51 (23.2)
100	15 (13.6)	13 (11.8)	28 (12.7)
Missing	0	0	0
Karnofsky Performance Status < 80, n (%)	72 (65.5)	69 (62.7)	141 (64.1)

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

a Age (years) = (date of randomization – date of birth+1)/365.25

b BMI (kg/m^2) = $weight/height^2$

Table 17: CLL disease history of study GS-US-312-0116 (ITT analysis set)

	IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
Time Since Diagnosis (months)[a]			
N	110	110	220
Mean (StD)	108.3 (62.28)	106.4 (52.73)	107.4 (57.58)
Median	94.2	103.1	102.0
Q1, Q3	69.4, 142.2	64.2, 144.3	65.8, 143.9
Min, Max	7.6, 318.7	8.6, 248.8	7.6, 318.7
Rai Stage at Screening, n (%)			
0	0	1 (0.9)	1 (0.5)
I	18 (16.4)	19 (17.3)	37 (16.8)
II	16 (14.5)	10 (9.1)	26 (11.8)
III	22 (20.0)	18 (16.4)	40 (18.2)
IV	48 (43.6)	54 (49.1)	102 (46.4)
Not Available	0	0	0
Missing	6 (5.5)	8 (7.3)	14 (6.4)
Binet Stage at Screening, n (%)			
A	7 (6.4)	4 (3.6)	11 (5.0)
B	29 (26.4)	32 (29.1)	61 (27.7)
C	63 (57.3)	60 (54.5)	123 (55.9)
Not Available	0	0	0
Missing	11 (10.0)	14 (12.7)	25 (11.4)

The ITT analysis set included all subjects randomized in the study, with treatment group designated according to initial randomization.

a Time Since Diagnosis is calculated as (date of randomization – date of diagnosis)/30.4375.

Table 18: Subject Distribution by Key Stratification Factors (ITT Analysis Set)

	IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
17p deletion and/or *TP53* mutation			
Either	46 (41.8)	49 (44.5)	95 (43.2%)
Neither	64 (58.2)	61 (55.5)	125 (56.8%)
IGHV mutations status			
Yes	19 (17.3)	17 (15.5)	36 (16.4%)
No	91 (82.7)	93 (84.5)	184 (83.6%)
Prior anti-CD20 therapy			
No	3 (2.7)	6 (5.5)	9 (4.1%)
Yes	107 (97.3)	104 (94.5)	211 (95.9%)

The ITT analysis set included all subjects randomized in the study, with treatment group designated according to initial randomization. Analysis was based on the actual values as documented in the eCRF.

Table 19: Summary of baseline haematology and comorbidities (ITT Analysis Set)

	IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
Platelet Count < 100 x 10^9/L, n (%)	50 (45.5)	55 (50.5)	105 (47.9)
Hemoglobin < 12.5 g/dL, n (%)	87 (79.1)	90 (82.6)	177 (80.8)
Absolute Neutrophil Count < 1.5 x 10^9/L, n (%)	27 (24.5)	28 (25.9)	55 (25.2)
Median (Q1, Q3) CIRS Score	8.5 (7.0, 11.0)	8.0 (7.0, 10.0)	8.0 (7.0, 10.0)
Total CIRS Score > 6, n (%)	97 (88.2)	90 (81.8)	187 (85.0)
CIRS Score of 3 or 4 for Any Organ System, n (%)	39 (35.5)	43 (39.1)	82 (37.3)
CIRS Score > 0 in at Least 3 Organ Systems, n (%)	108 (98.2)	98 (89.1)	206 (93.6)
CIRS Cardiac Comorbidity, n (%)	46 (41.8)	35 (31.8)	81 (36.8)
CIRS Respiratory Comorbidity, n (%)	59 (53.6)	55 (50.0)	114 (51.8)
CIRS Renal Comorbidity, n (%)	45 (40.9)	42 (38.2)	87 (39.5)
CIRS Endocrine/Metabolic Comorbidity, n (%)	55 (50.0)	38 (34.5)	93 (42.3)

The ITT analysis set included all subjects randomized in the study, with treatment group designated according to initial randomization.

Table 20: Prior Therapy (ITT Analysis Set)

	IDELA + R (N=110)	Placebo + R (N=110)	Total (N=220)
Number of Prior Regimens			
N	110	110	220
Mean (StD)	3.9 (2.51)	3.4 (2.02)	3.7 (2.29)
Median	3.0	3.0	3.0
Q1, Q3	2.0, 5.0	2.0, 5.0	2.0, 5.0
Min, Max	1.0, 12.0	1.0, 10.0	1.0, 12.0
Most Common Prior Regimens, n (%)[a]			
BR	50 (45.5)	48 (43.6)	98 (44.5)
FCR	36 (32.7)	39 (35.5)	75 (34.1)
R	34 (30.9)	33 (30.0)	67 (30.5)
FR	17 (15.5)	20 (18.2)	37 (16.8)
Chl	20 (18.2)	16 (14.5)	36 (16.4)
Alemtuzumab	17 (15.5)	14 (12.7)	31 (14.1)
Ofa	15 (13.6)	14 (12.7)	29 (13.2)
R-CVP	15 (13.6)	8 (7.3)	23 (10.5)
FC	13 (11.8)	15 (13.6)	28 (12.7)
B	11 (10.1)	7 (6.4)	18 (8.2)
R-CHOP	11 (10.0)	3 (2.7)	14 (6.4)
F	10 (9.1)	13 (11.8)	23 (10.5)
ChlR	10 (9.1)	3 (2.7)	13 (5.9)

The ITT analysis set included all subjects randomized in the study, with treatment group designated according to initial randomization. Analysis was based on the actual values as documented in the eCRF.

BR = bendamustine + rituximab; FCR = fludarabine + cyclophosphamide + rituximab; R = rituximab; FR = fludarabine + rituximab; Ch = chlorambucil; Ofa = ofatumumab; FC = fludarabine + cyclophosphamide; R-CVP = rituximab + cyclophosphamide + vincristine; F = fludarabine; B = bendamustine;
R-CHOP = rituximab + doxorubicin + vincristine + cyclophosphamide; Ch = chlorambucil + rituximab

a Regimens received by ≥ 10 subjects in either treatment group; 49 unique regimens were administered overall.

Numbers analysed

Table 21: Disposition of subjects (ITT analysis set)

Subject Disposition, n (%)	IDELA + R (N=110) 30-AUG-2013	09-OCT-2013	Placebo + R (N=110) 30-AUG-2013	09-OCT-2013	Total (N=220) 30-AUG-2013	09-SEP-2013
Randomized	110 (100)	110 (100)	110 (100)	110(100)	220 (100)	220 (100)
Randomized but Not Treated[a]	0	0	3 (2.7)	2 (1,8)	3 (1.4)	2 (0,9)
Treated	110 (100)	110 (100)	107 (97.3)	108 (98,2)	217 (98.6)	218 (99,1)
Ongoing on Study	89 (80.9)	83(75,5)	57 (51.8)	50 (45,5)	147 (66.8)	133 (60,5)
Met Primary Study Endpoint and Discontinued Study	8 (7.3)	12 (10,9)	43 (39.1)	50 (45,5)	51 (23.2)	62 (28,2)
Disease Progression	5 (4.5)	7 (6,4)	34 (39.1)	41 (37,3)	39 (17.7)	48 (21,8)
Death	3 (2.7)	5 (4,5)	9 (8.2)	9 (8,2)	12 (5.5)	14 (6,4)
Discontinued Study	13 (11.8)	15 (13,6)	10 (9.1)	10 (9.1)	23 (10.5)	25 (11,4)
Adverse Events	5 (4.5)	5 (4,5)	6 (5.5)	6 (5.5)	11 (5.0)	11 (5,0)
Physician Decision	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	2 (0.9)	2 (0,9)
Withdrawal by Subject	6 (5.5)	9 (8,2)	3 (2.7)	3 (2.7)	9 (4.1)	12 (5,5)
Other	1 (0.9)	0	0	0	1 (0.5)	0

Outcomes and estimation

Primary endpoint: PFS

Table 22: Progression-Free Survival by IRC Assessment (ITT Analysis Set)

	Interim 1		Interim 2	
	IDELA + R (N = 110)	**Placebo + R (N = 110)**	**IDELA + R (N = 110)**	**Placebo + R (N = 110)**
Number (%) of Subjects with Events	12 (10.9)	53 (48.2)	16 (14.5)	59 (53.6)
Disease Progression	9 (8.2)	45 (40.9)	11 (10.0)	51 (46.4)
Death	3 (2.7)	8 (7.3)	5 (4.5)	8 (7.3)
Number (%) of Subjects Censored[a]	98 (89.1)	57 (51.8)	94 (85.5)	51 (46.4)
Ongoing	88 (80.0)	52 (47.3)	82 (74.5)	46 (41.8)
Discontinued Study without Event	10 (9.1)	5 (4.5)	12 (10.9)	5 (4.5)
Received Another Antitumor Treatment	0	0	0	0
Missed ≥ 2 Consecutive Tumor Measurements	0	0	0	0
KM Estimate of PFS[c] (Months)				
Q1 (95% CI)	8.5 (6.9, NR)	2.1 (1.8, 3.6)	8.3 (6.9, NR)	2.9 (1.8, 3.7)
Median (95% CI)	NR (12.1, NR)	5.5 (3.7, 6.9)	NR (10.7, NR)	5.5 (3.8, 7.1)
Q3 (95% CI)	NR (NR, NR)	8.3 (6.9, 11.1)	NR (NR, NR)	8.3 (7.1, 13.8)
Adjusted Hazard Ratio (95% CI)[c]	0.15 (0.08, 0.28)		0.18 (0.10, 0.32)	
P-value[d]	3.0×10^{-11}		6.0×10^{-11}	

NR = not reached
a Due to the ongoing nature of data collection for this study, a small number of subjects had progressed per IRC (ie, were not censored from PFS) but had not yet been confirmed (per case report form) to have discontinued at time of the interim analysis.
b The interval from the date of randomization to the earlier of the first documentation of PD or death from any cause: (minimum [date of PD, date of death] - date of randomization +1)/30.4375.
c Hazard ratio and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (17p deletion/*TP53* mutation and *IGHV* mutation).
d P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/*TP53* mutation and *IGHV* mutation).

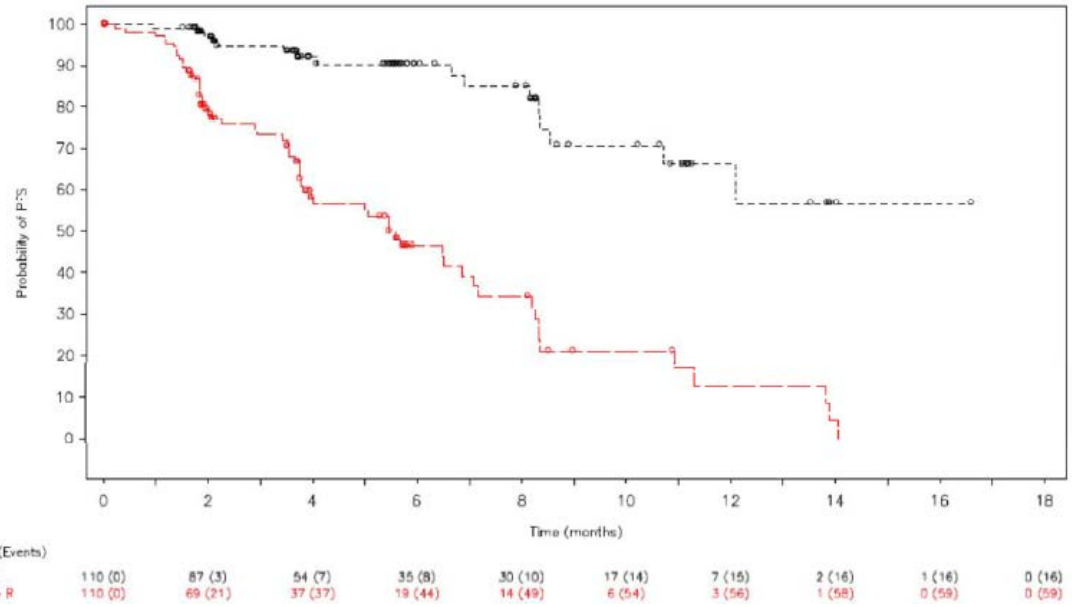


Figure 2: Kaplan-Meier curve of PFS (ITT Analysis Set, Interim 2)

The reasons for progressive disease are outlined for both treatment arms in Table 23.

Table 23: Number of subjects by reasons for PD assessment (Subjects with PD, Interim 1)

Number of Subjects	IDELA + R (N = 9)	Placebo + R (N = 45)	Total (N = 54)
One Reason for PD Assessment			
Index Lesion Increase	4	10	14
New Lesion	0	3	3
Non-Index Lesion Increase	0	10	10
Hepatomegaly	0	3	3
Splenomegaly	0	2	2
Hematologic Progression Confirmed by Bone Marrow Evidence of CLL Infiltration	1	8	9
Two Reasons for PD Assessment			
Index Lesion Increase, Non-Index Lesion Increase	1	4	5
New Lesion, Non-Index Lesion Increase	0	2	2
New Lesion, Splenomegaly	0	1	1
Non-Index Lesion Increase, Splenomegaly	0	1	1
Hepatomegaly, Hematologic Progression Confirmed by Bone Marrow Results	1	0	1
Three Reasons for PD Assessment			
Index Lesion Increase, Non-Index Lesion Increase, Splenomegaly	2	1	3

Index Lesion increase of ≥ 50% from nadir in sum of the products of the perpendicular diameters of measured lymph nodes (SPD) or LD that now has a longest diameter (LD) > 1.5 cm and an LPD of > 1.0 cm
Non-Index Lesion with unequivocal increase in size
New Lesion: >1.5 cm in the LD and >1.0 cm in the longest perpendicular diameter (LPD)
Hepatomegaly: increase of ≥ 50% from nadir and minimum 20 mm increase in the enlargement of the liver in its LVD
Splenomegaly: increase of ≥ 50% from nadir and minimum 20 mm increase in the enlargement of the spleen in its LVD
Hematologic/Bone Marrow Results: decrease ≥ 50% from zenith in platelet count or hemoglobin that is attributable to CLL confirmed by bone marrow evidence of CLL infiltration

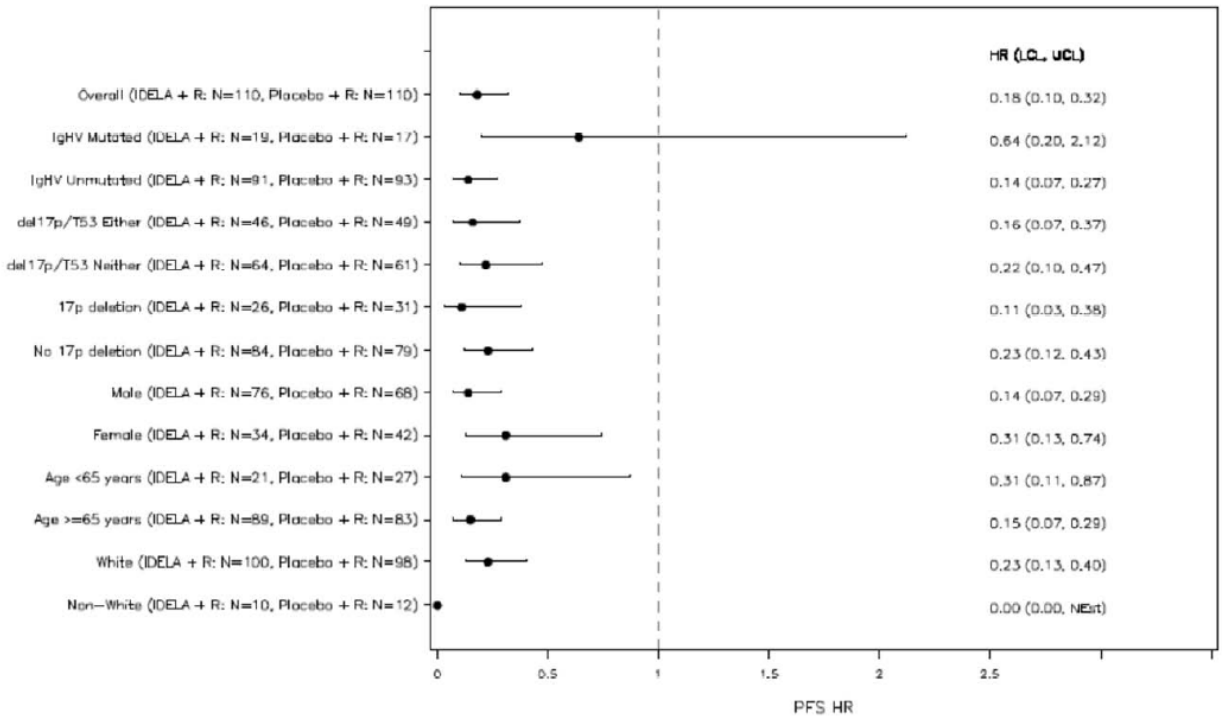


Figure 3: Forest Plot of PFS per IRC Comparison Assessment by Subgroup (ITT Analysis Set)

Table 24: Summary of PFS and response rates in pre-specified subgroups from study 312-0116

		Idelalisib + R	Placebo + R
17p deletion/*TP53* mutation		**N = 46**	**N = 49**
	PFS median (months) (95% CI)	NR (8.3, NR)	4.0 (3.5, 5.7)
	Hazard ratio (95% CI)	0.16 (0.07, 0.37)	
	ORR (95% CI)	78.3% (63.6, 89.1)	12.2% (4.6, 24.8)
Unmutated *IGHV*		**N = 91**	**N = 93**
	PFS median (months) (95% CI)	NR (NR, NR)	5.5 (3.8, 6.9)
	Hazard ratio (95% CI)	0.14 (0.07, 0.27)	
	ORR (95% CI)	73.6% (63.3, 82.3)	15.1% (8.5, 24.0)
Age ≥ 65 years		**N = 89**	**N = 83**
	PFS median (months) (95% CI)	NR (12.1, NR)	5.5 (3.7, 7.1)
	Hazard ratio (95% CI)	0.15 (0.07, 0.29)	
	ORR (95% CI)	74.2% (63.8, 82.9)	15.7% (8.6, 25.3)

CI: confidence interval; R: rituximab; N: number of subjects per group; NR: not reached

Overall Response Rate (ORR)

For subjects in the ITT Analysis Set who had at least 1 post baseline assessment (N = 176), ORR (95% CI) in the idelalisib + R group (N = 88) was 81% (71%, 88%), and for subjects in the placebo + R group (N = 88), the ORR (95% CI) was 13% (6%, 21%). The odds ratio (95% CI) for the ORR was 30 (13; 70).

In the 2nd Interim, ORR (95% CI) (classified as CR or PR) for the full ITT analysis set (including 7 subjects with no postbaseline scans at this second interim analysis) was 74.5% (65.4%, 82.4%) for the idelalisib + R group and 14.5% (8.5%, 22.5%) for subjects in the placebo + R group. The odds ratio (95% CI) for the ORR was 17.28 (8.66, 34.46), which favoured idelalisib + R compared with placebo + R (p-value = 6.3×10^{-19}).

ORR consistently favoured the experimental arm in subgroup analyses, thereby providing important support for the PFS analyses. This was unchanged in the 2nd Interim.

Table 25: Overall Response Rate (Odds Ratios) for predefined subgroups (ITT Analysis Set)

Subgroup Factor	Odds Ratio (95% CI)
Either 17p deletion and/or *TP53* Mutation Present	25.80 (8.55, 77.88)
Neither 17p deletion nor *TP53* Mutation Present	13.03 (5.46, 31.1)
Mutated *IGHV*	28.13 (4.46, 177.46)
Unmutated *IGHV*	15.75 (7.55, 32.86)
17p deletion	81.43 (9.27, 715.08)
No 17p deletion	12.80 (6.06, 27.05)
Males	19.64 (8.04, 47.96)
Females	16.39 (5.28, 50.91)
Age < 65 years	25.60 (5.35, 122.42)
Age ≥ 65 years	15.45 (7.24, 33.00)
Whites	16.22 (7.91, 33.25)
Non-Whites	45 (3.47, 584.34)

Time to response (TTR)

The median TTR was 2.0 months for subjects treated with idelalisib + R (N = 71), with a range of 1.3 to 5.5 months. The median TTR was 2.1 months for subjects treated with placebo + R (N = 11), with a range

of 1.9 to 8.5 months. In the 2nd Interim, median TTR was 2.0 and 3,6 months in the active and placebo arm, respectively.

Overall Survival (OS)

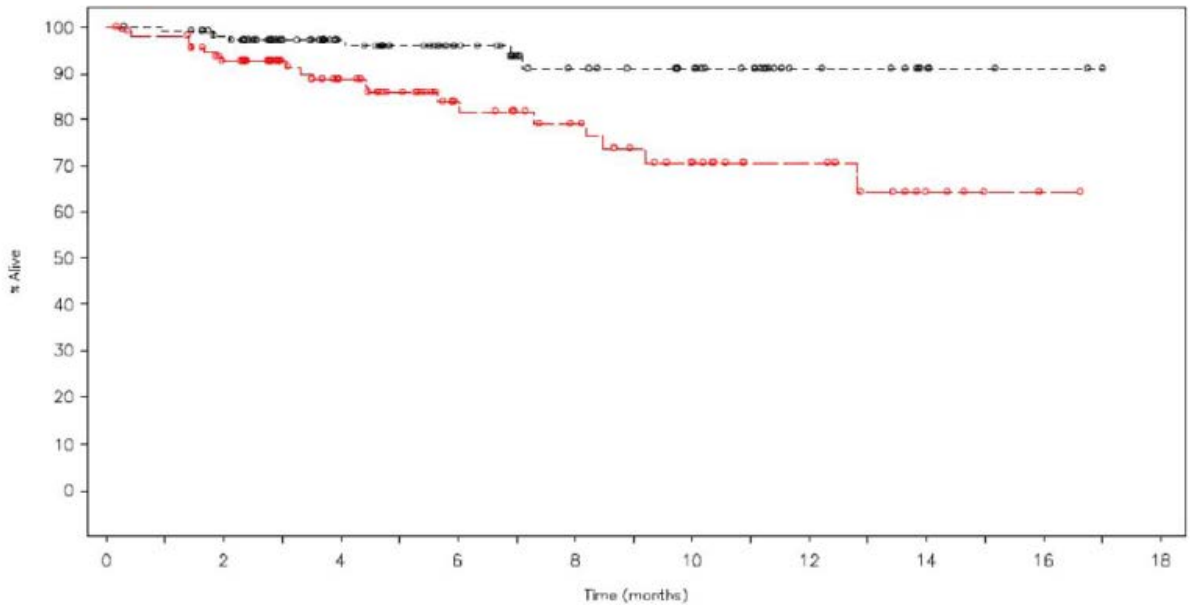


Figure 4

As of the data cut-off, there were 16 subjects who died (idelalisib + R: 3.6%, 4 subjects; placebo + R: 10.9%, 12 subjects) while participating in the study. In the updated results, 19 patients had died (idelalisib + R: 5.5%, 6 subjects; placebo + R: 11.8%, 13 subjects).

