NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	Prospective non-interventional post authorization safety study (PASS) of idelalisib in Germany
Protocol ID	GS-DE-312-1750
Protocol Version/Date:	Final / 27 April 2015
EU PAS Register No	ENCEPP/SDPP/9564
Clinical Trials.gov Identifier	Study not registered
Active substance	Idelalisib, ATC group L01XX47
Medicinal Product	Zydelig®
Product reference	EU/1/14/938/001 and EU/1/14/938/002
Procedure number	Not applicable
Joint PASS	No
Research Question and Objectives	To describe the effectiveness and safety of idelalisib in patients with CLL or non-Hodgkin lymphoma (NHL) up to 3 years per patient in clinical routine. The primary objectives of this study are to assess: o Progression-Free Survival (PFS) (rate and time to progression) o Overall Response Rate (ORR) o Overall survival (OS) (rate and survival duration) The secondary objectives are to assess: o Incidence of adverse drug reactions (ADRs) and serious ADRs as well as fatal events (regardless of causality) and cause of death o Incidence, risk factors, management and outcome of

	diarrhea/colitis (ADR of special interest) o Incidence, risk factors, management and outcome of pneumonitis (ADR of special interest) o Incidence, risk factors, management and outcome of liver enzyme elevation (ADR of special interest) o Patient reported outcome including physical and mental health-related quality of life and health status using standardized general and disease-specific questionnaires (EORTC QLQ-C30, EORTC-QLQ-CLL16, SF-12) o Health resource utilization including frequency and duration of hospitalization o Type, incidence and outcome of Special Situation Reports (SSRs)	
Country of study	Germany	
Gilead Study Director / Author/Contact Person:	Name: Telephone: Fax:	Holger Krönig +49 (0) 89 899890 126 +49 (0) 89 899890 90
Marketing Authorization Holder		Gilead Sciences Ltd. Cambridge, CB21 6GT United Kingdom
MAH contact person	Name: Telephone: Fax: Mobile: Address:	Armin Schuster +49 (0) 89 89 98 90 51 +49 (0) 89 89 98 90 62 +49 (0) 172 218 19 44 Fraunhoferstr 17 82152 Martinsried Germany
Gilead Qualified Person Responsible for Pharmacovigilance:	Name: Telephone: Fax:	Anne-Ruth van Troostenburg de Bruyn +44 (0) 1223 824 641 +44 (0) 1223 897 290

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

(e)CRF	(electronic) Case report form
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AMG	German drug act (deutsches Arzneimittelgesetz)
AST	Aspartate transaminase
BR	Best Response
CLL	Chronic Lymphocytic Leukemia
COPD	Chronic obstructive pulmonary disease
CRO	Clinical research organisation
CSR	Clinical study report
DOR	Duration of Response
DOT	Duration of Treatment
DSPH	Drug Safety & Public Health
EMA	European Medicines Agency
EU	European Union
FDA	(United States) Food and Drug Administration
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GVP	Good Pharmacovigilance Practices (guidelines for)
ICH	International Conference on Harmonization
IEC	Independent ethics committee
LPL	Lymphoplasmacytoid Lymphoma
MZL	Marginal Zone Lymphoma
(i)NHL	(indolent) Non-Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PFS	Progression Free Survival
PRO	Patient Reported Outcome
QPPV	Qualified person responsible for pharmacovigilance
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SLL	Small Lymphocytic Lymphoma
SSR	Special situation report
SUSAR	Suspected Unexpected Serious Adverse Reaction
US, USA	United States, United States of America

Analytical dataset	The minimum set of data required to perform the statistical analyses leading to the results of the primary objective(s) of the study
Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Cases	Group of individuals with the condition of interest
Cohort	Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication)
Date at which a study commences	Date of the start of data collection
End of data collection	The date from which the analytical dataset is completely available
Exposure	A variable whose effect is of interest and is being studied
External validity	Whether or not the results from the study can be generalized to other populations
Internal validity	Whether or not the study provides an unbiased estimate of what it claims to estimate
Odds	The ratio of the probability that an event will happen to the probability that it will not happen
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Start of data collection	Date from which information on the first study patient is first recorded in the study dataset

1. RESPONSIBLE PARTIES

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Sponsor	Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried / Munich Germany	Email: info@gilead-sciences.de Phone: +49 89 899 8900 Fax: +49 89 899 89090
Lead Investigator (for NHL)	Dr. med. Wolfgang Abenhardt Prielmayerstr. 1 80335 München Germany	Email: w.abenhardt@onkologie-elisenhof.de Phone: +49 89 550 79 820 Fax: +49 89 550 79 821
Lead Investigator (for CLL)	Prof. Dr. med. Wolfgang Knauf Im Prüfling 17-19 60389 Frankfurt a.M. Germany	Email: wolfgang.knauf@telemed.de Phone: +49 69 451 080 Fax: +49 69 560 056 22
CRO	iOMEDICO AG Hanferstr. 28 79108 Freiburg Germany	Email: franziska.kalio@iomedico.com Phone: +49 761 15242 61 Fax: +49 761 15242 80
Pharmacovigilance	DSPH FC Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 27717-0530, USA	Email: Safety_fc@gilead.com Phone: +1 800 445-3235 Fax: +1 (650) 522-5477
Epidemiology/Statistics	Rui Jiang, MD, DrPH Gilead Sciences, Inc. 310 Lakeside Drive Foster City, CA 94404-0530, USA	Email: Rui.Jiang@gilead.com Phone: +1 (650) 358-1054 Fax: +1 (650 522-5953)

2. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences GmbH
Fraunhoferstr. 17
82152 Martinsried, Germany

Title:	Prospective non-interventional post authorization safety study (PASS) of idelalisib in Germany
Rationale and Background:	The efficacy and safety of idelalisib is established by data from randomized and single arm clinical trials in patients with chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin's lymphoma (iNHL), such as Gilead sponsored trials GS-US-312-0116 (NCT01539512) and extension study GS-US-312-0117 (NCT01539291) and 101-09 (NCT01282424). These clinical studies investigate the efficacy and safety of idelalisib in predefined populations, therefore providing high internal validity. Data generated in real-life settings allows for investigating the external validity of the effects seen in clinical studies. Thus the real-life treatment outcomes of the drug can be investigated in observational studies such as non-interventional studies (NIS). This prospective real-life study of idelalisib allows the evaluation of up to 3 years treatment outcomes and confirmation of the safety profile for idelalisib.
Research Question and Objectives:	To describe the effectiveness and safety of idelalisib in patients with CLL or non-Hodgkin lymphoma (NHL) up to 3 years per patient in clinical routine. The primary objectives of this study are to assess: • Progression-Free Survival (PFS) (rate and time to progression) • Overall Response Rate (ORR) • Overall Survival (OS) (rate and survival duration) The secondary objectives of this study are to assess: • Incidence of adverse drug reactions (ADRs) and serious ADRs as well as fatal events (regardless of causality) and cause of death • Incidence, risk factors, management and outcome of diarrhea/colitis (ADR of special interest) • Incidence, risk factors, management and outcome of pneumonitis (ADR of special interest) • Incidence, risk factors, management and outcome of liver enzyme elevation (ADR of special interest)

- Patient Reported Outcome including physical and mental health-related quality of life and health status using standardized general and disease-specific questionnaires (EORTC QLQ-C30, EORTC-QLQ-CLL16, SF-12)
- Health resource utilization including frequency and duration of hospitalization
- Type, incidence and outcome of Special Situation Reports (SSRs)

Study Design: This is a multicenter, non-interventional, two cohort (CLL and NHL), prospective post authorization safety study (PASS) to evaluate the clinical effectiveness and safety of idelalisib for treatment of patients with CLL or non-Hodgkin lymphoma (NHL). This design was chosen to assess the effectiveness and safety of therapy with idelalisib up to 3 years per patient in clinical routine.

This non-interventional study does not influence the therapeutic strategy of the participating physician. It is the discretion of the respective physician if a specific patient will be treated and what regimen will be used. Only after these decisions have been made the patient may be consented to be included in the study. The selection of diagnostic or monitoring procedures (e.g. laboratory parameters) is the decision of the treating physician. Only available data from routine medical care will be transferred from patient medical records into the study eCRF.

Population: The study will enroll adult patients with either CLL or NHL with initiation of treatment with idelalisib alone or in combination with other antineoplastic agents and/or monoclonal antibodies.