Best Percent Change in SPD

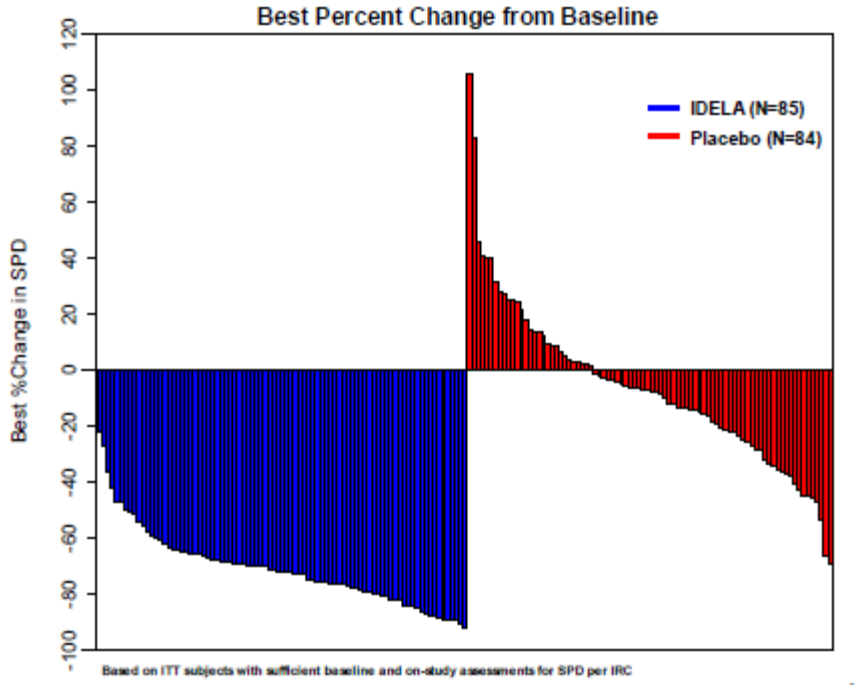


Figure 5: Waterfall Plot of Best Percent Change from Baseline in SPD by IRC Assessment (ITT Analysis Set)

Lymph node response rate is defined as the proportion of subjects who achieve a ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes. For subjects in the idelalisib + R group, the LNR rate (95% CI) was 93% (85%, 97%) and for subjects in the placebo + R group, the LNR rate (95% CI) was 4% (1%, 10%).

Ancillary analyses

Hepatomegaly and splenomegaly response rates strongly favoured idelalisib + R over placebo + R (data not shown).

The response in absolute lymphocyte count rate was comparable between treatment groups, and this was also the case for absolute neutrophil count (ANC) response between the two arms. Platelet and haemoglobin response were higher in the idelalisib + R group compared with placebo + R: 77% versus 59%, 73% versus 37%, respectively. These results were not significantly changed in the 2nd Interim analysis.

The 2nd Interim also included results on HR-QoL. The results show that in this population of elderly subjects with poor prognosis, advanced CLL, and limited treatment options, subjects receiving IDELA + rituximab consistently experienced statistically significant and clinically meaningful improvements in HRQL FACT-Leu measurements of physical and functional well-being (PWB and FWB, respectively), Additional Concerns (a disease specific measure for patients with leukaemia) and the Trial Outcome Index compared to subjects receiving placebo + rituximab. In addition, subjects receiving IDELA + rituximab experienced statistically significant and clinically meaningful improvements in general health status as measured by the EQ-5D self-reported questionnaire visual analog scale (VAS) and utility index compared to subjects receiving placebo + rituximab. Subjects in the IDELA + rituximab arm rapidly achieved superior symptom control and their improvement was sustained. Based on the mixed-effects model (MEM) used to assess the between-treatment difference in change from baseline for all FACT-Leu endpoints, subjects on IDELA+R reported statistically significantly better improvement over time for PWB ($p = 0.015$), FWB ($p = 0.014$), Additional Concerns ($p = 0.001$), Trial Outcome Index ($p = 0.002$), and FACT-Leu Total ($p = 0.006$). Subjects' symptoms improved rapidly by Week 2, and the median changes from baseline in the Additional Concerns subscale of the FACT-Leu and the ED-5Q Utility Index reached their MIDs of 4 by Week 6 and 0.06 by Week 12, respectively.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application.

Table 26: Summary of Efficacy for trial GS-US-312-0116

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia.		
Study identifier	GS-US-312-0116	
Design	Multicentre, 2-arm, randomised, double-blind, placebo-controlled	
	Duration of main phase:	Until subject progression of CLL, study drug-related toxicity, pregnancy, noncompliance with study procedures, or study discontinuation
Hypothesis	Superiority	

Treatments groups	Arm A		Idelalisib + rituximab, n=110 patients Rituximab: 8 infusions (every 2 weeks for 4 infusions and every 4 weeks for a further 4 infusions) at a dose of 375 mg/m2 on Day 1 (Week 0) and continued with a dose of 500 mg/m2 from Day 15 (dose 2 to 8; maximum 8 infusions). Idelalisib: 150 mg twice per day continuously until disease progression (or intolerability, etc.)
	Arm B		Placebo + rituximab, n=110 patients Rituximab: 8 infusions of (every 2 weeks for 4 infusions and every 4 weeks for a further 4 infusions) at a dose of 375 mg/m2 on Day 1 (Week 0) and continued with a dose of 500 mg/m2 from Day 15 (dose 2 to 8; maximum 8 infusions). Placebo: 150 mg twice per day continuously until disease progression (or intolerability, etc.)
Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	Interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause
	Secondary endpoints	Overall response rate (ORR) Overall survival (OS), Lymph node response (LNR)	Standard definition of ORR and OS. LNR is ≥50% decrease in SPD
	Other endpoints	Duration of response (DOR), Best % change in SPD of index lymph nodes	Interval from the first documentation of CR or PR (or MR for subjects with WM) to the earlier of the first documentation of disease progression or death from any cause
Database lock	9 October 2013 (2nd Interim analysis)		

Results and Analysis At the first pre-specified interim analysis, the study was stopped on the recommendation of the data and safety monitoring board owing to overwhelming efficacy regarding PFS (primary endpoint).

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Arm A	Arm B
	Number of subject	110	110
	Median PFS (months)	Not reached (10.7, NR)	5.5 (3.8, 7.1)
	adjusted hazard ratio (95% CI) 2-sided p-value of based on a stratified log-rank test	0.18 (0.10-0.32) < 0.0001 (crossed the prespecified efficacy stopping boundary at the 2-sided significance level of 0.001)	
	ORR (%) (95% CI)	74.5 (65.4, 82.4)	14.5 (8.5, 22.5)
	Odds Ratio (95% CI)	17.28 (8.66, 34.46) p-value < 0.0001	
	Lymph Node Response Rate (95% CI)	92.2% (85.1%, 96.6%)	5.9% (2.2%, 12.5%)
	Odds Ratio (95% CI)	165.5 (52.17, 524.98), p < 0.0001	
	Median OS (months)	NR (NR, NR)	NR (12.8, NR)
	Hazard ratio (95% CI)	0.28 (0.11, 0.69) p-value = 0.003	

	HRQoL	Statistically significant and clinically meaningful improvements in HRQL FACT-Leu measurements of physical and functional well-being (PWB and FWB, respectively) vs the control arm.

Supportive studies

Study 101-07

A phase I Study to Investigate the Safety and Clinical Activity of idelalisib in Combination with Chemotherapeutic Agents and Anti-CD20 mAb in Patients with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma, Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia (interim study report)

In this exploratory study idelalisib was combined with different medicinal products known to be active in B-cell malignancies: rituximab (R), ofatumumab (O), bendamustin (B), fludarabine (F) and everolimus (E) (only in mantle cell lymphoma).

A total of 11 study centres in the United States participated in the study.

Date first patient screened: 25-MAR-2010

Eligibility:

Subjects ≥ 18 years with a documented diagnosis iNHL (SLL, MZL, FL or MCL), previously treated with relapsed or refractory disease (according to a standard criteria) were eligible for the study. Subjects with CLL should show symptomatic disease that mandated treatment as defined by the IWCLL 2008 criteria, whereas subjects with iNHL and MCL should have measurable disease by computed tomography (CT) scan. All subjects were to show a WHO performance status of ≤ 2.

Summary of main results

CLL	Id+R	CR: 0/19	PR: 17/19	Withdrawal due to AE:	1/19
	Id+B	CR: 0/18	PR: 14/18		2/18
	Id+BR	CR: 2/15	PR: 11/15		2/15
	Id+O	CR: 2/21	PR: 13/21		3/21
	Id+F	CR: 0/12	PR: 11/12		3/12’
iNHL	Id+R	CR: 6/32	PR: 17/32	Withdrawal due to AE:	6/32
	Id+B	CR: 9/33	PR: 20/33		6/33
	Id+BR	CR: 6/14	PR: 4/14		4/14

Combination therapy resulted in high response rates, but there were few CR in the CLL group. Withdrawal rates due to AEs were rather high in these patients with a median of about 3-4 prior lines of therapy.

Eligibility criteria do not stipulate clear treatment indication for iNHL and MCL (only measurable disease that is relapsed or refractory).

Data in patients with 17p deletion and/or TP53 mutation included in study 101-07 are presented in the table below.

Table 27: Efficacy of idelalisib in CLL Subjects with 17p deletion and/or TP53 Mutation in study 101-07 (ITT Analysis Set).

		PFS[a]				OS[a]	
N	ORR[a]	25%	Median (months)	At 6 months	At 1 year	At 6 months	At 1 year
24	75.0% (53.3%, 90.2%)	9.5 (1.8, 19.0)	19.9 (9.5, 28.5)	81.3% (57.5%, 92.6%)	67.0% (42.9%, 82.7%)	95.0% (69.5%, 99.3%)	74.4% (48.9%, 88.5%)

a 95% CI results presented parenthetically

Study 101-08

A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of idelalisib in Combination with Rituximab in Elderly Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (interim analysis)

A total of 5 sites in the United States (US) participated in this study

First subject screened: 28-SEP-2010

Last subject observation: 22-MAR-2013

Eligibility

Patients ≥ 65 years with CLL or SLL Binet Stage C or Rai Stage III or IV or active and symptomatic disease and World Health Organization (WHO) performance status of ≤ 2. Patients should have had no prior therapy for CLL or SLL, except corticosteroids for symptom relief

Experimental/treatment

All subjects received idelalisib 150 mg BID orally on Days 1 through 28 of each 28-day cycle for 48 weeks and rituximab 375 mg/m2 intravenously weekly for 8 doses (Cycles 1 and 2). Subjects completing Protocol 101-08 with a clinical response following 48 weeks of idelalisib treatment were eligible to continue the treatment under a long-term extension protocol (101-99).

Primary endpoint: ORR. A result of 70% ORR with the addition of idelalisib to rituximab was considered to be clinically meaningful for this study.

The mean and median age was about 71-72 years with a range from 65 to 90. Altogether 1/3 patients did not complete 48 weeks of therapy thereof none for disease progression, but 17/64 for AEs.

Of high-risk criteria, unmutated IGHV was present in a majority (58%) of the subjects, whereas only 14 % were positive for TP53 Mutation/del (17p).

Results

Study 101-08/99 enrolled 64 subjects with previously untreated CLL, including 5 subjects with small lymphocytic lymphoma (SLL).

Table 28: Overall Response Rate (ITT Analysis Set)

Best Overall Response	IDELA + Rituximab (N = 64) n (%) Total (N = 64)	17p-/TP53 Mutation[a] Either (N = 9)	Neither (N = 52)	IGHV Mutation[a] Mutated (N = 23)	Unmutated (N = 37)
Complete Response	9 (14.1)	3 (33.3)	4 (7.7)	5 (21.7)	2 (5.4)
Partial Response	53 (82.8)	6 (66.7)	46 (88.5)	17 (73.9)	34 (91.9)
Stable Disease	0	0	0	0	0
Progressive Disease	0	0	0	0	0
Not Evaluable	0	0	0	0	0
Not Done[b]	2 (3.1)	0	2 (3.8)	1 (4.3)	1 (2.7)
Overall Response Rate[c]	62 (96.9)	9 (100.0)	50 (96.2)	22 (95.7)	36 (97.3)
95% CI[d]	89.2 – 99.6	66.4 – 100	86.8 – 99.5	78.1 – 99.9	85.8 – 99.9

a Subjects with missing mutation data were not included.
b ORR was not done for subjects 102-08029 and 115-08012. Subject 102-08029 did not continue the study due to dose limiting toxicity (Grade 3 rash, elevated ALT and elevated AST), and subject 115-08012 discontinued the study prematurely before completion of cycle 2 due to dose-limiting toxicity (Grade 3 rash).
c Subjects who had a complete or partial response fall in best overall response category.
d 95% exact binomial confidence interval of overall response rate
Source: [illegible] Listing 1.1, Listing 2.5, and Listing 3.3

The overall response rate of 97% is very high and included in this first-line elderly population CR in about 14%. No subjects had a relapse while on the study.

Forty-nine of 50 subjects (98%) had lymph node response. Two subjects for whom the response assessment was “not done” had withdrawn from the study due to dose limiting toxicity (Grade 3 rash, elevated ALT and AST and Grade 3 rash, respectively). The CR rate of 14 % indicates that BM biopsies showed remaining tumour infiltration. After a median follow-up of 14+ months, PFS data are immature, but there are no events of PD.

Data in patients with 17p deletion and/or TP53 mutation included in study 101-08 are presented in the table below.

Table 29: Efficacy of idelalisib in CLL Subjects with 17p deletion and/or TP53 Mutation in study 101-08 (ITT Analysis Set).

N	ORR[a]	PFS[a] 25%	Median (months)	At 6 months	At 1 year	OS[a] At 6 months	At 1 year
9	100% (66.4%, 100%)	NR (NR, NR)	NR (NR, NR)	100%	100%	100%	100%

a 95% CI results presented parenthetically

2.5.3. Efficacy in iNHL

2.5.3.1. Main study

A phase 2 study (101-09) to assess the efficacy and safety of idelalisib in subjects with indolent B-cell non-Hodgkin lymphomas refractory to rituximab and alkylating agents (final primary study report).

Methods

Study Participants

Main inclusion criteria:

- Karnofsky performance score of ≥60 (Eastern Cooperative Oncology Group [ECOG] performance score of 0, 1, or 2)

- Histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to the following based on criteria established by the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissues:
    - Follicular lymphoma (FL) of any grade (not grade 3b; see amendment 1 below)
    - Small lymphocytic lymphoma (SLL) with absolute lymphocyte count <5 x 109/L
    - Lymphoplasmacytoid lymphoma/Mb Waldenström (LPL)
    - Marginal zone lymphoma (MZL) (splenic, nodal, or extranodal)
- Histological materials documenting diagnosis of lymphoma available for review
- Measureable nodal disease, defined as the presence of ≥1 nodal lesion that measures ≥2 cm in a single dimension as assessed by CT or MRI
- Prior treatment with ≥2 prior chemotherapy- or immunotherapy-based regimens for iNHL.
- Prior treatment with rituximab and with an alkylating agent (eg, bendamustine, cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, nitrosoureas) for iNHL.
- Lymphoma that is refractory to rituximab and to an alkylating agent (review).
- Required baseline laboratory data within 2 weeks prior to start of study drug administration: ANC ≥1.0 x 109/L, Platelets ≥50 x 109/L, Haemoglobin ≥80 g/L total bilirubin ≤1.5 x ULN, ALT and AST ≤2.5 x ULN, serum creatinine <1.5 x ULN, negative HIV and antibody and Negative HBsAg (if serology positive for infection), HCV Negative viral RNA (if serology positive for infection).

Main exclusion criteria

- Known histological transformation from iNHL to diffuse large B-cell lymphoma. Biopsy documentation not required.
- Prior therapy with CAL-101/Idela
- Serious co-morbidity

Treatments

Idelalisib 150 mg BID. Lower dose levels (either Dose Level -1 [100 mg BID] or Dose Level -2 [75 mg BID]) were available for subjects requiring dose reduction. If a subject experienced an idelalisib -related AE requiring dose modification, study drug administration was held until the AE resolved or stabilized to an acceptable degree. Thereafter, idelalisib was readministered with the dose reduced by 1 dose level. If the subject tolerates a reduced dose of idelalisib for ≥ 4 weeks then the idelalisib dose could be increased to the next higher dose level, at the discretion of the investigator.

Objectives

Primary objective:

- To evaluate tumour regression as determined by overall response rate (ORR) in subjects receiving idelalisib for treatment of indolent non-Hodgkin lymphoma (iNHL) refractory to rituximab and alkylating agents

Secondary objectives:

- To determine the onset, magnitude, and duration of tumor control and of treatment success in subjects receiving idelalisib
- To characterize health-related quality of life (HRQL) as reported by subjects with iNHL receiving idelalisib
- To evaluate the effects of idelalisib on subject performance status
- To assess the pharmacodynamic effects of idelalisib
- To evaluate idelalisib treatment administration and compliance with idelalisib therapy
- To describe the safety profile of idelalisib
- To characterize idelalisib plasma exposure over time
- To generate pharmacokinetic (PK) data with the final tablet formulation of idelalisib in subjects with iNHL (through conduct of a PK sub-study)

Outcomes/endpoints

Primary endpoint:

- ORR - defined as the proportion of subjects who achieved a CR or PR (or MR for subjects with WM) during the idelalisib treatment. The determination of iNHL response and progression will be based on standardized criteria[1]. Imaging-based evaluation is preferred to evaluation by clinical examination. CT or MRI scans are the required methods for tumor assessments. A BOR of CR, PR, SD, PD, NE, and ND was allowed. For subjects with WM, MR was also allowed.

Secondary efficacy endpoints:

- DOR – defined as the interval from the first documentation of CR or PR (or MR for subjects with WM) to the earlier of the first documentation of PD or death from any cause
- LNR – defined as the proportion of subjects who achieved a ≥ 50% decrease from baseline in the SPD of index lymph nodes
- TTR – defined as the interval from the start of idelalisib treatment to the first documentation of CR or PR (or MR for subjects with WM)
- PFS – defined as the interval from the start of idelalisib treatment to the earlier of the first documentation of PD or death from any cause
- OS - defined as the interval from the date of first idelalisib to death from any cause
- Changes in HRQL as reported by subjects using the FACT-Lym
- Changes in performance status as documented using the Karnofsky performance criteria
- Safety

[1] Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25 (5):579-86.

Sample size

With a total intended sample size of 100 subjects, the study had more than 90% power to achieve a 1-sided significance level of 0.005 and provided an adequate safety database.

Randomisation

N/A

Blinding (masking)

N/A

Statistical methods

This study tested the null hypothesis that the IRC-reviewed ORR was ≤ 20% against the alternative hypothesis that it was ≥ 39% (ie, ≥ ~40%). Using Simon's optimal 2-stage design, a sample size of 100 subjects had > 90% power to achieve a 1-sided significance level of < 0.005 and provided an adequate safety database.

Results

Participant flow

Up to 125 subjects were enrolled in order to ensure enrolment of ≥ 100 subjects (31 in Stage 1, and 69 in Stage 2) who had a documented diagnosis of lymphoma, who had confirmed refractory disease, and who could be evaluated for tumour response with baseline and on-study scans (through ≥ 24-week, follow-up tumour assessment).

Recruitment

Table 30: Key dates of study 101-09

Event	Date
First Subject Screened	18 March 2011
First Subject Treated	05 May 2011
Last Subject Treated	17 October 2012
Last Subject Observation	25 June 2013
Database Finalization	19 July 2013

Conduct of the study

Protocol amendments:

No 1 (before start of enrolment): FL grade 3b not eligible.

No 3 (Gilead) clarification regarding the inclusion of patients with small lymphocytic lymphoma (SLL) to state that the absolute lymphocyte count (ALC) must be ≤5 x 109/L at the time of diagnosis and at the time of study entry. This clarification is made to ensure that patients with chronic lymphocytic leukaemia (CLL) are excluded.

No 4 (Gilead) to update with clinical and non-clinical results and statistical analysis plan (eg removal of reference to stratification)

No 5 (Gilead) to correct instructions for SAE reporting.

Baseline data

Disposition of Study Subjects

Table 31: Disposition of Subjects (ITT Analysis Set)

	25-JUN-2013	09-SEP-2013
	Total (N = 125)	Total (N = 125)
Subject Status	**n (%)**	**n (%)**
Treatment Ongoing	40 (32.0)	35 (28)
Treatment Completed	49 (39.2)	52 (41,6)
Treatment Completed Due to Disease Progression	41 (32.8)	44 (35,2)
Treatment Completed Due to Death	8 (6.4)	8 (6.4)
Treatment Discontinued	36 (28.8)	38 (30,4)
Adverse Event	25 (20.0)	27 (21,6)
Withdrew Consent	4 (3.2)	4 (3.2)
Investigator Request	7 (5.6)	7 (5.6)

Of the 125 subjects enrolled in the study, 35 subjects (28.0%) are ongoing (as of 9 September 2013).

Study population

Overall, ages ranged from 33 to 87 years with a median of 64 years. The majority of subjects were male (64.0%) and white (89%).

Table 32: Demographics and Baseline Characteristics (ITT Analysis Set)

Characteristic		Total (N=125)
Gender, n (%)	Male	80 (64.0)
	Female	45 (36.0)
Age (years)	n	125
	Mean (StD)	62 (11.4)
	95%CI	60, 64
	Median	64
	Q1, Q3	54, 71
	Min, Max	33, 87
	< 65 years	69 (55.2)
	≥ 65 years	56 (44.8)
Race (n, %)	White/Caucasian	110 (88.7)
	Black or African American	2 (1.6)
	Native Hawaiian or Other Pacific Islander	0
	Asian	3 (2.4)
	American Indian or Alaska Native	1 (0.8)
	Other	8 (6.5)
Ethnicity (n, %)	Hispanic or Latino	6 (4.9)
	Not Hispanic or Latino	117 (95.1)
BMI (kg/m^2)	n	124
	Mean (StD)	27.0 (5.58)
	95%CI	26.0, 28.0
	Median	25.9
	Q1, Q3	23.4, 29.2
	Min, Max	17.2, 51.1

Table 33: Baseline Disease History and Status (ITT Analysis Set)

	Total (N=125)
FL, n (%)	72 (57.6)
Grade 1	21/72 (29.2)
Grade 2	39/72 (54.2)
Grade 3a	12/72 (16.7)
Current FL International Prognostic Index Score, n (%)	
Low (≤ 1)	15/72 (20.8)
Intermediate (2)	18/72 (25.0)
High (≥ 3)	39/72 (54.2)
SLL, n (%)	28 (22.4)
LPL/WM, n (%)	10 (8.0)
MZL, n (%)	15 (12.0)
Splenic	1/15 (6.7)
Nodal	5/15 (33.3)
Extranodal	9/15 (60.0)
Time Since Initial Diagnosis (Years)	
n	125
Mean (StD)	5.9 (3.96)

Table 34: Prior Therapy (ITT Analysis Set)

	Total (N=125)
Number of Subjects with Prior Therapy, n (%)	125 (100)
Number of Total Prior Regimens	
n	125
Mean (StD)	4 (2.1)
Median (95% CI)	4 (4.0 ,5.0)
Min, Max	2, 12
Number of Subjects Treated with, n (%)	
1 Regimen	0
2 Regimens	33 (26.4)
3 Regimens	19 (15.2)
4 Regimens	30 (24.0)
5 Regimens	18 (14.4)
≥ 6 Regimens	25 (20.0)
Number of Subjects Refractory to, n (%)	
1 Regimen	26 (20.8)
2 Regimens	64 (51.2)
3 Regimens	22 (17.6)
≥ 4 Regimens	13 (10.4)

The median (range) number of prior regimens received was 4 (2 - 12), with 73 subjects (58%) treated with 4 or more prior regimens. Among alkylating agents, 111 subjects (89%) had received cyclophosphamide and 81 subjects (65%) had received bendamustine. All subjects were refractory to rituximab and 124 subjects (99%) were refractory to an alkylating agent.

Eligibility criteria in study 101-09 included no definition of “need for therapy”, except for LPL/WM. Baseline disease status shows presence of conditions requiring therapy (eg bulky disease, cytopenias, LDH>ULN) in ~85 % of subjects.

Table 35: Time since Completion of and Responses to Most Recent Regimen Prior to Study (ITT Analysis Set)

	Total (N = 125)
Time Since Completion of Last Regimen (Months)	
n	125
Mean (StD)	6.5 (7.76)
95% CI	5.1, 7.8
Median	3.9
Q1, Q3	1.9, 7.5
Min, Max	0.7, 41.4
Number of Subjects Refractory[a] to Last Regimen, n (%)	112 (89.6)
Best Response to Last Regimen, n (%)	
CR	13 (10.4)
PR	16 (12.8)
SD	52 (41.6)
PD	42 (33.6)
NE	2 (1.6)

Analysis Sets

The ITT analysis set includes subjects who received at least 1 dose of idelalisib (N = 125). The PP analysis set includes subjects in the ITT analysis set who had a diagnosis of lymphoma, measurable nodal disease, and who could be evaluated for tumour response with both a baseline and at least 1 on-study tumour evaluation (N = 123).

Primary endpoint, ORR

Table 36: Overall Response Rate, n (%) (ITT Analysis Set)

Best Overall Response	Total (N = 125)	
	IRC Assessment	Investigator Assessment
CR	7 (5.6)	7 (5.6)
PR	63 (50.4)	64 (51.2)
MR	1 (0.8)	1 (0.8)
SD	42 (33.6)	41 (32.8)
PD	10 (8.0)	11 (8.8)
NE[a]	2 (1.6)	1 (0.8)
ORR[b]	71 (56.8)	72 (57.6)
95% CI [c]	47.6 – 65.6	48.4 – 66.4
P-value [d]	< 0.001	< 0.001
Agreement (%)[e]	84.8	

In the updated results submitted during the procedure, two patients had improved responses from PR to CR (not shown in table above) but the ORR was unchanged. ORR was consistent in subgroups by age (</≥65 y), gender, and race).

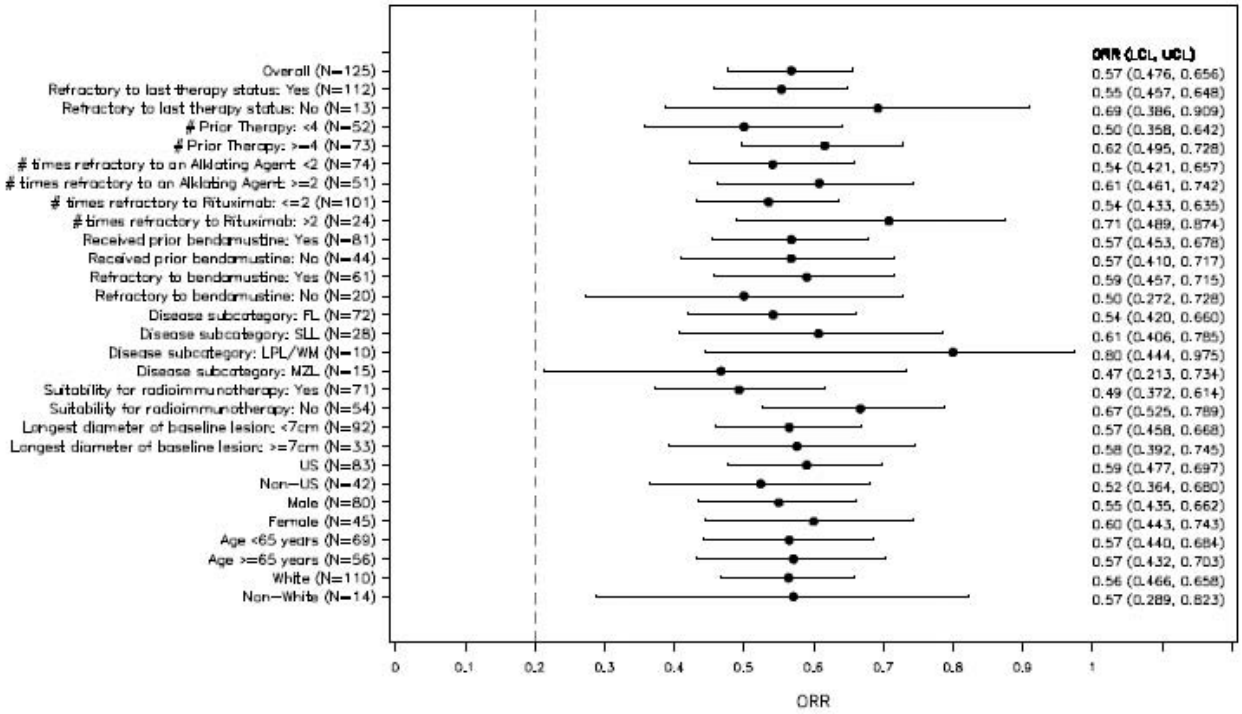


Figure 6: Forest Plot of ORR and 95% CI – IRC Assessment, ITT Analysis Set

From the updated results (09-SEP-2013) separate forest plots for the lymphoma subgroups have been added, and those for FL and SLL are shown below.

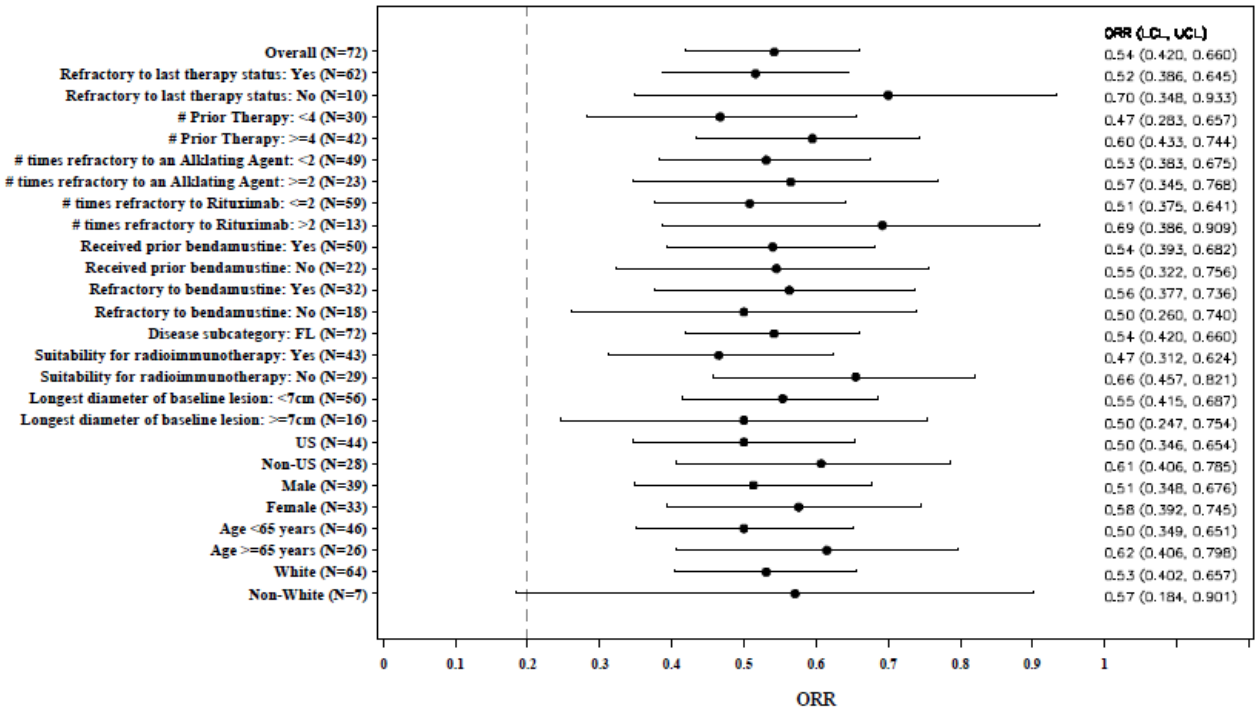


Figure 7: Forest plot of ORR and 95% CI (IRC assessments), ITT analysis sets in FL

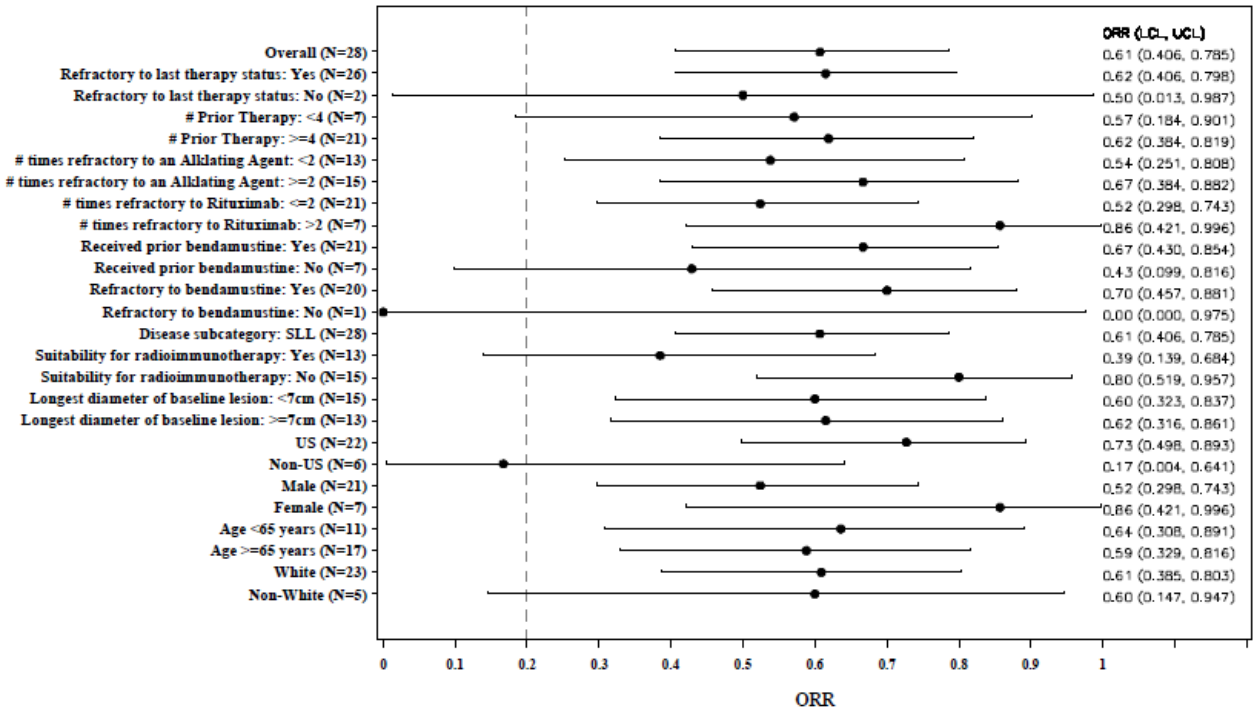


Figure 8: Forest plot of ORR and 95% CI (IRC assessments), ITT analysis sets in SLL

The number of subjects who had a CR or PR to their preceding therapy was 13 (10 %) and 16 (13 %), i.e, the ORR rate after idelalisib monotherapy was higher but the CR rate was lower.

Secondary endpoints

DOR

The median DOR for all subjects was 12.5 months (12.5 months for SLL subjects, and not reached for FL, LPL/WM and MZL subjects). Analysis by age group showed moderate difference for subjects < 65 years of age and ≥ 65 years of age, median DOR was 12.5 months (n = 39) and 7.4 months (n = 32), respectively.

Lymph node response

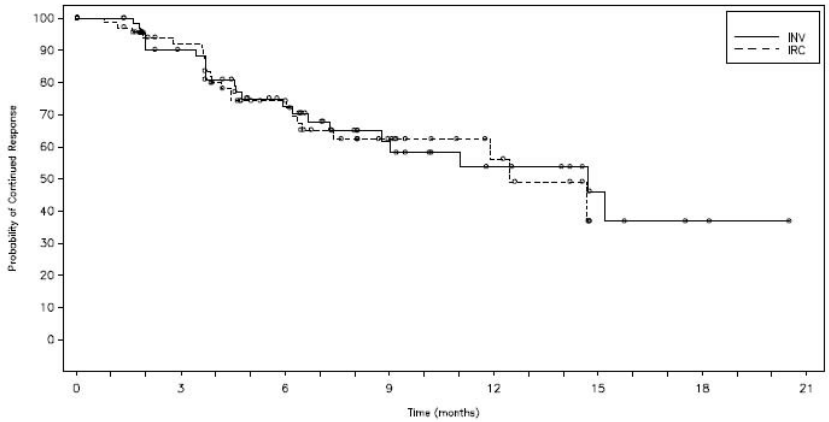


Figure 9: Kaplan-Meier Curve of DOR – IRC and Investigator Assessments, ITT Analysis Set

Among the 122 subjects with measurable lymph nodes at both baseline and post baseline, 67 subjects (54.9%) achieved a ≥ 50% decrease from baseline in the sum of the products of the diameters (SPD) of index lesions.

Time to response (TTR)

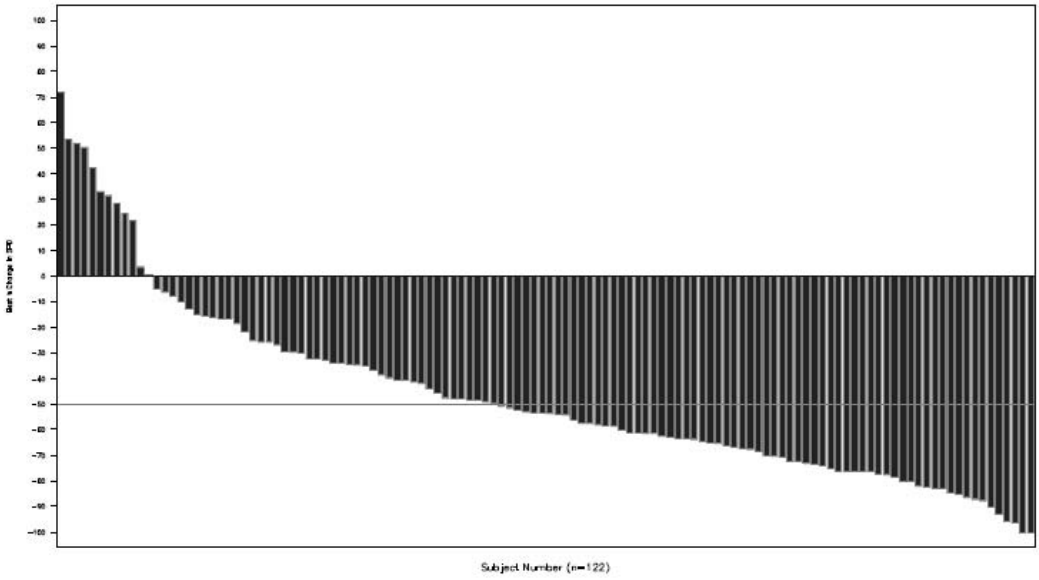


Figure 10: Waterfall Plot of Best Percent Change from Baseline in SPD – IRC Assessments, ITT Analysis Set

The median TTR was 1.9 months as assessed by the IRC (n = 71) and the investigators (n = 72), corresponding to the first time response was evaluated (Study Visit 6, Week 8).

The latest time point for achieving CR was 12.2 months (median time to CR 3.7 months, range 1.9 to 12.2 months).

Progression free survival

Based on the IRC, the median PFS for all subjects (N = 125) was 11 months, the proportion of subjects remaining progression-free at 48 weeks was estimated to be 47%. Subgroup analysis (FL, SLL, LPL and MZL) suggests longer PFS in LPL, although this group was very small.

Overall Survival

The KM estimate of median OS was 20 months and the proportion of subjects surviving at 48 weeks was estimated to be 82%.

Out of a total of 28 deaths, 19 occurred prior to Week 48 and 9 occurred after Week 48.

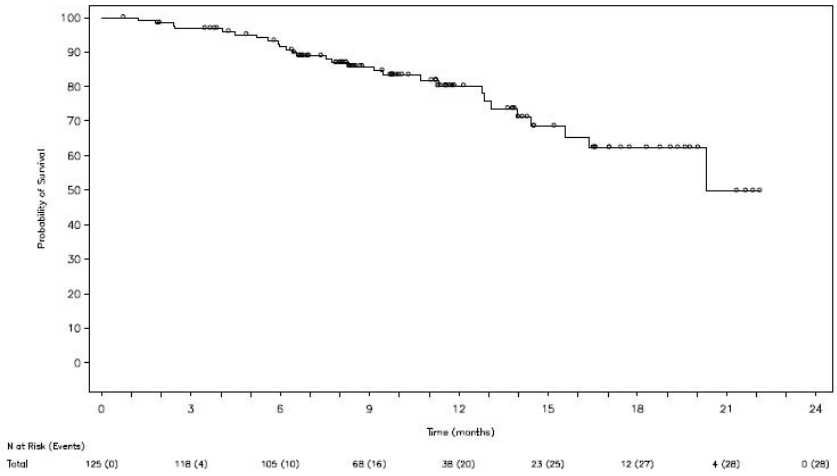
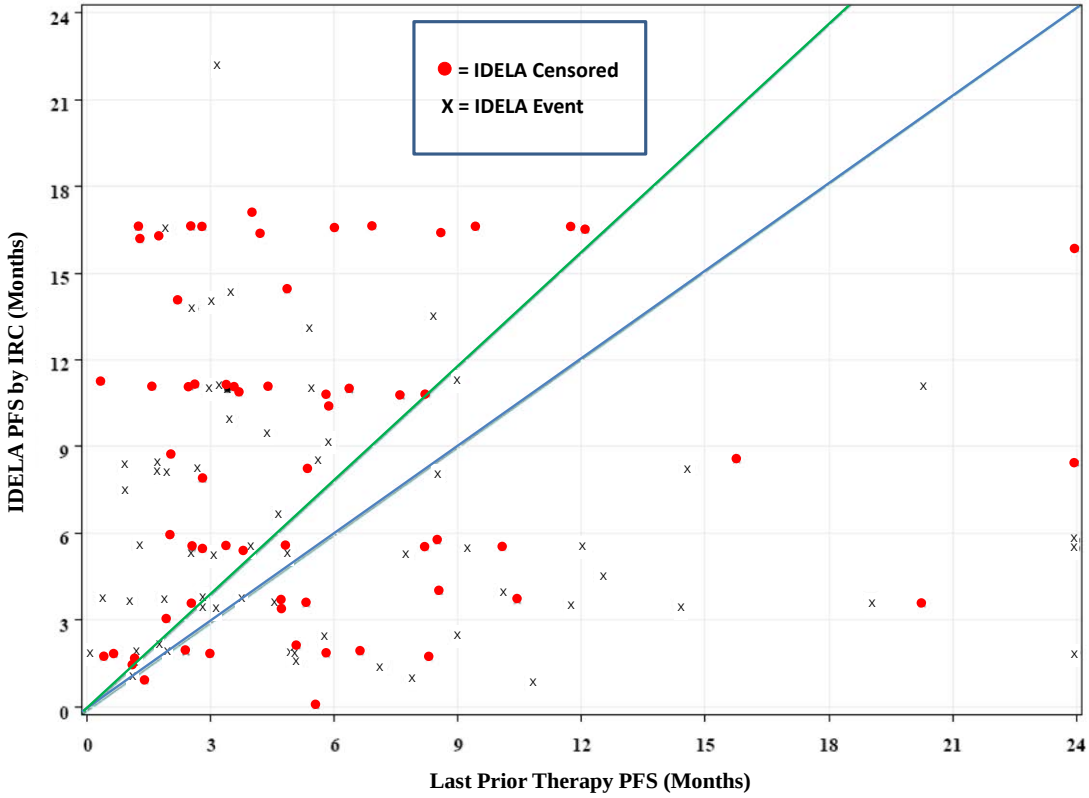


Figure 11: KM Curve of Overall Survival Including Long-Term Follow-Up, ITT Analysis Set

A within-individual analysis of time to progression on prior regimen compared with an update PFS on study therapy was performed:



PFS Ratio: Median (Q1, Q3): 1.5 (0.6, 3.2)
PFS Ratio > 1.3: (72/125 (57.6%)

Note: Several subjects with very long pretreatment PFS were cut at 24 months for data presentation purposes.

Source: m5.3.5.3, Figure 82-09-3 and Table 82-09-2

Figure 12: Study 101-09: Scatter Plot of Time to Disease Progression on Last Prior Therapy Compared with PFS on idelalisib by Subject

Of the 125 subjects in the study, 79 (63.2%) had a PFS ratio of > 1.0, that is, the individual subject's PFS on idelalisib exceeded the PFS of the prior therapy and 57.6% had a PFS ratio of ≥ 1.3. Overall, the median PFS ratio was 1.5. There were 5 subjects with PFS longer than 18 months on last prior therapy and

clearly shorter duration of PFS on idelalisib. In three of these patients, treatment with idelalisib was stopped due to AEs. There were no other specific findings in their treatment history or baseline characteristics. For overall survival and proportion of survival at different times in study 101-09, there were no data per disease for the previous data cut-off of 25 June 2013. As shown in the table below comparing results from the two cut-off dates, the median ORR and PFS remain unchanged for FL and SLL. Concerning FL, the median duration of response (DOR) has now been estimated at 7.4 months (Q1, Q3: 3.8, NR). This current estimation of the DOR in FL is thus lower than the overall value of 12.5 months estimated at the previous cut-off date for the whole group of 125 patients in the study. A summarized comparison of previous and updated results is presented below:

Table 37: Summary of updated Efficacy data for FL and SLL

	Data Cut-off	**FL (N = 72)**	**SLL (N = 28)**
ORR % and 95% CI (%)	25 June 2013	54.2% (42.0, 66.0)	60.7% (40.6, 78.5)
	9 September 2013	Unchanged	Unchanged
DOR (months) Median (Q1, Q3)	25 June 2013	(NR (95% CI 4.5, NR) [N=39]	12.5 (95% CI 4.5, 14.7) [N=17]
	9 September 2013	**7.4 (3.8, NR)** [N=39]	12.5 (7.4, 14.7) [N=17]
PFS (months) Median	25 June 2013	8.5 (95% CI 5.7, 13.1)	11.4 (95% CI 5.6, 16.5),
	9 September 2013	8.5 (Q1, Q3 4.5, NR)	11.4 ((Q1, Q3 5.6, NR)
OS (months)	9 September 2013	NR (NR, NR)	20.3 (10.7, NR)
Proportion of Survival % (95% CI) At 24 weeks	9 September 2013	97.1 (93.1, 101.1)	89.1 (77.5, 100.8)
Proportion of Survival % (95% CI) At 36 weeks	9 September 2013	90.7 (83.5, 97.8)	74.1 (57.5, 90.7)
Proportion of Survival % (95% CI) At 48 weeks	9 September 2013	88.8 (80.9, 96.7)	70.0 (52.5, 87.5)

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application.