Participating study sites (hospitals and private practitioners) are specialized on treating oncology patients. All study sites are located in Germany.

Variables: At the start of treatment with idelalisib, the following should be documented (as available from medical records):

- Inclusion/Exclusion criteria
- Demographic data
- Vital signs
- Physical examination
- Karnofsky Performance Status
- Medical history incl. previous treatments
- Prior Anti-Cancer Therapies (compound/PFS/DOT/DOR/BR/Reason for discontinuation)
- Tumor staging
- Concomitant diseases
- Concomitant medication

- Safety laboratory
- Idelalisib therapy start
- Liver function tests
- Tumor assessment
- Patient questionnaires

During each visit the following should be documented (approximately every 3 months, as available from medical records):

- Vital signs
- Physical Examination
- Karnofsky Performance Status
- Concomitant diseases
- Concomitant medication
- Liver function tests
- Safety laboratory
- (Serious) Adverse Drug Reactions, fatal events (including cause of death, causality assessment for relationship to idelalisib) and SSRs
- Tumor response evaluation
- Idelalisib dosing
- Reason for and date of treatment discontinuation
- Patient questionnaires
- Resource utilization

In case of end of treatment the following should be documented (as available from medical records):

- Vital signs
- Physical Examination
- Karnofsky Performance Status
- Concomitant diseases
- Concomitant medication
- Liver function tests
- Safety laboratory
- (Serious) Adverse Drug Reactions (plus any occurring within 4 weeks following end of treatment) and SSRs
- Tumor response evaluation
- Idelalisib dosing prior to end of treatment
- Reason for and date of treatment discontinuation
- Patient questionnaires
- Resource utilization

Please refer to section 7.4 for further details.

Data Sources: Routine visit data as documented in the medical record will be entered in the eCRF and questionnaires completed by the patients will be collected.

Study Size: The study will be conducted in approximately 100 medical centers distributed over all states of Germany, the centers being hospitals and private practitioners willing to participate in this study. The study will include 300 adult patients with CLL or NHL.

150 patients will be enrolled per cohort based on their actual treatment situation:

- Cohort A: Initiating idelalisib regime in CLL patients, n=150
- Cohort B: Initiating idelalisib regime in NHL patients, n=150

Precision estimates for CLL endpoints are included in section 7.6.

Data Analysis: The statistical analysis of the data will be primarily descriptive. SAS in the version 9.4 or higher will be used for the analysis.

Summary statistics will be presented by cohort (CLL or NHL) and will include:

- nominal variables: frequencies and percentages.
- ordinal variables: frequencies, percentages, median, minimum and maximum.
- continuous variables: number (N) of observations, mean, standard deviation, 25th percentile, median, 75th percentile, minimum and maximum.

All data listings will be sorted by cohort, center ID and patient ID.

Patients enter the study at different times and some may leave before the end of the study (e.g. withdraw, death, etc.).

For ADR events, in addition to frequencies and percentages, incidence rate in person-time will be calculated by dividing number of new cases by the total number of person-time at risk to account for varying length of follow-up.

Kaplan-Meier plots of progression-free survival, overall response rate, and overall survival will be produced. The median duration of progression-free survival, overall response rate, and overall survival will also be determined.

If not otherwise specified, p-values will be presented as two-sided and the level of significance is set to 5% (two-sided). 95%-confidence intervals will be provided, where applicable.

Interim analyses (4 in total) are planned in approximately annual frequency. The 1st interim analysis is planned after 50 patients (independent of cohort) have received 3 months idelalisib treatment. The interim analyses will analyze the full available data set at that

	time point.
Milestones:	Start of data collection : approx. July 2015
	End of Data collection: approx. July 2020
	Final Study report: approx. Q1 2021

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

3. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
none				

Protocol Modifications

Protocol modifications may only be performed by Gilead Sciences GmbH. Approval must be obtained before changes can be implemented.