Table 38: Summary of efficacy for trial 101-09

Title: A phase 2 study to assess the efficacy and safety of idelalisib in subjects with indolent B-cell non-Hodgkin lymphomas refractory to rituximab and alkylating agents.			
Study identifier	Study 101-09		
Design	Phase 2, single-arm, 2-stage, efficacy, safety, PK, and pharmacodynamics study of idelalisib in subjects with previously-treated iNHL that is refractory both to rituximab and to alkylating-agent-containing chemotherapy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28,5 months (Sep-09-2013) NA NA
Hypothesis	The study tested the hypothesis that ORR is ≥ 39% against the null hypothesis that it was ≤ 20%. The ORR and 95% confidence interval (CI) were presented along with the corresponding p-value from the exact binomial test.		
Treatments groups	Study cohort		Idelalisib 150 mg BID continuously until the occurrence of any events requiring treatment discontinuation. Lower dose levels (either 100 mg BID or 75 mg BID were available for subjects requiring dose reduction).
Endpoints and definitions	Primary endpoint	Overall response rate (ORR)	The proportion of subjects who achieved a CR or PR (or MR for subjects with WM) during the idelalisib treatment.
	Secondary endpoint	Progression free survival (PFS)	The interval from the start of treatment to the earlier of the first documentation of PD or death from any cause
	Secondary endpoint	Overall survival (OS)	The interval from the date of first idelalisib to death from any cause
Database lock	Last subject observation for the present report 13-SEP-2013		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The intent-to-treat (ITT) analysis set consisted of all subjects who received ≥ 1 dose of idelalisib. The ITT analysis set was used in the analyses of ORR, PFS, OS, safety, and study drug administration and compliance. The ITT analysis set was the primary analysis set for all the efficacy variables (N=125). The PP analysis set includes subjects in the ITT analysis set who had a diagnosis of lymphoma, measurable nodal disease, and who could be evaluated for tumour response with both a baseline and at least 1 on-study tumour evaluation (N = 123). One subject had no baseline or on-study tumor assessment and 1 subject did not have documented refractory disease were excluded from the PP analysis set.			
Descriptive statistics and estimate variability	Treatment group	Study cohort	FL	SLL
	Number of subject	125	72	28
	ORR (95% CI)	~57 % (IRC estimate) (47.6 – 65.6)	54,2 % (42,0, 66,0) CR: 8.3 % PR: 45.8 %	60,7% (40,6, 78,5)
	PFS	Median PFS for all subjects (N = 125) was 11.0 months (IRC)	8,5	11,4
		(95% CI) (8.2, 13.6)	IQR (4,5, NR)	IQR (5,6, NR)
	OS	Median OS including long-term follow-up for all subjects (N = 125) was NR (NR, NR)	NR (NR, NR)	20,3 (10,7, NR)

IQR, Interquartile range

NR, Not reached

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

Not applicable.

Clinical studies in special populations

No dedicated clinical studies were conducted in special populations. The below table provide information on the number of patients enrolled in the clinical development programme of idelalisib by age group.

Table 39: Number of Subjects by Age Group (ITT Analysis Set)

Study Type; n (%)	Age < 65 years (N = 588)	Age 65 to 74 years (N = 309)	Age 75 to 84 years (N = 120)	Age ≥ 85 years (N = 16)	Total (N = 1033)
Efficacy and Safety Studies	317 (53.9)	299 (96.8)	120 (100)	16 (100)	752 (72.8)
Human PK Studies	208 (35.4)	10 (3.2)	0	0	218 (21.1)
Human PD Studies	48 (8.2)	0	0	0	48 (4.6)
Biopharmaceutical Studies	15 (2.6)	0	0	0	15 (1.5)

Only subjects who received or were randomized to receive (ie, Study 312-0116) at least one dose of idelalisib were included

2.5.4. Discussion on clinical efficacy

Design and conduct of clinical studies

CLL

Efficacy in CLL is based upon the interim report from the pivotal phase 3 study GS-US-312-0116 (n=220 of whom 110 were exposed to idelalisib) in combination therapy and is further supported by two interim reports from single arm studies (101-07, and 101-08) in combination therapy and one final report from a monotherapy study (101-02/99). SLL patients enrolled in the monotherapy study 101-09 provided additional support, as CLL and SLL are regarded as two forms of the same disease. The total number of patients with CLL/SLL exposed to idelalisib and evaluable for efficacy in these studies is 397 (337 with CLL and 60 with SLL).

It is accepted that patients with 17p deletion and/or TP53 mutation do respond poorly to fludarabine-based therapy and that this cytogenetic abnormality is an important prognostic factor, and hence the proposed stratification on deletion status of 17p and/or TP53 mutation status as a major prognostic factor is agreed upon.

The design of the pivotal study and the choice of primary and secondary endpoints are considered appropriate and support an indication in previously treated patients not suitable for chemotherapy. The choice of the comparator arm seems reasonable as the use of single-agent rituximab has documented activity in patients with previously treated CLL.

iNHL

Efficacy in iNHL is based upon the interim report from the pivotal single arm study 101-09 in idelalisib monotherapy, further supported by data in the final report of the phase 1/2 dose finding study 101-02.

Additional support from combined therapy comes from the interim analysis of the phase 1 study 101-07. The total number of patients with iNHL exposed to idelalisib and evaluable for efficacy in these studies is 269 (including 60 with SLL).

The inclusion of a comparator arm in study 101-09 using Investigator's best choice, might have allowed more direct comparisons, however, further to the SAG-oncology feedback, it was acknowledged that a randomized study is considered challenging in this disease setting. The size of the population available for clinical studies is limited and there is no single standard treatment option.

Efficacy data and additional analyses

CLL

In study GS-US-312-0116 the efficacy outcomes all clearly favoured the experimental arm with a PFS HR of 0.18 and consistent effects in all reasonably defined subgroups. In addition, ORR data show that the activity appears unaffected by p53 and IgHV status. Early OS data also show superiority for the idelalisib arm, HR 0.28, p=0.003.

Longer Follow-up in the experimental arm of GS-US-312-0116 (time to next treatment, overall survival) is of importance to show sustained major benefit. This follow-up will be provided by the applicant by Q4 2017 (see Annex II and RMP).

In study GS-US-312-0116, standard criteria for PD were used and results were assessed by IRC. Among subjects with either 17p deletion and/or TP53 mutation (n=95; experimental arm: n=46; control arm: n=49), results were in favour of idelalisib + R compared with placebo + R, with an unadjusted hazard ratio (95% CI) of 0.16 (0.07, 0.37). This is a significant improvement result for this high-risk sub-population, and its relevance is not diminished by the fact that the subjects in the study were previously treated.

In study 101-08 the ORR of ~97 % in elderly untreated patients is also significant, and also the large proportion of subjects with 100 % resolution of enlarged lymph nodes. Here also, the results were consistent across subgroups of various risk factors for aggressive and refractory disease (e.g. del17p/*TP53* and IgHV mutation status).

After a median follow-up of 14+ months, PFS data are still immature, but there are no events of PD. Further follow-up is needed and will be provided post authorisation (see RMP).

In study 101-07 the ORR of ~82 % in relapsed and refractory CLL patients for combination therapy with idelalisib is significant. The median KM estimate of DOR for subjects who continued treatment in Study 101-99 was 23.9 (17.2, not reached) months. The rate of CR was however not better than for last previous regimen.

Of special interest is the activity of idelalisib in patients with CLL and del17/TP53 mutations. The largest subgroup of patients with the del17p / TP53 mutations derive from the randomized rituximab comparative study (total 95/220 subjects, n=46 in the idelalisib + rituximab arm and n=49 in the placebo + rituximab arm), with similar findings in studies 101-07 (n=24) and 101-08 (n=9). Less extreme but still significant results were observed in study 101-02, i.e. the dose finding study conducted in heavily pretreated patients. In this study the ORR was 53.8% and PFS at 6 and 12 months. were 35% and 17%. Front-line experience for idelalisib in del17p / TP53 based on 9 patients showing consistent results (with ORR and 6 and 12 months PFS of 100%).

The combination treatment is considered appropriate for SLL patients based on the fact that SLL and CLL are different manifestations of the same disease, with SLL being the tissue equivalent of CLL and based on the high response rate observed in monotherapy.

iNHL

The applicant initially claimed approval in patients with refractory iNHL, however this indication could not be approved as it is not considered as a single disease entity if not supported by data showing a positive Benefit/Risk in all subsets of the condition covered by this umbrella term.

In pivotal study 101-09 in patients with iNHL refractory to rituximab and an alkylator, the ORR of ~56 % of iNHL patients for idelalisib monotherapy is clinically significant. The median DOR was 11.9 months and exceeded the median DOR of the study population who responded to their last therapy (4.6 months). There was a good agreement of IRC vs. investigator assessments. Interestingly, there was no relationship between response and the degree of prior therapy or the frequency of refractoriness. For example, the ORRs were higher for those refractory to bendamustine compared to those who were not (59% versus 50%), for those refractory to rituximab ≥ 2 times compared to those refractory ≤ 2 times (71% versus 54%), for those treated with ≥ 4 prior therapies compared to those treated with < 4 prior therapies (62% versus 50%), and for those refractory to an alkylating agent ≥ 2 times compared to those refractory ≤ 2 times (61% versus 54%). Thus, idelalisib has limited drug-related mechanistic cross-resistance. However the development of drug-resistance has been added as missing information in the RMP in line with the discussion held during the SAG-oncology (see below). The mechanism of drug resistance will be further investigated in studies for CLL and iNHL (see RMP).

Duration of response (DOR) by age group showed moderate difference for subjects < 65 years of age and ≥ 65 years of age, the KM estimate of median DOR was 12.5 months (n = 39) and 7.4 months (n = 32), respectively.

Further to the CHMP request, ORR and other outcomes in study 101-09 have been presented separately for FL, MZL, SLL and LPL/WM. Results were comparable in all groups, but the numbers of patients were very different with n=72, 28, 10, and 15 with FL, SLL, LPL/WM, and MZL, respectively.

The claimed indication did not reflect the line of treatment and the extent of refractoriness to previous treatments. This was addressed by the revision of the indication to reflect the predominant disease subtype of FL and refractoriness to two prior lines of treatment as investigated in the pivotal trial.

In study 101-07 the ORR of ~78 % in relapsed and refractory iNHL patients for combination therapy with idelalisib is clinically significant. The median KM estimate of DOR was not reached, with a median follow-up time of 10.5 months.

In the dose finding study 101-02 with idelalisib monotherapy, the ORR for all subjects with iNHL was less extreme (45.3%). Still, in relapsed and refractory iNHL patients, this represents significant activity.

General CLL/iNHL

For a more precise evaluation of the efficacy of idelalisib in CLL and iNHL, long term effects (overall survival, time to next treatment) will be reported post approval.

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 10 June 2014 to provide advice on the following list of questions:

1. **With respect to the proposed indication in patients with chronic lymphocytic leukaemia (CLL), concerns were raised by the CHMP as in the phase III study (312-0116) the idelalisib + rituximab regimen has only been compared to rituximab alone. Therefore, the comparative efficacy and safety profile of idelalisib + rituximab in relation to other combination therapies requires further discussion. In particular please discuss the following issues;**

a. **Criteria were set up in order to define a study population sensitive to rituximab but not suitable for cytotoxic therapy. However, it is well known from the ESMO guideline (Eichhorst, 2011) and clinical studies with similar design that a large proportion of patients fulfilling these criteria nevertheless will be given chemotherapy after progression on study therapy. Please discuss how the absence of a rituximab +chemotherapy arm impacts the assessment of the benefit-risk balance for idelalisib in combination with rituximab.**

The CLL trial was conducted in a refractory population not suitable for chemotherapy as defined in the protocol. The size of the effect observed is unprecedented in this pre-treated and frail population (HR for PFS < .2). The activity observed in the subgroups of patients with 17p deletion and TP53 mutation was also important in view of poor responsiveness to conventional chemotherapy.

For the proposed indication, the lack of a rituximab+chemotherapy control arm in the pivotal study does not raise concerns provided that the population recruited can be considered as truly unsuitable to treatment with chemotherapy. The criteria for defining patients unsuitable to chemotherapy (or suitable for non-cytotoxic containing regimens) as defined in the protocol were somewhat arbitrary and possibly too inclusive (e.g., CrCl<60 ml/min as the only criterion met for inclusion was in principle sufficient). Furthermore, it is questionable to define what patients would not qualify for treatment with chlorambucil or low-dose chemotherapy regimens and indeed post-progression data are unavailable to confirm (acknowledging the caveats of this type of analysis) how many patients were ineligible for further chemotherapy. However, the criteria broadly reflect clinical practice and are based on those proposed by the German Leukaemia Study Group (CLL-11). More importantly, the effect shown is convincing compared to what can be expected with available chemotherapy options with minimal toxicity. Therefore, the control arm in the pivotal study is considered acceptable.

Uncertainties remain on how to further optimise the benefit-risk balance. Further data to explore markers of unresponsiveness, mechanisms of resistance, long term safety and drug combination therapy (versus monotherapy) will be of clinical interest to address these uncertainties. The applicant should investigate mutations in PIK3 delta signalling pathway kinase pathways and exome sequencing to pick up mechanisms of unresponsiveness and resistance. There are ongoing studies to address some of these possible markers for CLL (which is easier in terms of acquisition of tumour samples). Still, it would be useful to further study also FL based, e.g., on lymph node biopsies.

b. **Given the results from the above mentioned phase III study, what indication would be considered clinically appropriate considering the patient population studied as well as the outcome of the study?**

The indication considered clinically appropriate is in patients with relapsed CLL, in combination with rituximab, in patients not suitable for chemotherapy. A definition based on number of prior treatments was not considered appropriate since depending on the duration of response chemotherapy options might still be considered beyond second-line. It is difficult to define “not suitable for chemotherapy” in more details and this is best left to the decision of the clinicians, particularly based on duration of first remission and other criteria such as those outlined in the pivotal trial. This will generally include patients for whom the toxicity associated with chemotherapy is of concern (not suitable for chemotherapy) or where non-cytotoxic treatments might be a preferred option, e.g., slowly progressive disease (suitable for non-chemotherapy containing regimens).

2. **With respect to the proposed indication in patients with indolent non-Hodgkin lymphoma (iNHL), the CHMP raised concerns in relation to the pivotal monotherapy trial 101-09 and the proposed indication for the treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL). Due to the immaturity of data (PFS event rate about 30%)**

the Applicant has been requested to provide an update of efficacy data, separately reported for follicular lymphoma (FL), marginal zone lymphoma, small lymphocytic leukaemia and lympho-plasmocytoid lymphoma (Waldenström). Another concern raised by CHMP was that the study had a single arm, uncontrolled design. Please discuss;

c. **How is the benefit/risk assessment of idelalisib monotherapy in iNHL impacted by the absence of a randomized reference, e.g. investigators' best choice given the results of the study?**

The drug shows activity in FL however absence of comparative data makes it difficult to define the exact benefit in terms of clinical benefit endpoints. The response rate observed was high although the clinical relevance of this endpoint is questionable and PFS should be the preferred endpoint (Lugano Criteria, JCO 2014). Intra-patient comparisons of PFS indicated an overall longer PFS on idelalisib compared to prior treatment (acknowledging the caveats of this historical comparison). Nevertheless, the response rate is even higher than that of rituximab in the salvage setting (acknowledging the caveats of historical comparisons including different definitions of response) and overall it can be expected that the benefit in terms of clinically relevant endpoints will be at least of similar magnitude.

d. **What would be the estimated outcome (including overall survival and PFS) of an investigator's best choice regimen based on clinical experience and would a comparative study have been feasible? To the knowledge of the assessors, no relevant data in relation to what would be achievable with respect to treatment effect with currently licensed drugs in a similarly heavily pre-treated iNHL patient population is available.**

Concerning the expected treatment effect of available options it is difficult to give precise estimates. However, the high activity observed allows concluding that the benefits are expected to exceed any of the available options and are at least of similar magnitude than rituximab in the salvage setting.

In view of the recent experience, a randomized study is considered a challenge in this disease setting. This is mainly due to the fact that the size of the population available for clinical studies is limited and there is no single standard treatment option among the several dozen available ones that are used according to different investigator practices and individualised treatment approaches, which in turn would require large sample sizes in order to ensure sufficient power to detect important treatment effects.

e. **Considering the patient population studied (mainly patients with follicular lymphoma), please discuss the relevant target population for treatment with idelalisib, e.g. patients with follicular lymphoma refractory to rituximab and an alkylating agent.**

The relevant FL lymphoma population for idelalisib monotherapy is patients with FL who are refractory to two lines of therapy. These are patients with multiple prior regimens fulfilling standard criteria for treatment and for whom high-dose therapies with curative intent are generally not appropriate. The need to explicitly mention rituximab and an alkylating agent was not supported as the best available therapy might include different regimens. SLL is considered part of the CLL indication according to current classification and should not be specifically mentioned under the monotherapy indication (although this raises the question about idelalisib monotherapy in CLL versus combination therapy, see uncertainties under answers to question 1a).

2.5.5. Conclusions on the clinical efficacy

Idelalisib showed consistent activity across subgroups based on previous treatment responses or prognostic groups within CLL and FL.

The CHMP considers the following measures necessary to address issues related to efficacy:

- The applicant will submit the final study report for phase 3 study GS-US-312-0116, to evaluate the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated CLL by Q4 2017. Updates on PFS, OS and duration of response for patients with or without 17p Deletion/ TP53 Mutation and the whole population will be submitted in October 2014 and August 2015. The applicant will also provide the final data from the extension study GS-US-312-0117.

- The applicant will submit the final study report for phase 2 101-09 study to evaluate the efficacy and safety of idelalisib in subjects with indolent B-cell NHL refractory to rituximab and alkylating agents by Q3 2017. Updates on safety and efficacy results including overall survival and updates of the analyses of subjects with baseline lymphopenia, will be submitted by Q4 2014. The Applicant will also provide the final data from the extension study 101-99.

2.6. Clinical safety

The integrated clinical safety evaluation is based on the pivotal monotherapy Phase 2 Study 101-09, supported by pooled monotherapy studies (101-02, 101-10, and 101-11) and the extension Study 101-99. In addition, safety data from combination therapy studies (101-07 and 101-08) are provided.

The safety analyses are further organized within each of these 2 groups into subjects with iNHL, subjects with CLL, and all subjects combined.

Subjects Treated with Monotherapy

- Subjects with iNHL Treated with Monotherapy
- Subjects with CLL Treated with Monotherapy
- All Subjects Treated with Monotherapy

Subjects Treated with Combination Therapy

- Subjects with iNHL Treated with Combination Therapy
- Subjects with CLL Treated with Combination Therapy
- All Subjects Treated with Combination Therapy

Patient exposure

iNHL Monotherapy: The median (Q1, Q3) duration of exposure for subjects with iNHL treated with idelalisib monotherapy (N = 200) was 6.1 (2.5, 11.5) months. The maximum duration of exposure approached 3.5 years.

CLL Monotherapy: The median (Q1, Q3) duration of exposure for subjects with CLL treated with idelalisib monotherapy (N = 54) was 8.8 (3.1, 23.5) months. The maximum duration of exposure

exceeded 4 years.

Subjects with iNHL Treated with Idelalisib Combination Therapy

The median (Q1, Q3) duration of exposure for subjects with iNHL treated with combination therapy (N = 80) was 10.0 (3.7, 23.3) months. Twenty-nine subjects (36.3%) continue to receive idelalisib (1 subject in Study 101-07 and 28 subjects in extension Study 101-99).

Subjects with CLL Treated with Idelalisib Combination Therapy in Phase 1 and 2 Studies

The median (Q1, Q3) duration of exposure for subjects with CLL treated with idelalisib combination therapy (N = 178) was 11.3 (6.6, 21.4) months. The maximum duration of exposure was more than 2.5 years (33.6 months). Seventy-eight subjects (43.8%) continue to receive idelalisib (19 subjects in Studies 101-07 and 101-08, and 59 subjects in extension Study 101-99).

Extent of Exposure Pivotal Study 312-0116

Of the 220 subjects randomized in the study, 218 received at least 1 dose of study drug (idelalisib or placebo) as of the data cut-off for this report (09 October 2013), and were evaluable for safety. All 218 subjects correctly received the study drug to which they were assigned during randomization. The median (Q1, Q3) duration of exposure to study drug in the idelalisib + R group was 5.0 (3.0, 9.4) months, with a range of 0.3 to 17.3 months. The median (Q1, Q3) duration of exposure to study drug in the placebo + R group was 3.7 (2.4, 6.5) months, with a range of 0.1 to 14.6 months. Mean study drug exposure based on person months on therapy was approximately 36% higher in the idelalisib + R group compared with the placebo + R group. Thus, mean exposure in the randomized 312-0116 study was significantly shorter than in the phase 1/2 studies.

Table 40: Study 312-0116: study drug (idelalisib or placebo) exposure (safety analysis set)

	IDELA + R (N=110)	Placebo + R (N=108)	Total (N=218)
Duration of Exposure to IDELA/Placebo (months)[a]			
N	110	108	218
Mean (StD)	6.2 (4.09)	4.7 (3.23)	5.5 (3.76)
Median	5.0	3.7	4.2
Q1, Q3	3.0, 9.4	2.4, 6.5	2.6, 7.4
Min, Max	0.3, 17.3	0.1, 14.6	0.1, 17.3
Cumulative Exposure to IDELA/Placebo, n (%)			
≥ 1 Day	110 (100.0)	108 (100.0)	218 (100.0)
≥ 2 months	98 (89.1)	89 (82.4)	187 (85.8)
≥ 4 months	67 (60.9)	50 (46.3)	117 (53.7)
≥ 6 months	45 (40.9)	28 (25.9)	73 (33.5)
≥ 12 months	12 (10.9)	4 (3.7)	16 (7.3)
Adherence (%) Category[b], n (%)			
≥ 75%	110 (100.0)	106 (98.1)	216 (99.1)
< 75%	0	2 (1.9)	2 (0.9)
Subjects with Dose Modification, n (%)			
Dose Reduced to 100 mg BID	16 (14.5)	0	16 (7.3)
Dose Re-escalated to 150 mg BID	1 (0.9)	0	1 (0.5)

The safety analysis set includes all subjects who received ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.

a Duration of exposure (months) = (min(last IDELA/placebo dosing date as captured on study drug completion CRF page, data cutoff date) first IDELA/placebo dosing date + 1)/30.4375.

b Adherence (%) = (sum of pills dispensed – sum of pills returned) divided by (sum over all dosing period of (total daily pills x dosing duration), taking into account physician-prescribed reductions, escalations, and interruptions.

Source: Section 15.1, Table 1.11

Adverse events

Adverse event in all subjects treated with idelalisib monotherapy

The most frequent AEs of any grade reported for ≥ 20% of subjects with iNHL were diarrhoea (40.5%), fatigue (31.5%), nausea (28.0%), cough (24.5%), pyrexia (24.5) and neutropenia (24.0%). The most frequent AEs of any grade reported for ≥ 20% of subjects with CLL were fatigue (31.5%), diarrhoea (29.6%), pyrexia (27.8%), cough and thrombocytopenia (24.1% each), and anaemia, back pain, neutropenia, pneumonia, rash, and upper respiratory tract infection (22.2% each).

Table 41: AEs by SOC and PT Reported for ≥ 10% All Subjects Treated with Monotherapy

System Organ Class Preferred Term	< 150 mg IDELA BID or any QD IDELA N = 94	150 mg IDELA BID N = 206	> 150 mg IDELA BID N = 52	Total N = 352
Subjects with any AE	93 (98.9)	201 (97.6)	52 (100)	346 (98.3)
Gastrointestinal Disorders	56 (59.6)	136 (66.0)	37 (71.2)	229 (65.1)
Diarrhoea	32 (34.0)	76 (36.9)	15 (28.8)	123 (34.9)
Nausea	19 (20.2)	55 (26.7)	15 (28.8)	89 (25.3)
Vomiting	13 (13.8)	28 (13.6)	9 (17.3)	50 (14.2)
Constipation	7 (7.4)	22 (10.7)	8 (15.4)	37 (10.5)
Abdominal Pain	5 (5.3)	29 (14.1)	3 (5.8)	37 (10.5)
General Disorders and Administration Site Conditions	61 (64.9)	130 (63.1)	39 (75.0)	230 (65.1)
Fatigue	34 (36.2)	57 (27.7)	19 (36.5)	110 (31.3)
Pyrexia	20 (21.3)	59 (28.6)	14 (26.9)	93 (26.4)
Chills	15 (16.0)	22 (10.7)	10 (19.2)	47 (13.4)
Oedema Peripheral	5 (5.3)	21 (10.2)	10 (19.2)	36 (10.2)
Infections and Infestations	54 (57.4)	108 (52.4)	32 (61.5)	194 (55.1)
Upper Respiratory Tract Infection	22 (23.4)	23 (11.2)	6 (11.5)	51 (14.5)
Pneumonia	13 (13.8)	22 (10.7)	11 (21.2)	46 (13.1)
Respiratory, Thoracic and Mediastinal Disorders	36 (38.3)	98 (47.6)	31 (59.6)	165 (46.9)
Cough	11 (11.7)	57 (27.7)	10 (19.2)	78 (22.2)
Dyspnoea	7 (7.4)	31 (15.0)	5 (9.6)	43 (12.2)
Investigations	35 (37.2)	91 (44.2)	32 (61.5)	158 (44.9)
ALT Increased	16 (17.0)	35 (17.0)	13 (25.0)	64 (18.2)
AST Increased	14 (14.9)	34 (16.5)	16 (30.8)	64 (18.2)
Skin and Subcutaneous Tissue Disorders	35 (37.2)	91 (44.2)	29 (55.8)	155 (44.0)
Rash	18 (19.1)	30 (14.6)	12 (23.1)	60 (17.0)
Night Sweats	10 (10.6)	21 (10.2)	9 (17.3)	40 (11.4)
Blood and Lymphatic System Disorders	33 (35.1)	81 (39.3)	30 (57.7)	144 (40.9)
Neutropenia	12 (12.8)	47 (22.8)	13 (25.0)	72 (20.5)
Thrombocytopenia	10 (10.6)	31 (15.0)	10 (19.2)	51 (14.5)
Anaemia	13 (13.8)	24 (11.7)	12 (23.1)	49 (13.9)
Metabolism and Nutrition Disorders	27 (28.7)	79 (38.3)	21 (40.4)	127 (36.1)
Decreased Appetite	10 (10.6)	30 (14.6)	6 (11.5)	46 (13.1)
Nervous System Disorders	29 (30.9)	70 (34.0)	20 (38.5)	119 (33.8)
Headache	10 (10.6)	21 (10.2)	8 (15.4)	39 (11.1)
Musculoskeletal and Connective Tissue Disorders	30 (31.9)	65 (31.6)	20 (38.5)	115 (32.7)
Back Pain	11 (11.7)	20 (9.7)	6 (11.5)	37 (10.5)

Table 42: ≥ Grade 3 AEs by PT Reported for ≥ 2% of Subjects by Decreasing Frequency, All Subjects Treated with Monotherapy (Safety Analysis Set)

Preferred Term	< 150 mg IDELA BID or any QD IDELA N = 94	150 mg IDELA BID N = 206	> 150 mg IDELA BID N = 52	Total N = 352
Subjects with any ≥ Grade 3 AE	70 (74.5)	135 (65.5)	44 (84.6)	249 (70.7)
Neutropenia	8 (8.5)	35 (17.0)	9 (17.3)	52 (14.8)
ALT Increased	11 (11.7)	21 (10.2)	8 (15.4)	40 (11.4)
Pneumonia	12 (12.8)	17 (8.3)	10 (19.2)	39 (11.1)
Diarrhoea	10 (10.6)	18 (8.7)	4 (7.7)	32 (9.1)
AST Increased	8 (8.5)	13 (6.3)	7 (13.5)	28 (8.0)
Anaemia	6 (6.4)	12 (5.8)	7 (13.5)	25 (7.1)
Thrombocytopenia	5 (5.3)	10 (4.9)	7 (13.5)	22 (6.3)
Febrile Neutropenia	7 (7.4)	8 (3.9)	3 (5.8)	18 (5.1)
Colitis	4 (4.3)	5 (2.4)	2 (3.8)	11 (3.1)
Dehydration	2 (2.1)	7 (3.4)	1 (1.9)	10 (2.8)
Neutrophil Count Decreased	3 (3.2)	4 (1.9)	2 (3.8)	9 (2.6)
Renal Failure Acute	3 (3.2)	3 (1.5)	3 (5.8)	9 (2.6)
Decreased Appetite	4 (4.3)	2 (1.0)	2 (3.8)	8 (2.3)
Hypophosphataemia	3 (3.2)	4 (1.9)	1 (1.9)	8 (2.3)
Pulmonary Embolism	3 (3.2)	3 (1.5)	2 (3.8)	8 (2.3)
Hypokalaemia	0	7 (3.4)	0	7 (2.0)
Liver Function Test Abnormal	2 (2.1)	2 (1.0)	3 (5.8)	7 (2.0)
Rash	3 (3.2)	3 (1.5)	1 (1.9)	7 (2.0)

Source: Appendix 8.1, Table 7.17.3

Table 43: AEs Assessed by the Investigator as Related to Treatment Reported for ≥ 10% of Subjects by PT, All Subjects Treated with Monotherapy (Safety Analysis Set)

System Organ Class Preferred Term	< 150 mg IDELA BID or any QD IDELA N = 94	150 mg IDELA BID N = 206	> 150 mg IDELA BID N = 52	Total N = 352
Subject with any IDELA-related AE	67 (71.3)	156 (75.7)	40 (76.9)	263 (74.7)
Diarrhoea	18 (19.1)	50 (24.3)	6 (11.5)	74 (21.0)
ALT Increased	15 (16.0)	34 (16.5)	13 (25.0)	62 (17.6)
AST Increased	12 (12.8)	32 (15.5)	15 (28.8)	59 (16.8)
Nausea	13 (13.8)	32 (15.5)	8 (15.4)	53 (15.1)
Neutropenia	7 (7.4)	34 (16.5)	9 (17.3)	50 (14.2)
Fatigue	14 (14.9)	31 (15.0)	4 (7.7)	49 (13.9)
Rash	12 (12.8)	17 (8.3)	9 (17.3)	38 (10.8)

Source: Appendix 8.1, Table 7.18.3

For common adverse reactions, the treating physician is in the best position to grade causality. Without analyzing e.g., neutropenia and pneumonia in relation to response to the underlying disease conclusions as regards relatedness are hard to draw, the incidence of pneumonia is clearly high, however.

The tables above indicate the possibility of a dose AE relationship for some SOC terms, but there is also an interaction between disease and duration of therapy to be taken into account.

Adverse events in All Subjects Treated with Combination Therapy in Phase 1 and 2 Studies

The most frequent AEs of any grade (reported for ≥ 20% of subjects) were diarrhoea (46.2%), pyrexia (43.4%), cough (34.5%), neutropenia (34.5%), fatigue (34.1%), nausea (32.4%), rash (29.7%), ALT increased (21.7%), and chills (21.0%). The incidence of AEs was generally notably higher among all subjects in the combination therapy group compared with all subjects in the monotherapy group. Many of the AEs in the combination therapy cohorts were consistent with the known AE profiles of the agents used in the combination therapies.

Common Adverse Events, Subjects with CLL Treated with Combination Therapy in Phase 3 Randomized Study 312-0116

The most commonly reported AEs in the idelalisib + R group were pyrexia (34.5%, 38 subjects), neutropenia (27.3%, 30 subjects), and fatigue and nausea (each 25.5%, 28 subjects). The most commonly reported AEs in the placebo + R group were infusion-related reaction (29.6%, 32 subjects), fatigue and cough (27.8%, 30 subjects).

Table 44: Study 312-0116: Adverse Events in ≥ 10% of Subjects in Either Treatment Group, Sorted by Decreasing Incidence (Safety Analysis Set)

Adverse Event, n (%)	IDELA + R (N=110)	Placebo + R (N=108)
Gastrointestinal Disorders	69 (62.7)	63 (58.3)
Nausea	28 (25.5)	23 (21.3)
Diarrhea	21 (19.1)	16 (14.8)
Constipation	14 (12.7)	12 (11.1)
Vomiting	14 (12.7)	9 (8.3)
General Disorders and Administration Site Conditions	73 (66.4)	59 (54.6)
Fatigue	28 (25.5)	30 (27.8)
Pyrexia	38 (34.5)	18 (16.7)
Chills	23 (20.9)	17 (15.7)
Oedema peripheral	11 (10.0)	10 (9.3)
Respiratory, Thoracic, and Mediastinal Disorders	55 (50.0)	65 (60.2)
Cough	19 (17.3)	30 (27.8)
Dyspnea	14 (12.7)	21 (19.4)
Infections and Infestations	67 (60.9)	51 (47.2)
Pneumonia	11 (10.0)	14 (13.0)
Upper Respiratory Tract Infection	8 (7.3)	12 (11.1)
Skin and Subcutaneous Tissue Disorders	47 (42.7)	37 (34.3)
Night Sweats	12 (10.9)	11 (10.2)
Rash	11 (10.0)	5 (4.6)
Injury, Poisoning, and Procedural Complications	39 (35.5)	40 (37.0)
Infusion Related Reaction	21 (19.1)	32 (29.6)
Blood and Lymphatic System Disorders	42 (38.2)	34 (31.5)
Neutropenia	30 (27.3)	18 (16.7)
Anemia	9 (8.2)	11 (10.2)
Nervous System Disorders	32 (29.1)	27 (25.0)
Headache	11 (10.0)	5 (4.6)
Metabolism and Nutrition Disorders	27 (24.5)	25 (23.1)
Decreased Appetite	13 (11.8)	11 (10.2)

The safety analysis set included all subjects who receive ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.

AE was classified by PT using MedDRA version 15.1.

Subjects who experienced multiple events within the same PT (or HLT, SOC) were counted once per PT (or HLT, SOC)

Table 45: Study 312-0116: ≥ Grade 3 AEs Reported for ≥ 2% of Subjects (Safety Analysis Set)

System Organ Class Preferred Term	IDELA + R (N=110)	Placebo + R (N=108)
Blood and Lymphatic System Disorders	34 (30.9)	25 (23.1)
Neutropenia	24 (21.8)	13 (12.0)
Febrile Neutropenia	5 (4.5)	4 (3.7)
Anaemia	5 (4.5)	7 (6.5)
Thrombocytopenia	3 (2.7)	5 (4.6)
Infections and Infestations	31 (28.2)	25 (23.1)
Pneumonia	9 (8.2)	10 (9.3)
Sepsis	4 (3.6)	3 (2.8)
Pneumocystis jiroveci pneumonia	3 (2.7)	1 (0.9)
Respiratory, Thoracic, and Mediastinal Disorders	13 (11.8)	11 (10.2)
Dyspnoea	3 (2.7)	3 (2.8)
Pneumonitis	4 (3.6)	1 (0.9)
General Disorders and Administration Site Conditions	13 (11.8)	12 (11.1)
Fatigue	5 (4.5)	3 (2.8)
Asthenia	1 (0.9)	4 (3.7)
Pyrexia	3 (2.7)	1 (0.9)
Investigations	9 (8.2)	5 (4.6)
Transaminases Increased	3 (2.7)	1 (0.9)
Alanine Aminotransferase Increased	3 (2.7)	0
Gastrointestinal Disorders	10 (9.1)	2 (1.9)
Diarrhoea	4 (3.6)	0
Colitis	3 (2.7)	0
Injury, Poisoning, and Procedural Complications	0	5 (4.6)
Infusion Related Reaction	0	4 (3.7)

AEs are classified using MedDRA version 15.1.

Subjects who experienced multiple events within the same PT (or HLT, SOC) are counted once per PT (or HLT, SOC) in the highest severity grade.

Severity of AEs is graded according to the CTCAE, Version 4.03

Table 46: Study 312-0116: AEs Reported by the Investigator as Related to Study Drug for ≥ 2% of Subjects (Safety Analysis Set)

System Organ Class Preferred Term	IDELA + R (N=110)	Placebo + R (N=108)
Number of Subjects with any AE Reported by the Investigator as Related to Study Drug	52 (47.3)	22 (20.4)
Gastrointestinal Disorders	25 (22.7)	10 (9.3)
Diarrhoea	11 (10.0)	5 (4.6)
Nausea	7 (6.4)	1 (0.9)
Constipation	3 (2.7)	3 (2.8)
Stomatitis and ulceration	5 (4.5)	0
Stomatitis	4 (3.6)	0
General Disorders and Administration Site Conditions	17 (15.5)	7 (6.5)
Fatigue	10 (9.1)	3 (2.8)
Asthenia	4 (3.6)	1 (0.9)
Pyrexia	7 (6.4)	1 (0.9)
Chills	3 (2.7)	0
Pain	3 (2.7)	0
Skin and Subcutaneous Tissue Disorders	13 (11.8)	3 (2.8)
Rash	4 (3.6)	1 (0.9)
Rash Maculo-Papular	3 (2.7)	0
Night Sweats	3 (2.7)	1 (0.9)
Infections and Infestations	14 (12.7)	4 (3.7)
Pneumonia	3 (2.7)	1 (0.9)
Upper Respiratory Tract Infection	3 (2.7)	0
Blood and Lymphatic System Disorders	14 (12.7)	5 (4.6)
Neutropenia	12 (10.9)	4 (3.7)
Metabolism and Nutrition Disorders	8 (7.3)	4 (3.7)
Decreased Appetite	5 (4.5)	1 (0.9)
Investigations	12 (10.9)	3 (2.8)
Alanine Aminotransferase Increased	5 (4.5)	0
Aspartate Aminotransferase Increased	4 (3.6)	0
Respiratory, Thoracic, and Mediastinal Disorders	8 (7.3)	4 (3.7)
Pneumonitis	4 (3.6)	0

AEs are classified using MedDRA version 15.1.

Subjects who experienced multiple events within the same PT (or HLT, SOC) are counted once per PT (or HLT, SOC).

Table 47: Incidence of AEs by Time Interval

	0 to 12 Weeks		12 to 24 Weeks		> 24 Weeks	
Adverse Event, n (%)	IDELA + R (N=110)	Placebo + R (N=107)	IDELA + R (N=83)	Placebo + R (N=78)	IDELA + R (N=49)	Placebo + R (N=32)
Infusion Related Reaction	16 (14.5)	29 (27.1)	2 (2.4)	4 (5.2)	0	0
Pyrexia	26 (23.6)	12 (11.2)	6 (7.2)	3 (3.9)	5 (10.2)	4 (12.5)
Chills	22 (20.0)	16 (15.0)	2 (2.4)	2 (2.6)	1 (2.0)	0
Nausea	21 (19.1)	22 (20.6)	7 (8.4)	1 (1.3)	0	1 (3.1)
Fatigue	21 (19.1)	22 (20.6)	6 (7.2)	5 (6.5)	1 (2.0)	4 (12.5)
Neutropenia	20 (18.2)	11 (10.3)	8 (9.6)	2 (2.6)	3 (6.1)	1 (3.1)
Cough	10 (9.1)	19 (17.8)	5 (6.0)	4 (5.2)	1 (2.0)	6 (18.8)
Diarrhoea	16 (14.5)	13 (12.1)	6 (7.1)	4 (5.2)	5 (10.2)	2 (6.3)
Dyspnoea	11 (10.1)	14 (13.1)	2 (2.4)	6 (7.8)	2 (4.1)	3 (9.4)
Decreased Appetite	7 (6.4)	5 (4.7)	2 (2.4)	2 (6.3)	4 (8.2)	2 (6.3)
Constipation	10 (9.1)	11 (10.3)	3 (3.6)	1 (1.3)	0	0
Vomiting	11 (10.0)	6 (5.6)	2 (2.4)	2 (2.6)	0	0
Night Sweats	6 (5.5)	4 (3.7)	2 (2.4)	2 (2.6)	3 (6.1)	2 (6.3)
Rash	7 (6.4)	4 (3.7)	2 (2.4)	2 (2.6)	3 (6.1)	1 (3.1)

The safety analysis set included all subjects who receive ≥ 1 dose of study treatment, with treatment group designated according to the actual treatment received.
AE was classified by PT using MedDRA version 15.1.
Subjects who experienced multiple events within the same PT (or HLT, SOC) were counted once per PT (or HLT, SOC).

Note that infusion related reactions were decreased in the combination arm, whilst pyrexia is increased. Also beyond week 12, neutropenia is slightly more common in the idelalisib arm.

Table 48: Grade 3 AEs Reported for >2% of Subjects in Either Treatment Group by Decreasing SOC and PT (Safety Analysis)

System Organ Class Preferred Term	IDELA + R (N=110)	Placebo + R (N=108)
Blood and Lymphatic System Disorders	34 (30.9)	25 (23.1)
Neutropenia	24 (21.8)	13 (12.0)
Febrile Neutropenia	5 (4.5)	4 (3.7)
Anaemia	5 (4.5)	7 (6.5)
Thrombocytopenia	3 (2.7)	5 (4.6)
Infections and Infestations	31 (28.2)	25 (23.1)
Pneumonia	9 (8.2)	10 (9.3)
Sepsis	4 (3.6)	3 (2.8)
Pneumocystis jiroveci pneumonia	3 (2.7)	1 (0.9)
Respiratory, Thoracic, and Mediastinal Disorders	13 (11.8)	11 (10.2)
Dyspnoea	3 (2.7)	3 (2.8)
Pneumonitis	4 (3.6)	1 (0.9)
General Disorders and Administration Site Conditions	13 (11.8)	12 (11.1)
Fatigue	5 (4.5)	3 (2.8)
Asthenia	1 (0.9)	4 (3.7)
Pyrexia	3 (2.7)	1 (0.9)
Investigations	9 (8.2)	5 (4.6)
Transaminases Increased	3 (2.7)	1 (0.9)
Alanine Aminotransferase Increased	3 (2.7)	0
Gastrointestinal Disorders	10 (9.1)	2 (1.9)
Diarrhoea	4 (3.6)	0
Colitis	3 (2.7)	0
Injury, Poisoning, and Procedural Complications	0	5 (4.6)
Infusion Related Reaction	0	4 (3.7)

AEs are classified using MedDRA version 15.1.

Subjects who experienced multiple events within the same PT (or HLT, SOC) are counted once per PT (or HLT, SOC) in the highest severity grade.

Severity of AEs is graded according to the CTCAE, Version 4.03

Those events already discussed in relation to monotherapy were those where add-on activity was shown.

Adverse drug reactions

Assessment of adverse reactions is based on one Phase 3 study and seven Phase 1 and 2 studies. Phase 3 study 312-0116 was a randomised, double-blind, placebo-controlled study in which 220 patients with previously treated CLL were randomised 1:1 to receive idelalisib + rituximab or placebo + rituximab. The Phase 1 and 2 studies assessed the safety of idelalisib in 490 patients with haematologic malignancies, including 354 subjects who received idelalisib (any dose) as a single agent and 136 subjects who received idelalisib in combination with anti-CD20 monoclonal antibodies (see section 4.8 of the SmPC).

The most frequently observed ADRs in patients receiving idelalisib were infections, neutropenia and increased transaminase.

Table 49: Adverse drug reactions reported in clinical studies in patients with haematologic malignancies receiving idelalisib

Reaction	Any grade	Grade ≥ 3
Infections and infestations		
Infections	356 (59.3%)	168 (28.0%)
Blood and lymphatic system disorders		
Neutropenia	298 (49.7%)	165 (27.5%)
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	20 (3.3%)	13 (2.2%)
Gastrointestinal disorders		
Diarrhoea/colitis	229 (38.2%)	84 (14.0%)
Hepatobiliary disorders		
Transaminase increased	293 (48.8%)	89 (14.8%)
Skin and subcutaneous tissue disorders		
Rash*	146 (24.3%)	27 (4.5%)
General disorders and administration site conditions		
Pyrexia	189 (31.5%)	13 (2.2%)
Investigations		
Increased triglycerides	266 (44.3%)	21 (3.5%)

* Includes the preferred terms dermatitis exfoliative, drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash morbilliform, and exfoliative rash.

Analysis of Adverse Events by Organ System or Syndrome

Transaminase Elevations

iNHL monotherapy

The incidence of any grade elevated ALT was 48.5% in altogether 200 patients. Twenty-seven subjects (13.5%) developed a Grade 3 abnormality and 10 subjects (5.0%) developed a Grade 4 abnormality. The incidence of any grade elevated AST was 42.5%. Twenty-one subjects (10.5%) developed a Grade 3 abnormality and 6 subjects (3.0%) developed a Grade 4 abnormality.

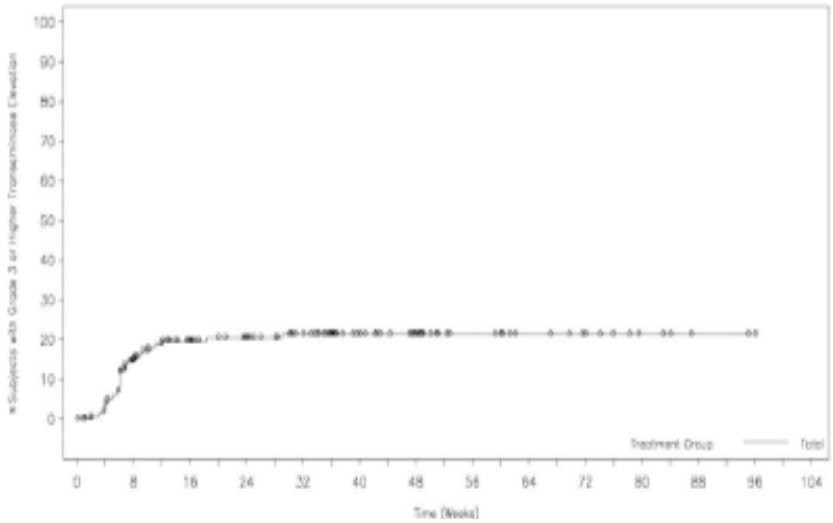


Figure 13: Time to Onset of First ≥ Grade 3 Treatment- Emergent Transaminase Elevation, Subjects with iNHL Treated with Monotherapy (Safety Analysis Set)

Among subjects with ≥ Grade 3 ALT or AST elevations, the median time to first onset of the event was 6.1 weeks (range: 2.0 to 29.1 weeks). Nearly all events (36 of 38) resolved to ≤ Grade 1 levels. Among those

subjects whose elevations resolved, the median time to resolution was 3.3 weeks, and 75% had resolved by 4.5 weeks.

CLL Monotherapy

Among subjects with CLL treated with monotherapy (N = 54), the incidence of any grade elevated ALT was 18.5%. No subject developed a Grade 3 ALT abnormality and 1 subject (1.9%) developed a Grade 4 ALT abnormality.

All subjects in phase 1-2 combined therapy

The incidence of any grade ALT elevation was 42.1%, the median time to first onset of the event was 6.1 weeks (range: 2.1 to 13.1 weeks). Nearly all events (41 of 43) resolved to ≤ Grade 1 levels. Among those subjects whose elevations resolved, the median time to resolution was 2.3 weeks, and 75% had resolved by 4 weeks.

In the Phase 1 and 2 studies, 2 subjects experienced AST or ALT > 3 times the upper limit of normal (ULN) concurrently with a total bilirubin > 2.0 x ULN and normal alkaline phosphatase. However, confounders were present that may have contributed to the elevations in transaminase and total bilirubin. According to the applicant, no case met the criteria for Hy's Law. However, patients with active hepatitis were excluded from all the studies and thus constitute a population with missing information.

Subjects with CLL Treated with idelalisib Combination Therapy in Phase 3 Randomized Study 312-0116

Transaminase elevations occurred more commonly in subjects in the idelalisib + R group compared with the placebo + R group. Most transaminase elevations were Grade 1 or Grade 2 in severity. The elevations typically occurred within the first 3 months of therapy, and were asymptomatic. Elevations (all grades) in ALT occurred in 38 subjects (34.5%) in the idelalisib + R group, with ≥ Grade 3 observed in 9 subjects (8.2%). ALT elevations (all grades) occurred in 11 subjects (10.2%) in the placebo + R group, with ≥ Grade 3 observed in 1 subject (0.9%). Elevations (all grades) in AST occurred in 27 subjects (24.5%) in the idelalisib + R group, with ≥ Grade 3 observed in 6 subjects (5.5%). AST elevations (all grades) occurred in 15 subjects (13.9%) in the placebo + R group, with ≥ Grade 3 observed in no subjects.