4. MILESTONES

Milestone	Planned Date
Start of data collection	July 2015
End of data collection	July 2020
<Study progress report 1>	NA
<Study progress report 2>	NA
<Study progress report n>	NA
Interim report 1	After 50 patients have received 3 months antineoplastic therapy
Interim report 2	After 110 patients have received 3 months antineoplastic therapy
Interim report 3	After 170 patients have received 3 months antineoplastic therapy
Interim report 4	After 230 patients have received 3 months antineoplastic therapy
Registration in the EU PAS register	April 2015
<Other important timeline 1>	NA
<Other important timeline 2>	NA
<Other important timeline n>	NA
Final report of study results	Q1 2021

4.1. Study Schedule

Proposed start date (FPI):	Q3 2015
Proposed end of recruitment period (LPI):	Q3 2017
Proposed end of last treatment period (LPO)	Q3 2020
Proposed study report	Q1 2021

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

Idelalisib is an oral, selective small-molecule inhibitor of Phosphatidylinositol-3-kinase delta (PI3Kδ) that is expressed in normal and malignant B-cells. Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Idelalisib inhibits several cell signaling pathways, including B-cell receptor (BCR) and CXCR4 and CXCR5 signaling, which are involved in trafficking and homing of B-cells to the lymph nodes and bone marrow. In phase I, phase II and phase III studies idelalisib showed a favorable safety profile and promising antitumor activity in patients with NHL and CLL.

5.1.1. Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia among adults in the Western World with an incidence of 4.2/100,000/year{24532}. In Germany about 2,250 men and 1,500 women are diagnosed with CLL per year. CLL is mainly diagnosed in older patients with a median age of 72 years. However, the percentage of younger patients increases, approximately 30% of patients initially diagnosed with CLL are younger than 55 years old.

5.1.1.1. Standard treatment of chronic lymphocytic leukemia

According to current knowledge CLL is not curable with conventional chemotherapies or antibody-based therapies. Standard treatments include combinations of purine analogues, alkylating agents, and monoclonal antibodies such as rituximab {27855},{17676}. These treatment options result in high response rates of constant length but show significant side effects in younger patients without major coexisting illnesses. In older patients and patients with complex comorbidities these treatments often show unacceptable toxicity.

Patients with relapsed CLL have limited treatment options. This is especially the case due to the development of resistance to, or persisting toxic effects of previous therapies in elderly patients and those with coexisting illnesses. Rituximab is regarded as a treatment option in this patient group, but has not been approved as monotherapy. The response rates to rituximab differ and the progression-free survival rate is generally short.

5.1.1.2. Clinical development of idelalisib in patients with chronic lymphocytic leukemia

In phase I studies, idelalisib had shown clinically significant activity with an acceptable toxicity profile in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). Based on these study results, idelalisib was evaluated in a randomized, double-blind, placebo-controlled phase III study in 220 patients with relapsed CLL {27855}. Patients were assigned to receive rituximab in combination with either idelalisib (at a dose of 150 mg) or placebo until disease progression or unacceptable toxicity. The primary endpoint of this study was progression free survival (PFS).

Following the first pre-specified interim analysis the trial was stopped due to efficacy results. In the placebo group the median progression-free survival was 5.5 months, but was not reached in the idelalisib group (HR 0.15; P<0.001). In patients receiving idelalisib versus those receiving placebo improved overall response rates (81% vs. 13%; odds ratio, 29.92; P<0.001) and overall survival of 12 months (92% vs. 80%; HR 0.28; P=0.02) were observed.

Most adverse events were grade 2 or lower across the two study groups and were consistent with those expected for this patient population. At least one adverse event occurred in more than 90 % of the patients. The five most common adverse events in the idelalisib group were pyrexia, fatigue, nausea, chills, and diarrhea. The most common adverse events in the placebo group were comparable to those observed in the idelalisib group and infusion-related reactions (fatigue, cough, nausea, and dyspnea). In the idelalisib group at least one serious adverse event occurred in 44 patients (40 %) and in the placebo group in 37 patients (35%). In both groups the most frequent serious adverse events were pneumonia, pyrexia, and febrile neutropenia. Study drug discontinuation induced by an adverse event was reported in 9 patients in the idelalisib group and in 11 patients (10 %) in the placebo group. In the idelalisib group, gastrointestinal and skin disorders leaded to 6 (5 %) discontinuations. In the placebo group, infections and respiratory disorders leaded to 8 (7 %) discontinuations.

Based on these study results European Commission granted marketing authorization for idelalisib in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia 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.

Patients with CLL and coexisting illnesses are often seen in clinical routine, but are less able to be treated with standard chemotherapy and are therefore often excluded from clinical trials. The study results show that the combination of idelalisib and rituximab may be a treatment option for these patients, but further studies are necessary to assess the safety profile of idelalisib in clinical routine.

5.1.2. Non-Hodgkin Lymphoma

NHL comprises a diverse group of malignancies arising in lymphoid tissue. The neoplasms represent a progressive clonal expansion of B cells, T cells, or natural killer cells arising from the accumulation of genetic lesions that affect proto-oncogenes or tumor suppressor genes, resulting in cell immortalization{22495}. A B-cell origin is documented in 80-85% of cases. Chromosomal translocations that reduce lymphocyte apoptosis are typical.

In Europe, it is anticipated that ~74,000 new cases per year will occur, leading to ~31,000 deaths {22456}. As mortality due to other causes has declined, the incidence of lymphoma has increased; almost exclusively a disease of adulthood, diagnosis most commonly occurs during in patients between 50 and 70 years of age {22495}.

Of the B-cell NHLs, 4 subtypes (follicular lymphoma [FL], small lymphocytic lymphoma [SLL], lymphoplasmacytoid lymphoma [LPL], and marginal zone lymphoma [MZL]) have differing pathological features {24170}, but are generally included among those characterized as indolent in nature because they have common clinical presentations, show a slowly progressive natural

history, and generally require similar treatments {22459}. Patients with iNHL typical present with painless and gradually progressive peripheral adenopathy {22458}, {22495}. Some patients may experience primary extranodal involvement or B symptoms (ie, temperature >38°C, night sweats, or weight loss >10% from baseline within 6 months). As the disease advances, fatigue is often noted. Bone marrow involvement is common and may result in cytopenias. Patients with iNHL commonly have splenomegaly and hepatomegaly. Elevated serum levels of lactate dehydrogenase (LDH) reflect general tumor burden. Abnormal transaminase values may indicate hepatic involvement or chronic lymphoma related inflammation. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the neck, chest, abdomen, and pelvis, as well as bone marrow aspirate and biopsy, are employed to stage iNHL {17692}. Positron-emission tomography (PET) is sometimes used to identify occult sites of disease in patients who appear to have localized iNHL based on CT and bone marrow biopsy {22476}. The Ann Arbor staging system categorizes patients by whether they have single sites of involvement (Stage 1), ≥2 sites of disease on the same side of the diaphragm (Stage 2), sites of disease on both sides of the diaphragm (Stage 3), or disseminated disease (Stage 4) {9512}. For follicular iNHL, the Follicular Lymphoma International Prognostic Index (FLIPI) has been developed to define outcomes {22475}. The FLIPI characterizes patients in terms of 5 adverse prognostic factors; age >60 years, Ann Arbor stage III-IV, hemoglobin<12 g/dL, number of nodal areas >4, and serum LDH above normal. Patients are scored as low risk (≤1 factor), intermediate risk (2 factors), or high risk (≥3 factors). While a protracted course is common in iNHL, life expectancy varies by the types of factors represented in the FLIPI score; median survival is ~4 to >10 years from diagnosis depending upon such prognostic characteristics {22475}. Patients are at risk of transformation of iNHL to aggressive, diffuse, large B-cell lymphoma (DLBCL) at a rate of 2 to 3% per year {22480}, {22465}; such transformation is usually associated with a poor clinical outcome.

5.1.2.1. Standard treatment of the iNHL

Radiation therapy to involved sites is the most common treatment for the infrequent patients with localized iNHL (Stage 1 or non-bulky Stage 2 disease) {22466}, {22462}. Systemic therapy is considered for the majority of patients with iNHL, in whom extensive lymphoma (Stage 2 bulky, Stage 3, or Stage 4 disease) is present {17692}. Watchful waiting is possible but patients are generally treated if they have lymphoma-related symptoms or end-organ dysfunction, bulky disease, cytopenias, persistent disease progression, or a strong preference for immediate therapy. Because iNHL requiring systemic therapy is essentially incurable and patients may be older and have comorbidities, the goal of therapy is primarily to alleviate lymphoma-related symptoms and prolong progression-free interval.