Diarrhoea and colitis

Diarrhoea/colitis is the most characteristic adverse reaction to treatment with idelalisib, especially colitis that occur after months of therapy and in the majority of cases (70%) not proceeded by reported diarrhoea grade 1/2.

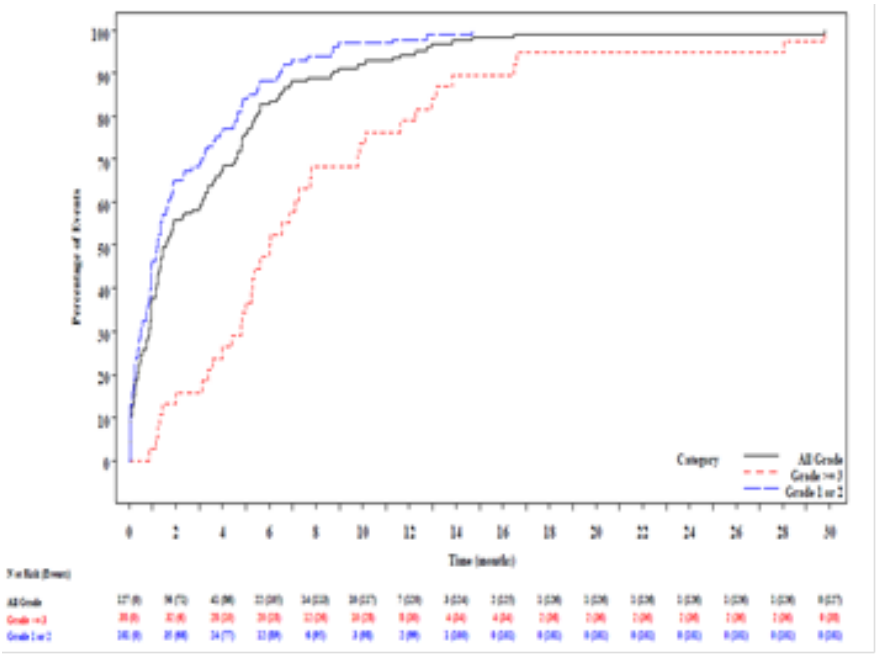


Figure 14: Time to Onset of Diarrhoea/Colitis, All Diseases, Monotherapy (Safety Analysis Set).

All Subjects Treated with Monotherapy

Diarrhoea was the most common AE observed in all subjects treated with monotherapy (N = 352, 123 subjects, 34.9%). Grade 3 diarrhoea was reported for 31 subjects (8.8%) and Grade 4 was reported for 1 subject. Diarrhoea resulted in study drug discontinuation for 7 subjects. No relationship to dose was shown.

Among subjects with diarrhoea of any grade (N = 117) in idelalisib monotherapy, the median time to onset was 1.4 months, whereas onset of more severe cases approximately 6-7 months. It is not sufficiently clear whether the symptoms of diarrhoea and/or colitis started with milder form and successively became more severe, or if it sometimes had a more acute onset.

All Subjects Treated with Combination Therapy in Phase 1 and 2 Studies

Among all subjects treated with combination therapy (N = 290), 134 subjects, 46.2%) reported diarrhoea of any grade. Grade 3 was reported for 38 subjects (13.1%) and Grade 4 diarrhoea was reported for 1 subject. Diarrhoea resulted in study drug discontinuation for 15 subjects (5.2%). Colitis of any grade was reported for 27 subjects (9.3%); Grade 3 colitis was reported for 23 subjects (7.9%), and Grade 4 was reported for 2 subjects (0.7%). Ten subjects had ≥ Grade 3 colitis and ≥ Grade 3 diarrhoea.

Colitis resulted in study drug discontinuation for 6 subjects (2.1%). Twenty-one (7.2%) SAEs of diarrhoea and 19 (6.6%) SAEs of colitis were reported; 1 subject had SAEs of diarrhoea and colitis.

Diarrhoea SAEs From Phase 1 and 2 Studies

In the total safety database of 642 subjects, altogether 66 subjects had at least one SAE reported as diarrhoea/colitis. For 44 subjects (6.9%) the more common aetiologies of diarrhoea anticipated for the study populations could not be readily identified and/or the subject had recurrence of diarrhoea upon rechallenge with idelalisib.

These 44 subjects generally presented after several months of treatment with a history of several weeks of watery diarrhoea that responded poorly to antidiarrheal or to empiric treatment with antimicrobials. Idelalisib administration was interrupted during the serious diarrhoea event for almost all of these

subjects. Treatment regimens associated with resolution were varied, and included budesonide for approximately half of subjects. The median time to resolution noted from the discontinuation of idelalisib regardless of treatment approach was approximately 1 month.

Of the 44 subjects, 13 subjects were rechallenged and diarrhoea recurred for 9 subjects following their first rechallenge.

Patients with IBD were excluded from some of the major studies (notably 312-0116) which has been reflected in the SmPC.

Diarrhoea in Study GS-US-312-0116

In Study GS-US-312-0116 through the database cut-off for this report, 21 subjects (19.1%) in the idelalisib + R group had an AE of diarrhoea (any grade), and 4 subjects (3.6%) had events that were ≥ Grade 3 in severity (3 subjects with Grade 3 and 1 subject with Grade 4). Two subjects in the idelalisib + R discontinued study drug due to diarrhoea or colitis; the events resolved following study drug discontinuation in 1 of the 2 subjects. The second subject (6708-10230) died of fungal pneumonia and febrile neutropenia before the diarrhoea resolved (Appendix 16.2, Listing 3.3.5). In the placebo + R group, 16 subjects (14.8%) had diarrhoea of any grade, and 0 subjects had diarrhoea events that were ≥ Grade 3 in severity.

Rash

In idelalisib monotherapy, 17 % of all subjects reported an AE of rash any grade. Among subjects treated with monotherapy (N = 352), grade 3 AEs occurred overall in 7 subjects (2.0%) receiving monotherapy; no Grade 4 events were reported. The proportion of subjects who had Grade 3 rash did not appear to increase over time.

To further investigate the occurrence of rash in the idelalisib development program, a review of all AE preferred terms potentially related to rash was conducted for the complete ISS population. Grade 3 AEs in the rash MST occurred in 4 subjects (2.0%) with iNHL, no subjects with CLL, and 7 subjects (2.0%) overall receiving monotherapy; no Grade 4 events were reported. Discontinuations of study drug due to AEs in the rash MST occurred in 1 subject (0.5%) with iNHL, no subjects with CLL, and 4 subjects (1.1%) overall receiving idelalisib monotherapy.

In study GS0116-312 eleven subjects 11 subjects (10.0%) in the idelalisib + R group had rash of any grade, and 1 subject (0.9%) had rash of Grade 3 in severity. There were no Grade 4 events of rash. In the placebo + R group, 5 subjects (4.6%) had rash, and the event was of Grade 3 severity in 0 subjects (Section 15.1, Table 3.1.15). Maculo-papular rash was reported for 3 subjects (2.7%) in the idelalisib + R group (1 event [0.9%] of Grade 3) and for 0 subjects in the placebo + R group.

Pneumonitis

Of the 7 SAEs of pneumonitis reported for all subjects on monotherapy in the Phase 1 and 2 studies, 2 subjects had imaging results and clinical presentations more consistent with pneumonia: 1 subject was successfully treated with antibiotics alone, and 1 subject with severe underlying COPD quickly responded to treatment with antibiotics and a steroid. Of the remaining 5 subjects, an underlying aetiology could not be identified (eg, infection, malignancy) despite investigation with bronchoscopy. All 5 events resolved with steroid therapy. In these 5 subjects, the time to onset of pneumonitis from the first dose of idelalisib ranged from approximately 3 weeks to 1 year. All 5 subjects had prior exposure to a chemoimmunotherapy. Three subjects were rechallenged and none had recurrence of pneumonitis.

In Study GS-US-312-0116 through the database cutoff for this report, 6 subjects (5.5%) in the idelalisib + R group had pneumonitis of any grade, and 4 subjects (3.6%) had pneumonitis of ≥ Grade 3 in severity.

In the placebo + R group, 1 subject (0.9%) had pneumonitis, and the event was of Grade 3 severity (Section 15.1, Table 3.1.15). There were no Grade 4 events of pneumonitis in either treatment group.

Subjects who were reported to have pneumonitis were confounded by underlying diseases such as COPD and chronic renal failure and concomitant medical events such as renal failure and deep vein thrombosis/pulmonary embolism.

Infections

In subjects treated with monotherapy, the incidence of infections and pneumonia was higher in subjects with CLL compared with subjects with iNHL.

Table 50: Incidence of ≥ Grade 3 Any Infection and Pneumonia, Monotherapy (Safety Analysis Set)

Preferred Term	< 150 mg IDELA BID or any QD IDELA	150 mg IDELA BID	> 150 mg IDELA BID	Total
Subjects with iNHL				
N	40	146	14	200
≥ Grade 3 Any Infection[a]	11 (27.5)	33 (22.6)	2 (14.3)	46 (23.0)
≥ Grade 3 Pneumonia	7 (17.5)	11 (7.5)	2 (14.3)	20 (10.0)
Subjects with CLL				
N	26	11	17	54
≥ Grade 3 Any Infection[a]	11 (42.3)	9 (81.8)	11 (64.7)	31 (57.4)
≥ Grade 3 Pneumonia	2 (7.7)	3 (27.3)	6 (35.3)	11 (20.4)
All Subjects				
N	94	206	52	352
≥ Grade 3 any Infection[a]	27 (28.7)	49 (23.8)	18 (34.6)	94 (26.7)
≥ Grade 3 Pneumonia	12 (12.8)	17 (8.3)	10 (19.2)	39 (11.1)

a Any Infection defined per MedDRA "Infections and Infestations" SOC
Source: Appendix 8.1, Table 7.3.1, 7.3.2, and 7.3.3

Grade 3 or higher infectious events were very common in patients with CLL, the sample size, however, is very small.

In the randomised study in CLL, the incidence of pneumonia in the idelalisib + rituximab arm was more as expected (6%) and numerically lower than in the rituximab alone arm. The short duration of therapy should be considered.

Serious adverse event / deaths / other significant events

Deaths

All subjects, monotherapy

To date, 57 of 352 subjects (16.2%) treated with monotherapy have died: 35 of these subjects died while on idelalisib therapy or within 30 days of their last dose of idelalisib. Twenty-four subjects (6.8%) developed an AE leading to death. AEs leading to death reported for ≥ 2 subjects included the following: pneumonia (5 subjects, 1.4%), multi-organ failure (3 subjects, 0.9%), *Pneumocystis jiroveci* pneumonia (2 subjects, 0.6%), and septic shock (2 subjects, 0.6%).

All Subjects Treated with Combination Therapy in Phase 1 and 2 Studies

Thirty-three of 290 subjects (11.4%) treated with combination therapy have died: 26 of these subjects died while on idelalisib therapy or within 30 days of their last dose. AEs leading to death reported for ≥ 2 subjects included the following: sepsis (4 subjects, 1.4%), cardiac arrest (3 subjects, 1.0%), pneumonia (3 subjects, 1.0%), dyspnoea (2 subjects, 0.7%), and pneumonitis (2 subjects, 0.7%).

Of subjects with iNHL, 4 of 80 (5.0%) treated with combination therapy have died: 3 of these subjects died while on idelalisib therapy or within 30 days of their last dose.

Of subjects with CLL, 24 of 178 (13.5%) treated with combination therapy have died: 18 of these subjects died while on idelalisib therapy or within 30 days of their last dose.

Deaths, Subjects with CLL treated with Combination Therapy in Phase 3 Randomized Study 312-0116

In Study 312-0116, 20 subjects died, nineteen during the study (through 30 days after the last dose of study medication), with a lower incidence of death observed among subjects in the idelalisib + R group (5.5%, 6 subjects) compared with the placebo + R group (12.0%, 13 subjects), and 1 additional subject who died after the study cut-off date.

Table 51: AEs Leading to Death by PT and Decreasing Frequency, Subjects with CLL treated with Combination Therapy in Randomized Study 312-0116 (Safety Analysis Set; Not updated)

Preferred Term	IDELA + R (N=110)	Placebo + R (N=107)
Subjects with any AE Leading to Death	1 (0.9)	11 (10.3)
Sepsis	0	2 (1.9)
Acute Respiratory Failure	0	1 (0.9)
Cardiac Failure	0	1 (0.9)
Chronic Obstructive Pulmonary Diesase	0	1 (0.9)
Febrile Neutropenia	1 (0.9)	0
General Physical Health Deterioration	0	1 (0.9)
Infection	0	1 (0.9)
Left Ventricular Failure	0	1 (0.9)
Lung Infection	0	1 (0.9)
Multi-Organ Failure	0	1 (0.9)
Pneumonia	0	1 (0.9)
Fungal Pneumonia	1 (0.9)	0
Pulmonary Oedema	0	1 (0.9)
Septic Shock	0	1 (0.9)

Source: m5.3.5.1, Study 312-0116 CSR Section 15.1, Table 3.1.20

Other serious adverse events

Table 52: SAEs Reported for ≥ 2% of Subjects by PT and Decreasing Frequency, All Subjects Treated with Monotherapy (Safety Analysis Set)

Preferred Term	< 150 mg IDELA BID or any QD IDELA N = 94	150 mg IDELA BID N = 206	> 150 mg IDELA BID N = 52	Total N = 352
Subjects with any SAE	43 (45.7)	101 (49.0)	30 (57.7)	174 (49.4)
Pneumonia	12 (12.8)	17 (8.3)	9 (17.3)	38 (10.8)
Diarrhoea	3 (3.2)	12 (5.8)	3 (5.8)	18 (5.1)
Febrile Neutropenia	5 (5.3)	9 (4.4)	3 (5.8)	17 (4.8)
Pyrexia	1 (1.1)	16 (7.8)	0	17 (4.8)
Colitis	4 (4.3)	5 (2.4)	2 (3.8)	11 (3.1)
Renal Failure Acute	3 (3.2)	4 (1.9)	3 (5.8)	10 (2.8)
Pneumonitis	1 (1.1)	5 (2.4)	1 (1.9)	7 (2.0)
Pulmonary Embolism	3 (3.2)	2 (1.0)	2 (3.8)	7 (2.0)

Source: Appendix 8.1, Table 7.21.3

Table 53: SAEs Assessed by the Investigator as Related to Treatment Reported for ≥ 2% of Subjects by PT and Decreasing Frequency, All Subjects Treated with Monotherapy (Safety Analysis Set)

Preferred Term	< 150 mg IDELA BID or any QD IDELA N = 94	150 mg IDELA BID N = 206	> 150 mg IDELA BID N = 52	Total N = 352
Subjects with any Treatment-Related SAE	18 (19.1)	53 (25.7)	15 (28.8)	86 (24.4)
Pneumonia	6 (6.4)	8 (3.9)	1 (1.9)	15 (4.3)
Diarrhoea	2 (2.1)	9 (4.4)	1 (1.9)	12 (3.4)
Colitis	4 (4.3)	5 (2.4)	0	9 (2.6)
Pyrexia	1 (1.1)	7 (3.4)	0	8 (2.3)
Febrile Neutropenia	4 (4.3)	3 (1.5)	0	7 (2.0)

Source: Appendix 8.1, Table 7.22.3

The events reported as related, were those expected to be seen at increased incidence.

All subjects combined therapy in phase 1/2 studies

181 of 290 subjects (62.4%) treated with combination therapy had an SAE. The most frequently reported SAEs (reported for ≥ 5% of subjects) were pneumonia (13.4%), pyrexia (9.0%), febrile neutropenia (7.9%), diarrhoea (7.2%), and colitis (6.6%).

One hundred three subjects (35.5%) had an SAE assessed by the investigator as related to treatment with idelalisib. The most frequently reported treatment-related SAEs (reported for ≥ 5% of subjects) were colitis (6.6%), diarrhoea (5.9%), and pneumonia (5.5%).

Subjects with CLL Treated with Combination Therapy in Phase 3 Randomized Study 312-0116

Table 54: Study 312-0116: SAEs Reported for at Least 2% of Subjects in Either Treatment Group (ITT Analysis Set)

System Organ Class Preferred Term	IDELA + R (N = 110)	Placebo + R (N = 108)
Number of Subjects (%) with any SAE	54 (49.1)	41 (38.0)
Pneumonia	10 (9.1)	11 (10.2)
Sepsis	5 (4.5)	3 (2.8)
Neutropenic Sepsis	2 (1.8)	0
Cellulitis	1 (0.9)	3 (2.8)
Pneumocystis jiroveci Pneumonia	3 (2.7)	1 (0.9)
Febrile Neutropenia	5 (4.5)	5 (4.6)
Neutropenia	2 (1.8)	0
Pyrexia	10 (9.1)	3 (2.8)
Asthenia	1 (0.9)	3 (2.8)
Dyspnoea	1 (0.9)	3 (2.8)
Pneumonitis	4 (3.6)	1 (0.9)
Diarrhoea	3 (2.7)	0

AEs are classified using MedDRA version 15.1.

Subjects who experienced multiple events within the same PT were counted once per PT.

Laboratory findings

Table 55: Haematology, treatment-emergent grade 3 or 4 laboratory abnormalities reported for ≥ 5% of total subjects, all subjects treated with idelalisib monotherapy (safety analysis set)

Parameter	< 150 mg IDELA BID or any QD IDELA N = 94	150 mg IDELA BID N = 206	> 150 mg IDELA BID N = 52	Total N = 352
Decreased Hemoglobin Level				
Any Decrease Postbaseline	24 (25.5)	57 (27.7)	19 (36.5)	100 (28.4)
Grade 3	5 (5.3)	8 (3.9)	4 (7.7)	17 (4.8)
Grade 4	0	0	0	0
Decreased Lymphocyte Count				
Any Decrease Postbaseline	20 (21.3)	67 (32.5)	16 (30.8)	103 (29.3)
Grade 3	8 (8.5)	28 (13.6)	8 (15.4)	44 (12.5)
Grade 4	1 (1.1)	9 (4.4)	0	10 (2.8)
Increased Lymphocyte Count				
Any Increase Postbaseline	25 (26.6)	33 (16.0)	14 (26.9)	72 (20.5)
Grade 3	11 (11.7)	13 (6.3)	10 (19.2)	34 (9.7)
Grade 4	0	0	0	0
Decreased Neutrophil Count				
Any Decrease Postbaseline	36 (38.3)	97 (47.1)	27 (51.9)	160 (45.5)
Grade 3	12 (12.8)	23 (11.2)	9 (17.3)	44 (12.5)
Grade 4	10 (10.6)	22 (10.7)	7 (13.5)	39 (11.1)
Decreased Platelet Count				
Any Decrease Postbaseline	26 (27.7)	51 (24.8)	14 (26.9)	91 (25.9)
Grade 3	3 (3.2)	7 (3.4)	6 (11.5)	16 (4.5)
Grade 4	6 (6.4)	11 (5.3)	4 (7.7)	21 (6.0)

Table 56: Study GS-US-312-0116: Summary of treatment-emergent haematology abnormalities of ≥ grade 3 severity (safety analysis set)

Parameter[a]	IDELA + R (N=110)	Placebo + R (N=107)
Hemoglobin decreased		
Any Grade	28 (25.5)	32 (29.9)
≥ Grade 3	6 (5.5)	15 (14.0)
Lymphocyte count increased		
Any Grade	27 (24.5)	12 (11.2)
≥ Grade 3	19 (17.3)	6 (5.6)
Neutrophil count decreased		
Any Grade	60 (54.5)	52 (48.6)
≥ Grade 3	37 (33.6)	24 (22.4)
Platelet count decreased		
Any Grade	19 (17.3)	28 (26.2)
≥ Grade 3	11 (10.0)	17 (15.9)

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

In the pivotal Study 101-09 (iNHL/SLL), clinically favourable changes in hematologic parameters were observed for haemoglobin and platelets with continuous administration of idelalisib in subjects with baseline cytopenias.

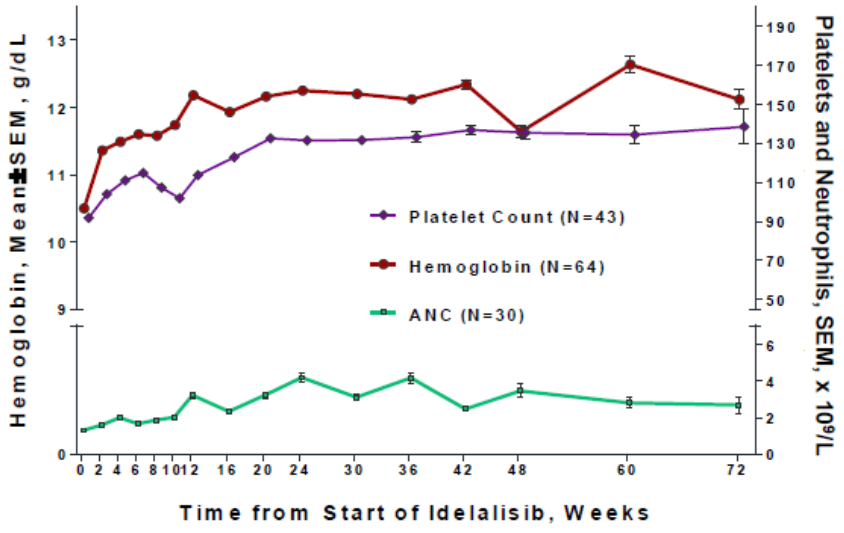


Figure 15: Improvement in Hemoglobin Concentration, ANC, and Platelet Count with Time for Subjects with Cytopenias at Baseline (ITT Analysis Set)

Improvements in haemoglobin and platelets were generally more pronounced in subjects with CLL.

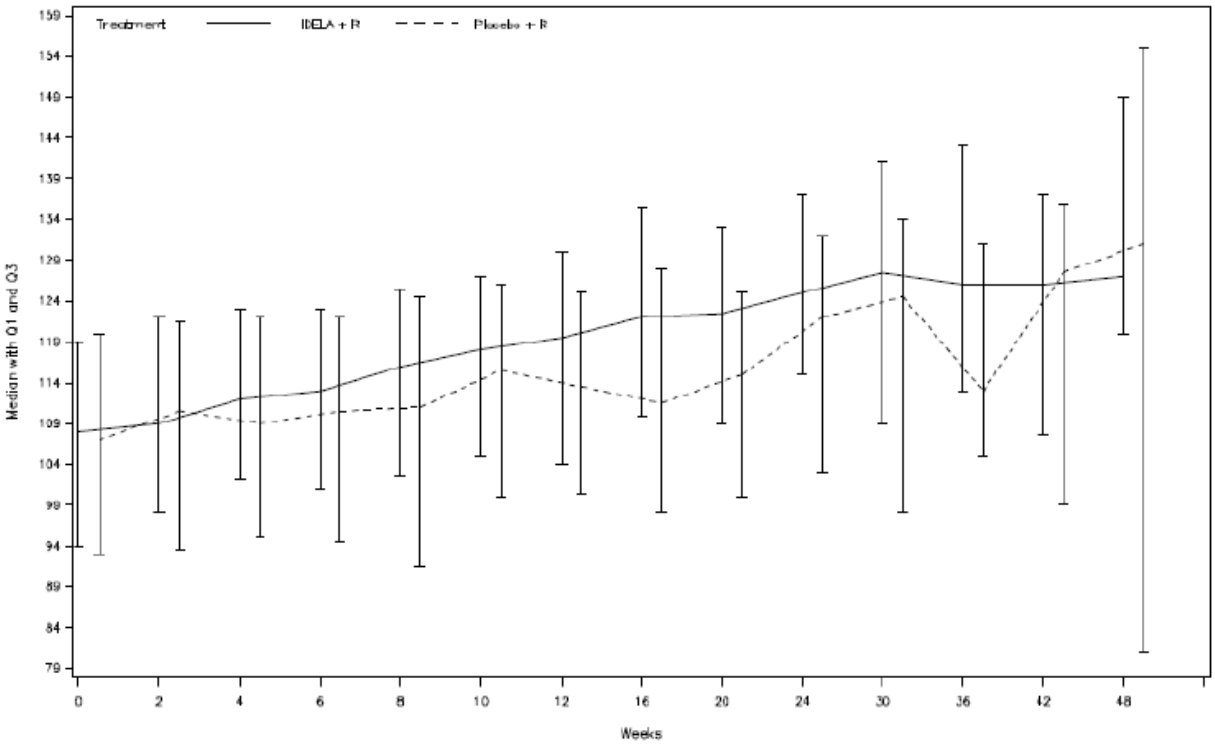


Figure 16: Study GS-US-312-0116: Median (Q1,Q3) haemoglobin (g/L) over time (safety analysis set)

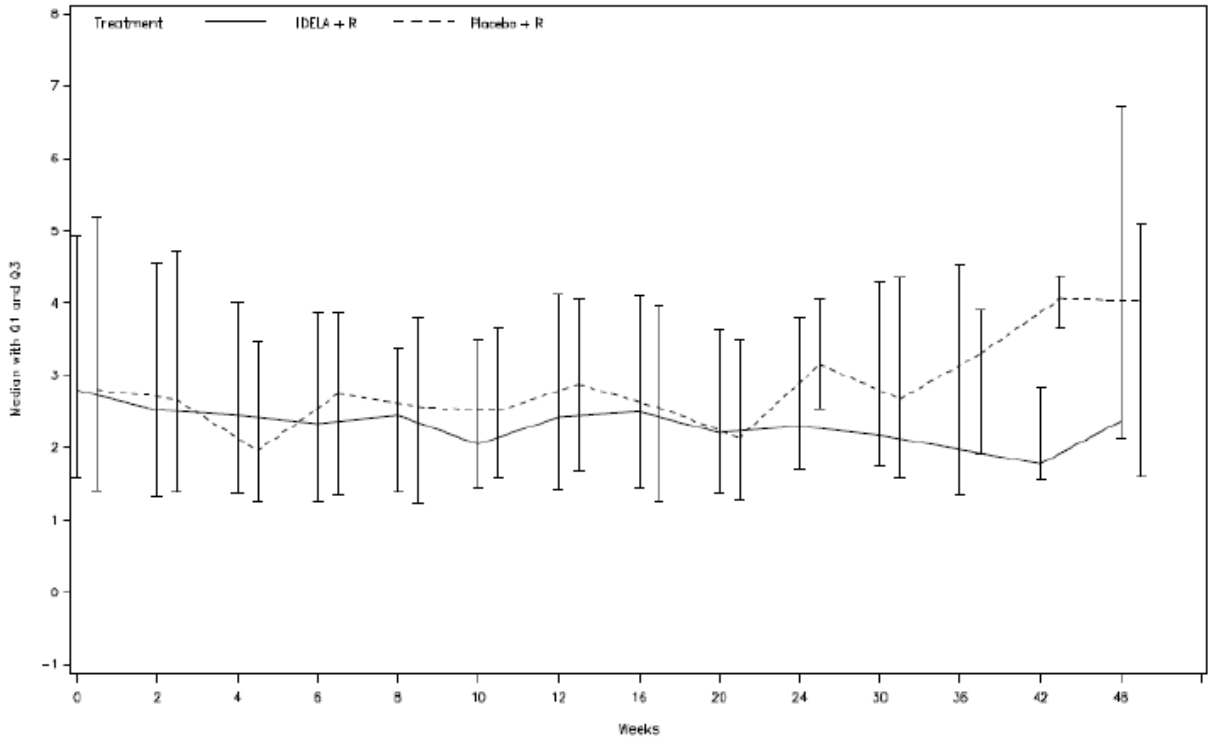


Figure 17: Study GS-US-312-0116: Median (Q1,Q3) total absolute neutrophil count (x10^9 g/L) over time (safety analysis set)

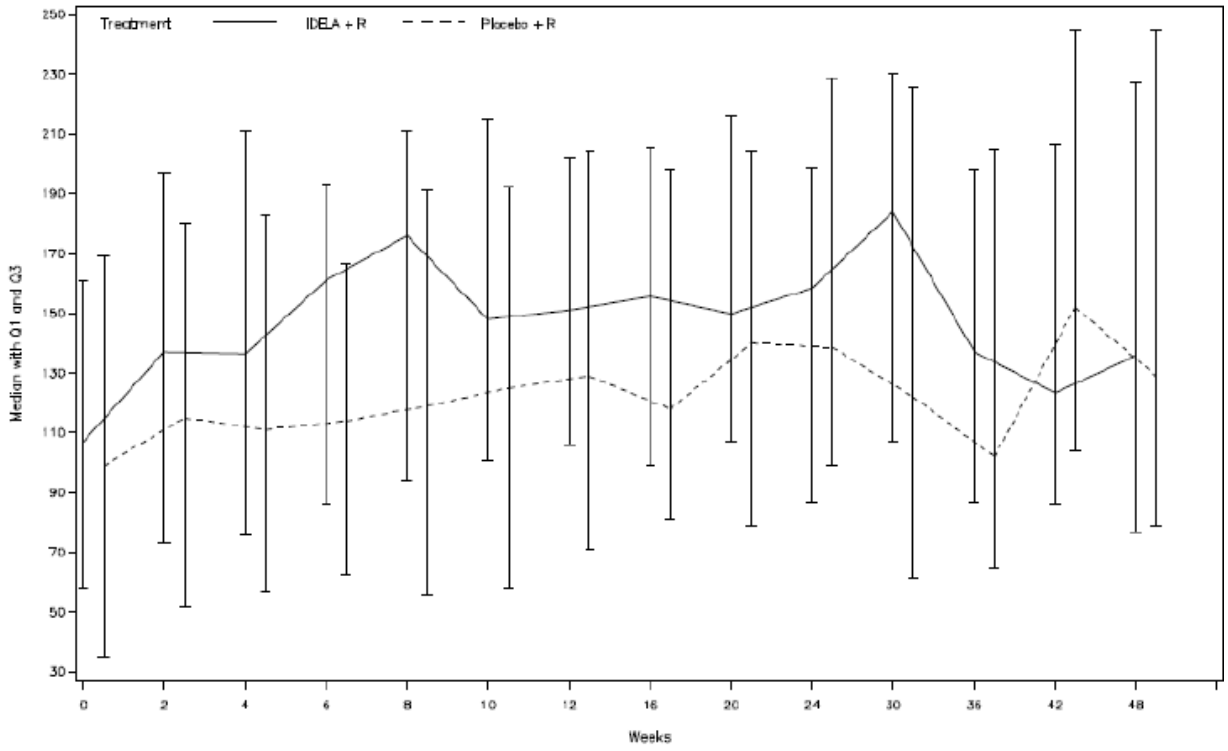


Figure 18: Study GS-US-312-0116: Median (Q1,Q3) platelet count (x10^9 g/L) over time (safety analysis set)

Chemistry

In the reporting of clinical chemistry, the CTCAE boundaries were given precedence, resulting in some reports of treatment-emergent laboratory abnormalities that were in fact within the laboratory normal ranges. Discrepancies between the CTCAE classification and the laboratory normal ranges were frequent for triglycerides among subjects treated with idelalisib monotherapy.

Mild to moderate increases in triglycerides and cholesterol have been detected and confirmed. Blood samples were not collected after fasting and causes of these changes have not been identified. Effects of idelalisib on lipid metabolism cannot be excluded.

Table 57: Chemistry, treatment-emergent grade 3 or 4 laboratory abnormalities reported for ≥ 5% of total subjects, all subjects treated with idelalisib monotherapy by decreasing frequency (safety analysis set)

Parameter	< 150 mg BID Monotherapy or any QD Monotherapy N = 94 n (%)	150 mg BID Monotherapy N = 206 n (%)	> 150 mg BID Monotherapy N = 52 n (%)	Total N = 352 n (%)
Elevated ALT				
Any Elevation Postbaseline	34 (36.2)	97 (47.1)	20 (38.5)	151 (42.9)
Grade 3	8 (8.5)	26 (12.6)	4 (7.7)	38 (10.8)
Grade 4	4 (4.3)	6 (2.9)	6 (11.5)	16 (4.5)
Elevated AST				
Any Elevation Postbaseline	40 (42.6)	85 (41.3)	22 (42.3)	147 (41.8)
Grade 3	8 (8.5)	18 (8.7)	7 (13.5)	33 (9.4)
Grade 4	2 (2.1)	4 (1.9)	1 (1.9)	7 (2.0)

Source: Appendix 8.1, Table 8.3.3

Table 58: Study GS-US-312-0116: Summary of treatment-emergent serum chemistry abnormalities of ≥ grade 3 severity (safety analysis set)

Parameter[a]	IDELA + R (N=110)	Placebo + R (N=107)
Albumin decreased		
Any Grade	12 (10.9)	17 (15.9)
≥ Grade 3	1 (0.9)	0
ALT increased		
Any Grade	34 (30.9)	10 (9.3)
≥ Grade 3	6 (5.5)	1 (0.9)
AST increased		
Any Grade	24 (21.8)	14 (13.1)
≥ Grade 3	4 (3.6)	0
Bilirubin increased		
Any Grade	6 (5.5)	8 (7.5)
≥ Grade 3	1 (0.9)	0
Albumin-corrected calcium increased		
Any Grade	7 (6.4)	7 (6.5)
≥ Grade 3	1 (0.9)	2 (1.9)
Creatinine increased		
Any Grade	13 (11.8)	9 (8.4)
≥ Grade 3	0	1 (0.9)
Creatinine clearance decreased		
Any Grade	16 (14.5)	17 (15.9)
≥ Grade 3	5 (4.5)	2 (1.9)
GGT increased		
Any Grade	24 (21.8)	13 (12.1)
≥ Grade 3	1 (0.9)	3 (2.8)
Glucose increased		
Any Grade	56 (50.9)	44 (41.1)
≥ Grade 3	8 (7.3)	2 (1.9)
Potassium decreased		
Any Grade	8 (7.3)	9 (8.4)
≥ Grade 3	0	3 (2.8)
Phosphate decreased		

Safety in special populations

Study 101-08 was a dedicated older (>65) patient, single arm, interim reported first-line CLL/SLL study (n=64) combining idelalisib and rituximab. Qualitatively reported events were as expected similar but the event rate appeared higher. Diarrhoea (Grade ≥ 3) occurred in 17% and Grade ≥ 3 transaminase elevations occurred in 11%. There were 4 deaths, with the following causes: (1) pneumonitis, (2) pneumonia and metastatic melanoma, (3) sepsis, and (4) respiratory failure and pneumonitis.

The table below provides a comparison of the safety profile of idelalisib in different age groups.

Table 59: Summary of idelalisib safety data by age group

MedDRA Terms	Age <65 Years N=317 N (%)	Age 65-74 Years N=299 N (%)	Age 75-84 Years N=120 N (%)	Age 85+ Years N=16 N (%)
Total ADRs[b]	236 (74.4)	216 (72.2)	85 (70.8)	10 (62.5)
Serious ADRs – Total[c,d]	82 (25.9)	82 (27.4)	35 (29.2)	4 (25.0)
- Fatal	7 (2.2)	10 (3.3)	2 (1.7)	0
- Hospitalization / prolong existing hospitalization	65 (20.5)	71 (23.7)	29 (24.2)	4 (25.0)
- Life-threatening	2 (0.6)	3 (1.0)	1 (0.8)	0
- Disability / incapacity	7 (2.2)	10 (3.3)	2 (1.7)	0
- Other (medically significant)	14 (4.4)	24 (8.0)	10 (8.3)	1 (6.3)
AE leading to drop-out	43 (13.6)	52 (17.4)	20 (16.7)	3 (18.8)
Psychiatric disorders (SOC)	11 (3.5)	8 (2.7)	2 (1.7)	1 (6.3)
Nervous system disorders (SOC)	45 (14.2)	26 (8.7)	17 (14.2)	1 (6.3)
Accidents and injuries (SMQ)	0	0	1 (0.8)	0
Cardiac disorders (SOC)	4 (1.3)	3 (1.0)	2 (1.7)	0
Vascular disorders (SOC)	14 (4.4)	10 (3.3)	5 (4.2)	1 (6.3)
Cerebrovascular disorders (SMQ)	0	1 (0.3)	0	0
Infections and infestations (SOC)	74 (23.3)	49 (16.4)	23 (19.2)	1 (6.3)
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	11 (3.5)	5 (1.7)	6 (5.0)	0

SMQ = standardised MedDRA query

A Includes Studies 101 02, 101 07, 101 08, 101 09, 101 10, 101 11, and 101 99 which were included in the Integrated Summary of Safety, and subjects randomized to treatment with IDELA on Study 312 0116

B Adverse Drug Reactions include treatment-emergent AEs assessed by the investigator as related to treatment with IDELA

C Serious criteria were not captured on case report forms; therefore, serious ADRs were collected from the Gilead safety database

D Serious ADRs include all SAEs assessed by the investigator as related to treatment with IDELA

Safety related to drug-drug interactions and other interactions

There were no dedicated PD interaction studies, with respect to PK interactions, see section 2.4.2.

Discontinuation due to adverse events

Adverse events leading to idelalisib discontinuation were reported for 20% of all subjects treated with monotherapy, 23% of subjects with iNHL, and 15% of subjects with CLL. No single AE resulting in study drug discontinuation was observed in ≥ 5% of subjects.

Table 60: AEs Leading to Idelalisib Discontinuation Reported for ≥ 2% of Subjects by PT and Decreasing Frequency, All Subjects Treated with Monotherapy (Safety Analysis Set)

Preferred Term	< 150 mg IDELA BID or any QD IDELA N = 94	150 mg IDELA BID N = 206	> 150 mg IDELA BID N = 52	Total N = 352
Subjects with any AE Leading to IDELA Discontinuation	21 (22.3)	40 (19.4)	9 (17.3)	70 (19.9)
ALT Increased	3 (3.2)	5 (2.4)	3 (5.8)	11 (3.1)
AST Increased	3 (3.2)	5 (2.4)	2 (3.8)	10 (2.8)
Pneumonia	3 (3.2)	5 (2.4)	2 (3.8)	10 (2.8)
Diarrhoea	5 (5.3)	2 (1.0)	0	7 (2.0)

In the phase 3 randomized study 312-0116 there were no noteworthy differences in the incidence or type of AEs that led to discontinuation of study drug (idelalisib or placebo) between the two arms.

Fifty-four of 352 subjects (15.3%) treated with monotherapy had an AE that led to dose reduction. No single AE resulting in dose reduction was observed in ≥ 5% of subjects.

In the randomized trial, 3/110 subjects (2.7%) had AEs that led to dose reduction. The events were Grade 3 pneumonitis, Grade 3 rash + Grade 1 maculopapular rash. None of the 107 subjects in the placebo +R group had a dose reduction of study drug due to an AE.

Post marketing experience

Not available.

2.6.1. Discussion on clinical safety

The total safety database of subjects exposed to idelalisib comprised 752 subjects. The two pivotal studies were conducted in “unfit” (=not suitable for chemotherapy) or heavily pretreated patients. A large proportion of the patients enrolled were elderly reflecting the age distributions of the diseases.

Response to therapy occurred early, whilst time to progression was long, meaning that the incentive to continue therapy probably decreases over time and might be reflected in the rather high discontinuation rates, overall about 20%.

The patterns of discontinuations were found to be different in the three described studies: for 101-08 a rather steady rate was observed during 12-15 months, in 101-09 discontinuations occurred primarily during the first 6 months, whereas in 312-0116 much lower percentages discontinued during the corresponding intervals. The overall lower number of drug discontinuations due to AEs in this trial (11 %) might partly be explained by the shorter duration of exposure as data cut-off was at the 1st interim analysis.

A potential factor in the higher rate of discontinuations in the Phase 1 and Phase 2 studies is the difference in the understanding of the idelalisib safety profile. As the idelalisib clinical program progressed from Phase 1 and 2 Studies (101-07 and 101-08) to the Phase 3 Study (312-0116), the approach for management of AEs by dose interruption and reduction was developed and Investigators gained experience in treating subjects with idelalisib, thus likely leading to a lower rate of discontinuation due to AEs in Study 312-0116.

Elevations in ALT and AST of Grade 3 and 4 (> 5 x ULN) have been observed in clinical studies of idelalisib. These laboratory findings were generally observed within the first 12 weeks of treatment, were generally asymptomatic, and were reversible with dose interruption. Most patients resumed treatment at a lower dose without recurrence (see section 4.2). ALT, AST, and total bilirubin must be monitored in all patients every 2 weeks for the first 3 months of treatment, then as clinically indicated. If Grade 2 or higher elevations in ALT and/or AST are observed, patients must be monitored weekly until the values return to Grade 1 or below. Treatment with idelalisib must be withheld in the event of a Grade 3 or 4 aminotransferase elevation. Once values have returned to Grade 1 or below (ALT/AST ≤ 3 x ULN), treatment can be resumed at 100 mg twice daily. If the event does not recur, the dose can be re escalated to 150 mg twice daily at the discretion of the treating physician. If the event recurs, treatment with idelalisib must be withheld until the values return to Grade 1 or less, after which re initiation at 100 mg twice daily may be considered at the discretion of the physician (see sections 4.2, 4.4 and 4.8 of the SmPC).

Cases of severe drug-related colitis occurred relatively late (months) after the start of therapy, sometimes with rapid aggravation, but resolved within a few weeks with dose interruption and additional symptomatic treatment (e.g., anti-inflammatory agents such as enteric budesonide). There is very limited experience from the treatment of patients with a history of inflammatory bowel disease.

Treatment with idelalisib must be withheld in the event of Grade 3 or 4 diarrhoea/colitis. Once diarrhoea/colitis has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If diarrhoea/colitis does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see sections 4.2, 4.4 and 4.8 of the SmPC).

Cases of pneumonitis have been reported in clinical studies with idelalisib. Patients presenting with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis. If pneumonitis is suspected, idelalisib should be interrupted and the patient treated accordingly. Treatment must be discontinued for moderate or severe symptomatic pneumonitis. Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100 mg twice daily can be considered (see sections 4.2, 4.4 and 4.8 of the SmPC).

Rash was generally mild to moderate and resulted in discontinuation of treatment in about 2% of patients. In study 312-0116, rash (reported as dermatitis exfoliative, rash, rash macular, rash maculo-papular, and rash pruritic) occurred in 13.6% of subjects who received idelalisib + rituximab and 5.6% who received placebo + rituximab. Of these, 2.7% who received idelalisib + rituximab and 0 subjects who received placebo + rituximab had rash of Grade 3, and no subjects had an adverse event of Grade 4. Rash typically resolved with treatment (e.g., topical and/or oral steroids, diphenhydramine) and dose interruption for severe cases. Treatment with idelalisib must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If rash does not recur, the dose can be re escalated to 150 mg twice daily at the discretion of the treating physician (see sections 4.2 and 4.8 and 5.3 of the SmPC).

Diarrhoea/colitis, sometimes severe, is the most obvious and clinically important side effect of idelalisib therapy. Of note, cases of colitis occurred sometimes after months of treatment and were in only 30% of cases preceded by grade 1/2 diarrhoea.

To disentangle the roles of the underlying disease and therapy with respect to infectious events is frequently impossible, however, the overall pattern with also late events of pneumonia indicate that there is an at least possible causal relationship with idelalisib therapy. Cases of opportunistic infections (pneumocytis, fungal) have been reported. This is not at all surprising in the study populations.

The incidence and type of SAEs reported for all subjects treated with monotherapy was very similar to the SAEs reported for subjects with iNHL. However, the incidence of SAEs reported for subjects with CLL treated with monotherapy was higher than for all subjects treated with monotherapy (66.7% and 49.4%, respectively). While pneumonia was reported for ≥ 5% of subjects with CLL treated with idelalisib monotherapy, febrile neutropenia, cellulitis, colitis, and pseudomonal bacteraemia were also reported for ≥ 5% of subjects.

In general, the causes of death reported in the idelalisib monotherapy and combined therapies appear heterogeneous as expected in these fragile patient groups. It is noted that the death rate in combined therapy in phase 1/2 (11.4 %) is lower than that seen in monotherapy (16,2 %), but study populations and differences in follow-up do not warrant direct comparison. No clear correlation is seen with AEs typically associated with idelalisib, e.g. transaminase elevations or diarrhoea/colitis.

In the randomised study 312-0116, the death-rate in the placebo + R arm seems high, especially considering the short exposure, but may reflect the advanced stage and vulnerability of the study population.

Idelalisib has not been studied in patients with chronic active hepatitis including viral hepatitis. Caution should be exercised when administering idelalisib in patients with active hepatitis (see section 4.4 of the SmPC).

No patients with severe hepatic impairment were included in clinical studies of idelalisib. Intensified monitoring of adverse reactions is recommended in patients with impaired hepatic function as exposure is expected to be increased in this population, in particular in patients with severe hepatic impairment.

No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see section 2.4.2).

Effects on ability to drive and use machines

Idelalisib has no or negligible influence on the ability to drive and use machines (see section 4.7 of the SmPC).

Overdose

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with idelalisb consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient (see section 4.9 of the SmPC).

Excipients:

Zydelig 100 mg contains the azo colouring agent sunset yellow FCF (E110), which may cause allergic reactions.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The most frequent adverse reactions related to the use of the idelalisib are infections, neutropenia, transaminase increased, increased triglycerides and diarrhoea/colitis.

The CHMP considers the following measures necessary to address issues related to safety:

- see section 2.5.5 (the same measures that will address issues related to efficacy will be used to address issues related to safety).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 0.3 is acceptable provided that the applicant implement the comments raised in the report. The PRAC endorsed the PRAC Rapporteur assessment report attached.

In addition, the CHMP requested the inclusion of additional non-clinical studies to further investigate the safety of the main human metabolite (GS-563117) considered as missing information in the RMP. These studies will consist of 4-week toxicity and toxicokinetic study in mice and a radioligand binding assay with GS-563117.

The CHMP also requested the inclusion of mechanistic studies on the effect of idelalisib on immune function to evaluate available data on immunological effects and auto-immunity.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 0.5 with the following content:

Safety concerns

Table 61: Summary of Safety Concerns

Important Identified Risks	Transaminase elevation
	Severe diarrhoea/colitis
	Pneumonitis
	Neutropenia
	Rash
Important Potential Risks	Reproductive toxicity including teratogenicity
	Drug-drug interaction with CYP3A inducers
	Drug-drug interaction with CYP3A substrates
	Photosensitivity
	Skin cancer

Missing Information	Development of drug resistance
	Carcinogenicity
	Long-term safety
	Safety in patients with severe hepatic impairment
	Safety in patients with severe renal impairment
	Safety in patients with chronic active hepatitis
	Safety of patients with concomitant immunization
	Immunological effects and auto-immunity
	Safety in children
	Safety of breastfeeding
	Drug-drug interaction with oral contraceptive

Pharmacovigilance plan

Table 62: Table of Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Category 1 (Interventional studies)				
Study GS-US-312-0116 (A Phase 3, Randomized, Double-Blind, Placebo Controlled 2-Arm Study to Assess the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab as Compared to Rituximab Plus Placebo in Patients with Relapsed Chronic Lymphocytic Leukemia)	Evaluate the safety and efficacy of IDELA plus rituximab in subjects with relapsed CLL	Long term safety and efficacy	Ongoing	December 2014
Study GS-US-312-0117 (A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia. [*A Companion Trial to Study GS-US-312-0116]*)	Evaluate the safety and efficacy of IDELA plus rituximab in subjects with relapsed CLL	Long term safety and efficacy	Ongoing	Q4 2017
Study 101-09 (A Phase 2 Study to Assess the Efficacy and Safety of CAL-101 in Patients With Indolent B-Cell Non-Hodgkin Lymphoma Refractory to Rituximab and Alkylating Agents)	Evaluate the safety and efficacy of IDELA monotherapy in subjects with refractory iNHL	Long term safety and efficacy	Ongoing	December 2015

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Study 101-99 (An Extension Study to Investigate the Safety and Durability of Clinical Activity of CAL-101 in Patients With Hematologic Malignancies)	Evaluate the safety and efficacy of IDELA monotherapy in subjects with refractory iNHL	Long term safety and efficacy	Ongoing	Q3 2017
Category 3 (Interventional studies)				
Study 101-08 (A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of CAL-101 in Combination With Rituximab in Elderly Patients With Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma)	To evaluate safety and efficacy of IDLEA in combination with rituximab in untreated elderly subjects with CLL	Long term safety and data to further support efficacy in patients with 17p Deletion/TP53 Mutation	Ongoing	Q4 2017
Study 101-07 (A Phase I Study to Investigate the Safety and Clinical Activity of CAL-101 in Combination with Chemotherapeutic Agents and Anti-CD20 mAb in Patients with Relapsed or Refractory Indolent B cell Non-Hodgkin Lymphoma, Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia)	Evaluate safety and efficacy of IDELA in subjects with relapsed/refractory iNHL and CLL	Long term safety and data to further support efficacy in patients with 17p Deletion/TP53 Mutation	Ongoing	Q3 2017
Study XXXXXXX – An in vivo interaction (induction) study with oral contraceptive	To evaluate the effect of IDELA co-administration on the PK of a representative oral contraceptive	Drug-drug interaction with oral contraceptive	Planned	February 2015 (Feasibility report and proposal for study design)
Category 3 (Nonclinical studies)				
Further studies on the human enzymology of IDELA oxidation	To determine the role of aldehyde oxidase on the metabolism of IDELA	Drug-drug interactions with aldehyde oxidase	Planned	December 2014
In vitro assessment of GS-1101 as a substrate for human OATP1B1 and OATP1B3 over an extended concentration range	To determine the OATP1B1 and OATP1B3 substrate characteristics of IDELA	Drug-drug interactions with transport substrates	Planned	December 2014
A 2-Year Oral (Gavage) Carcinogenicity Study of Idelalisib in Sprague Dawley Rats	To evaluate carcinogenicity with IDELA therapy	Carcinogenicity	Ongoing	Q2 2017
26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Idelalisib in RasH2 [001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic] Mice	To evaluate carcinogenicity with IDELA therapy	Carcinogenicity	Planned	Q2 2017
4-Week Oral Dose Range-Finding Toxicity and Toxicokinetic Oral Gavage Study with Idelalisib in 001178-W (Wild Type) RasH2 Mice	To determine the safety of the main human metabolite GS-563117	Missing information	Ongoing	Q4 2014

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Radioligand binding assay with GS-563117	To determine the safety of the main human metabolite GS-563117	Missing information	Ongoing	Q4 2014
Multiple Studies – Mechanistic studies on the effect of Idelalisib on immune function	To evaluate data on immunological effects and auto-immunity	Immunological effects and auto-immunity	Planned	March 2015
Drug mechanism of resistance studies for CLL (samples collected from completed and ongoing studies: GS-312-0116, GS-312-0117 and GS-312-0119) and iNHL	To investigate the mechanism of drug resistance with IDELA.	Development of drug resistance	Started	December 2014 (CLL) To be determined (iNHL)

Risk minimisation measures

Table 63: Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important identified risk(s)		
Transaminase elevation	The SmPC section 4.2, Posology and method of administration, provides instruction for dose modification in the event of elevated liver transaminases: "Treatment with Zydelig must be withheld in the event of a Grade 3 or 4 aminotransferase elevation (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] > 5 x upper limit of normal [ULN]). Once values have returned to Grade 1 or below (ALT/AST ≤ 3 x ULN), treatment can be resumed at 100 mg twice daily. If the event does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician. If the event recurs, treatment with Zydelig must be withheld until the values return to Grade 1 or less, after which re-initiation at 100 mg twice daily may be considered at the discretion of the physician (see section 4.4 and section 4.8)." Section 4.4, Special warnings and precautions for use, states: "Elevations in ALT and AST of Grade 3 and 4 (> 5 x ULN) have been observed in clinical studies of idelalisib. These laboratory findings were generally observed within the first 12 weeks of treatment, were generally asymptomatic, and were reversible with dose interruption. Most patients resumed treatment at a lower dose without recurrence (see section 4.2). ALT, AST, and total bilirubin must be monitored in all patients every 2 weeks for the first 3 months of treatment, then as clinically indicated. If Grade 2 or higher elevations in ALT and/or AST are observed, patients must be monitored weekly until the values return to Grade 1 or below." Section 4.8, Undesirable effects, lists "transaminase increased" as a very common (≥ 10%) adverse drug	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	reaction.	
Severe diarrhoea/colitis	The SmPC section 4.2, Posology and method of administration, provides instruction for dose modification in the event of diarrhoea: "Treatment with Zydelig must be withheld in the event of Grade 3 or 4diarrhoea/colitis. Once diarrhoea/colitis has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If diarrhoea/colitis does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8)." Section 4.4, Special warnings and precautions for use, states: "Cases of severe drug-related colitis occurred relatively late (months) after the start of therapy sometimes with rapid aggravation, but resolved within a few weeks with dose interruption and additional symptomatic treatment (e.g., anti-inflammatory agents such as enteric budesonide). There is very limited experience from the treatment of patients with a history of inflammatory bowel disease." Section 4.8, Undesirable effects, lists "Diarrhoea/colitis" as a very common (≥ 10%) adverse drug reaction.	None
Pneumonitis	The SmPC, section 4.2, Posology and method of administration, states: "Treatment with Zydelig must be withheld in the event of suspected pneumonitis. Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100 mg twice daily can be considered (see sections 4.4 and 4.8)." The SmPC, section 4.4, Special warnings and precautions for use, states: "Cases of pneumonitis have been reported in clinical studies with idelalisib. Patients presenting with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis. If pneumonitis is suspected, idelalisib should be interrupted and the patient treated accordingly. Treatment must be discontinued for moderate or severe symptomatic pneumonitis." Section 4.8, Undesirable effects, lists "pneumonitis" as a common (≥ 1%) adverse drug reaction.	None
Neutropenia	The SmPC Section 4.8, Undesirable effects, lists "neutropenia" as a very common (≥ 10%) adverse drug reaction.	None
Rash	The SmPC Section 4.2, Posology and method of administration states: "Treatment with Zydelig must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to Grade 1 or below, treatment can be resumed at 100 mg twice daily. If rash does not recur, the dose can be re-escalated to 150 mg twice daily at the discretion of the treating physician (see section 4.8)." Section 4.8, Undesirable effects, lists "rash" as a very common (≥ 10%) adverse drug reaction (Any Grade) and common (≥ 1 to <10%) for Grade ≥ 3. Section 4.8, Undesirable effects, Description of selected adverse reactions states:	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	"Rash was generally mild to moderate and resulted in discontinuation of treatment in about 2% of patients. In study 312-0116, rash (reported as dermatitis exfoliative, rash, rash macular, rash maculo-papular, and rash pruritic) occurred in 13.6% of subjects who received idelalisib + rituximab and 5.6% who received placebo + rituximab. Of these, 2.7% who received idelalisib + rituximab and 0 subjects who received placebo + rituximab had rash of Grade 3, and no subjects had an adverse event of Grade 4. Rash typically resolved with treatment (e.g., topical and/or oral steroids, diphenhydramine) and dose interruption for severe cases (see section 5.3 phototoxicity)."	
Important potential risk(s)		
Reproductive toxicity including teratogenicity	Section 4.4, Special warnings and precautions for use states: "Women of childbearing potential must use highly effective contraception while taking idelalisib and for 1-month after stopping treatment (see section 4.6). Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives." The SmPC Section 4.6, Fertility, pregnancy and lactation states: "Women of childbearing potential: Based on findings in animals, idelalisib may cause foetal harm. Women should avoid becoming pregnant while taking Zydelig, and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraception while taking Zydelig and for 1 month after stopping treatment. It is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method as a second form of contraception. Pregnancy: There are no or limited amount of data from the use of idelalisib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Zydelig is not recommended during pregnancy and in women of childbearing potential not using contraception. Fertility: No human data on the effect of idelalisib on fertility are available. Animal studies indicate the potential for harmful effects of idelalisib on fertility and foetal development (see section 5.3)." Section 5.3, Preclinical safety data states under "Reproductive and Developmental Toxicity": "In an embryo-foetal development study in rats, increased post-implantation loss, malformations (absence of caudal vertebrae and in some cases also of sacral vertebrae), skeletal variations and lower foetal body weights were observed. Malformations were observed at exposures from 12 times the human exposure based on AUC. Effects on embryo-foetal development were not investigated in a second species. Degeneration of the seminiferous tubules in the testes was observed in 2- to 13-week repeated dose studies in	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	dogs and rats, but not in studies of 26 weeks and longer duration. In a rat male fertility study, decreases in epididymides and testes weight were observed but no adverse effects on mating or fertility parameters, and no degeneration or loss in spermatogenesis were observed. Female fertility was not affected in rats."	
Drug-drug interaction with CYP3A inducers	The SmPC, section 4.4, Special warnings and precautions for use states "CYP3A inducers: Idelalisib exposure may be reduced when co-administered with CYP3A inducers such as rifampicin, phenytoin, St. John's wort (*Hypericum perforatum*), or carbamazepine. Since a reduction in idelalisib plasma concentrations may result in decreased efficacy, co-administration of Zydelig with moderate or strong CYP3A inducers should be avoided (see section 4.5)." The SmPC, section 4.5, Interaction with other medicinal products and other forms of interaction, recommend to avoid co-administration of IDELA with strong CYP3A inducers: "*CYP3A Inducers*: A clinical drug interaction study found that co-administration of a single dose of 150 mg idelalisib with rifampicin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib AUC_{inf}. Co-administration of Zydelig with moderate or strong CYP3A inducers such as rifampicin, phenytoin, St. John's wort, or carbamazepine should be avoided as this may result in decreased efficacy (see section 4.4)."	None
Drug-drug interaction with CYP3A substrates	The SmPC, section 4.4, Special warnings and precautions for use, states "The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor. Thus, idelalisib has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product (see section 4.5). When idelalisib is co-administered with other medicinal products, the Summary of Product Characteristics (SmPC) for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life-threatening side effects (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible." The SmPC, section 4.5, Interaction with other medicinal products and other forms of interaction, recommended caution if Zydelig is co-administered with CYP3A substrates: "*CYP3A Substrates:* The primary metabolite of idelalisib, GS-563117, is a strong CYP3A inhibitor. A clinical drug interaction study found that co-administration of idelalisib with midazolam (a sensitive CYP3A substrate) resulted in a ~140% increase in C_{max} and a ~440% increase in AUC_{inf} of midazolam due to the CYP3A inhibition by GS-563117. Co-administration of idelalisib with CYP3A substrates may increase their systemic exposures and increase or prolong their therapeutic activity and adverse reactions. *In vitro*, the CYP3A4 inhibition was irreversible, and return to normal enzyme activity is therefore expected to take several days after stopping idelalisib administration. Potential interactions between idelalisib and	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	co-administered medicinal products that are CYP3A substrates are listed in Table 1 (increase is indicated as "↑"). This list is not exhaustive and is intended to serve as guidance only. In general, the SmPC for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors (see section 4.4)."	
Photosensitivity	The SmPC section 5.3, Preclinical safety data states "Evaluation of the potential for phototoxicity in the embryonic murine fibroblast cell line BALB/c 3T3 was inconclusive for idelalisib due to cytotoxicity in the in vitro assay. The major metabolite, GS-563117, may enhance phototoxicity when cells are simultaneously exposed to UVA light. There is a potential risk that idelalisib, via its major metabolite, GS-563117, may cause photosensitivity in treated patients. "	None
Skin cancer	Update of labeling as appropriate based on analysis of safety data that may arise from any ongoing or future studies.	None
Missing Information		
Development of drug resistance	Update of labeling as appropriate based on analysis of safety data that may arise from any ongoing or future studies.	None
Carcinogenicity	Update of labeling as appropriate based on analysis of safety data that may arise from any ongoing or future studies.	None
Long-term safety	Update of labeling as appropriate based on analysis of safety data that may arise from any ongoing or future studies.	None
Safety in patients with severe hepatic impairment	The SmPC sections 4.2, states: "No dose adjustment is required when initiating treatment with Zydelig in patients with mild or moderate hepatic impairment, but an intensified monitoring of adverse reactions is recommended (see sections 4.4 and 5.2). There is insufficient data to make dose recommendations for patients with severe hepatic impairment. Therefore, caution is recommended when administering Zydelig in this population and an intensified monitoring of adverse reactions is recommended (see sections 4.4 and 5.2)." The SmPC, section 4.4, states: "Intensified monitoring of adverse reactions is recommended in patients with impaired hepatic function as exposure is expected to be increased in this population, in particular in patients with severe hepatic impairment. No patients with severe hepatic impairment were included in clinical studies of idelalisib. Caution is recommended when administering Zydelig in this population." The SmPC, section 5.2, states: "A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. Following a single 150 mg dose, idelalisib overall (i.e., bound plus unbound) AUC was ~60% higher in moderate and severe impairment compared to matched controls, which is not considered to be clinically relevant. The idelalisib AUC (unbound), after accounting for differences in protein binding, was ~80% (1.8-fold) higher in moderate and ~152% (2.5-fold)	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	higher in severe impairment compared to matched controls."	
Safety in patients with severe renal impairment	The SmPC sections 4.2, states: "No dose adjustment is required for patients with mild, moderate, or severe renal impairment (see section 5.2)." The SmPC section 5.2, states: "A study of pharmacokinetics and safety of idelalisib was performed in healthy subjects and subjects with severe renal impairment (estimated ClCr 15 to 29 mL/min). Following a single 150 mg dose, no clinically relevant changes in exposures to idelalisib or GS-563117 were observed in subjects with severe renal impairment compared to healthy subjects."	None
Safety in patients with chronic active hepatitis	The SmPC, section 4.4, states under Special warnings and precautions for use: "Chronic hepatitis: Idelalisib has not been studied in patients with chronic active hepatitis including viral hepatitis. Caution should be exercised when administering Zydelig in patients with active hepatitis."	None
Safety of patients with concomitant immunisation	Update of labeling as appropriate based on analysis of safety data that may arise from any ongoing or future studies.	None
Immunological effects and auto-immunity	Update of labeling as appropriate based on analysis of safety data that may arise from any ongoing or future studies.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Safety in children	The SmPC, section 4.2, states under paediatrics: "The safety and efficacy of Zydelig in children under the age of 18 years have not been established. No data are available."	None
Safety of breastfeeding	The SmPC sections 4.6, states: "It is unknown whether idelalisib and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zydelig therapy taking into account the benefit of breast- feeding for the child and the benefit of therapy for the woman."	None
Drug-drug interaction with oral contraceptive	The SmPC section 4.4, Special warnings and precautions for use states: "Women of childbearing potential must use highly effective contraception while taking idelalisib and for 1-month after stopping treatment (see section 4.6). Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives." The SmPC section 4.6, Fertility, pregnancy and lactation states: "Based on findings in animals, idelalisib may cause foetal harm. Women should avoid becoming pregnant while taking Zydelig, and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraception while taking Zydelig and for 1 month after stopping treatment. It is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method as a second form of contraception."	None

2.9. Product information / User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

CLL / SLL: Idelalisib plus rituximab in patients with CLL not suitable for chemotherapy was associated with a PFS HR of 0.18 compared to placebo+rituximab. In secondary analyses, OS data also showed a favourable effect for the idelalisib arm, with a HR of 0.28. There was also an ongoing first-line single arm study in elderly patients (101-08; n=64) with the same combination showing high activity (ORR 62/64). The development program for idelalisib in CLL has to date reported on clinical outcomes from 153 subjects

with either 17p deletion or TP53 mutation. The largest subgroup of patients with the del17p / TP53 mutations derive from the randomized rituximab comparative study (n=46, ORR 78%, PFS at 6 months 87%, at 1 year 71% in the idelalisib + rituximab arm; n=49 in the placebo + rituximab arm), fully in-line with the findings in studies 101-07 (n=24) and 101-08 (n=9).

Monotherapy data derive from a small number of patients in single arm studies with variable degree of resistance to prior therapy. The number of patients is too small to support a monotherapy indication.

FL: In a single arm idelalisib monotherapy study conducted in patients with iNHL refractory to rituximab and an alkylator, an ORR of ~56%, a PFS rate of 47% (95% CI 36; 58%) at 48 weeks and a duration of response of about 12 months were observed. In the subgroup follicular lymphoma (n=72), ORR was 54.2% and median DOR was found to be about 7.4 months.

Activity was seemingly unrelated to number of prior regimens in this heavily pretreated patient population with large proportions of patients refractory not only to rituximab and an alkylator, but to most lymphoma drugs, including bendamustin (n=62).

Uncertainty in the knowledge about the beneficial effects.

The pivotal CLL study (i.e 312-0116) was terminated early due to efficacy. There are thus no data on long term efficacy. The magnitude of the treatment effect is therefore not well defined and further follow-up is needed. Further long-term data will be submitted by the applicant within updates of study 312-0116 and as part of the extension study 312-0117 (see annex II of the opinion and RMP).

Risks

Unfavourable effects

The most common side effects are infections, neutropenia, increased transaminase, increased triglycerides, diarrhoea/colitis, rash and pyrexia.

Idelalisib is classified as a strong inhibitor of CYP3A4, thus affecting the pharmacokinetics of CYP3A4 substrates.

Uncertainty in the knowledge about the unfavourable effects

Whether the major metabolite GS-563117 contributes to adverse reactions by inhibition of lymphocyte oriented (LOK) and/or Ste20-like kinases (SLK) is unknown and there are currently no non-clinical data guiding the search for target organs of toxicity. The applicant will conduct a 4-week toxicology study in mice and a radioligand binding assay to further investigate the safety of the metabolite.

Autoimmune phenomena are commonly reported in lymphoproliferative diseases, especially in CLL. Due to its immune modulating effects, potential consequences of idelalisib therapy are of interest, but until now no signal has been identified, fully acknowledging that the pathophysiology behind colitis remains unexplained. The applicant has outlined a study program including in vitro evaluation of the effect of idealisib on T-cell proliferation, cytokine production and specific studies with regulatory T-cells (see RMP).

Due to the early interim analysis, median duration of exposure is about 5 months in the idelalisib + rituximab arm of the pivotal CLL study. Since long treatment duration is expected in clinical practice, the applicant has committed to submit the results of a number of ongoing studies in order to address the missing information of long-term safety of idelalisib (see RMP).

Plasma exposure is higher in patients with moderate hepatic impairment and ALT/AST increase is common. This implies uncertainty as regards liver safety in this population. A warning recommending intensified monitoring in patients with impaired hepatic function has been included in section 4.4 of the SmPC.

CLL is associated with an increased incidence of skin cancer assumed to be related to immune suppressive effects of the disease and treatment, e.g. with alkylating agents. Due to the immune modulating effects of idelalisib, skin cancer has been listed as an important potential risk in the RMP and events will be addressed as events of special interest in ongoing and future clinical trials (see RMP).

Non-clinical data indicate a potential for phototoxicity and it is noted that there was one case reported as Grade 2 photosensitivity in a subject on combination therapy and one case in monotherapy study 101-02 described as sunburn. The need for in vitro photoxicity studies and the potential risk of photosensitivity have been included in the SmPC and the RMP.

Co-administration with ketoconazole resulted in a moderate increase in idelalisib AUCinf (about 80%). As the exposure-response relationship appears relatively flat, it is accepted not to adjust the starting dose when idelalisib is combined with strong CYP3A4/Pgp inhibitors, however section 4.5 of the SmPC was updated to include instructions that intensified monitoring of side effects should be given.

Benefit-risk balance

Importance of favourable and unfavourable effects

The results from studies conducted in the CLL indication are of high clinical relevance. The activity of idelalisib was demonstrated across trials. The positive results in the high risk patients with del17p / TP53 mutations are of particular importance and support an indication in first line for those patients who are unsuitable for chemo-immunotherapy.

Convincing and clinically relevant results were observed in patients with follicular lymphoma treated with idelalisib monotherapy. Although the pivotal study is a single arm study, the activity seen in terms of ORR, and DOR is considered sufficiently important and at least as clinically significant as with other available options in this heavily pre-treated patient population to support approval.

Discontinuation due to toxicity was infrequent and overall the toxicity was considered manageable.

Benefit-risk balance

The important benefits observed in the two indications outweigh the risks related to the use of idelalisib.

Discussion on the benefit-risk balance

Of major importance in the assessment of benefit is the consistently shown high activity of idelalisib irrespective of refractoriness to prior therapy or unfavourable prognostic factors in patients with FL and CLL.

The high response rates and long durations of response at acceptable toxicity are acknowledged, although the long-term data are not yet available. As a consequence, efficacy and safety data from ongoing studies will be regularly updated to provide additional information about long-term benefits and risks.

CLL: The indication for use as combination therapy with rituximab in relapsed CLL is acceptable considering that patients after 1 line of therapy as well as after 2 or more lines of therapy could be included in the pivotal study.

In patients with del17p/TP53 mutations the activity appears similar to available fludarabine or alemtuzumab combination regimens. As these regimens are too toxic for large proportions of patients, benefit-risk is considered clearly favourable for patients non-suitable for immuno-chemotherapy in case of mutations del17p/TP53, regardless of prior treatment experience.

iNHL:

The applicant initially claimed approval in patients with refractory iNHL, however this indication could not be approved as it is not considered as a single disease entity if not supported by data showing a positive Benefit/Risk in all subsets of the condition covered by this umbrella term.

However, the Benefit/risk of Zydelig as monotherapy for the treatment of adult patients with follicular lymphoma (a subset of iNHL) that is refractory to two prior lines of treatment is considered positive by the CHMP.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Zydelig is not similar to Arzerra, Gazyvaro and Litak within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zydelig in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL):

- who have received at least one prior therapy, or
- as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The applicant should submit the final study report for phase 3 study GS-US-312-0116, to evaluate the efficacy and safety of Idelalisib (GS-1101) in combination with Rituximab for Previously Treated CLL. Updates on PFS, OS and Duration of response for patients with or without 17p Deletion/ TP53 Mutation and the whole population should be submitted. The Applicant will also provide the final data from the extension study GS-US-312-0117.	31 December 2017
The applicant should submit the final study report for phase 2 101-09 study to evaluate the efficacy and safety of idelalisib in subjects with indolent B-cell NHL refractory to rituximab and alkylating agents. Updates on safety and efficacy results including overall survival and updates of the analyses of subjects with baseline lymphopenia, should be submitted. The Applicant will also provide the final data from the extension study 101-99, for patients enrolled from study 101-09.	30 September 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that idelalisib is qualified as a new active substance.