For older or infirm patients, single-agent rituximab MabThera® or alkylating agents such as cyclophosphamide or chlorambucil may be administered {17692}. Most patients receive chemoimmunotherapy in which rituximab is given together with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) {11857}, {22460} or cyclophosphamide, vincristine, prednisone (R-CVP) {22478, 22501}. Alternative regimens include rituximab with the alkylating agent, bendamustine, or fludarabine- or mitoxantrone-based therapy that may include an alkylating agent {22502, 22492}.

Meta-analysis data from randomized trials indicate that the addition of rituximab to chemotherapy not only improves tumor control but also extends overall survival (OS) in previously untreated patients {21029}. Based on controlled trials, rituximab has formal regulatory approval for use as a component of front-line chemoimmunotherapy of iNHL. In addition, maintenance or consolidation therapy with rituximab or yttrium$_{90}$-ibritumomab tiuxetan (Zevalin®) has been shown to prolong PFS {23834, 22454, 22463}.

Despite the chemosensitivity of iNHL to front-line therapy, existing systemic therapies for iNHL are not curative. Some patients will be refractory to initial therapy and most patients will ultimately relapse. Several treatments have received regulatory approval in the United States and/or Europe for treatment of refractory or relapsed disease, including rituximab, yttrium$_{90}$-ibritumomab tiuxetan, iodine$_{131}$-tositumomab (Bexxar®), and bendamustine (Treanda®). The principal support for use in these settings has comprised non-randomized single-arm trials that have focused on documenting treatment-related tumor responses in populations of patients with disease that has become resistant to either alkylating agents or rituximab immunotherapy {22496, 22489, 22498, 24036, 22481, 22494, 22464, 22467, 22469, 22497, 22471, 22470, 22473, 22479, 22472, 22468}.

Yttrium$_{90}$-ibritumomab tiuxetan and iodine$_{131}$-tositumomab use has been limited because of medical and practical restrictions on the use of these agents; these drugs are contraindicated in patients with substantial pre-existing myelotoxicity or bone marrow lymphoma involvement and their use is constrained by the complexity of dosimetry calculations and drug preparation, the need for administration by specifically trained clinicians at specially equipped sites, protracted Grade 3-4 hematological toxicity that commonly results in infectious complications and impedes subsequent therapy, and long-term risks of hypothyroidism.

Other approaches that may be attempted off-label include alkylating agent monotherapy, alkylating-agent-based combination therapy (CVP, CHOP), or administration of purine analogues (fludarabine, cladribine) {17692}. Similarly, patients may be treated off-label with bortezomib (Velcade®) or lenalidomide (Revlimid®) {22491, 22490, 21041}. Due to the acquisition of drug resistance, progressively less activity is observed, particularly when administering previously used therapies; the disease course is characterized by a continuous decrease in the quality and the duration of tumor response with each subsequent treatment {21042}. Patients face the burden of cumulative myelosuppressive toxicity, a problem that has been documented with fludarabine {22482} and commonly limits continued therapy with cytotoxic agents such as bendamustine {22472, 22468}. In addition, there is a well-document risk of myelodysplasia and/or acute myelogenous leukemia associated with use of alkylating agents, doxorubicin, fludarabine, iodine$_{131}$-tositumomab, and Y$_{90}$-ibritumomab tiuxetan {22488}. Consequently, new therapies with novel mechanisms of action are needed to offer additional treatment options for patients with iNHL.

The need is especially acute in those patients whose disease has become refractory to existing chemoimmunotherapeutic approaches, particularly in those with lymphoma that is refractory to both rituximab and alkylating agents.

5.1.2.2. Clinical development of idelalisib in patients with iNHL

In a single-group, open-label, phase II study, 125 patients diagnosed with indolent non-Hodgkin's lymphoma received idelalisib, 150 mg twice daily {30736}. Besides other non-Hodgkin lymphomas the collective included 72 patients diagnosed with FL. All patients had not developed a response to rituximab and an alkylating agent or had shown a relapse within 6 months after receipt of those therapies. They were treated until disease progression or until the patient withdrew from the study. The primary end point was overall response rate, defined as the number of patients who reached complete or partial response. The secondary end points were defined as the duration of response, progression-free survival, and safety.

The median duration of response was 12.5 months and the median progression-free survival was 11 months. Seven patients (6 %) showed a complete response and 63 patients (50 %) a partial response. The median overall survival of all patients was 20.3 months.

More than 80% of the patients developed at least one adverse event. The most common adverse events were diarrhea, fatigue, nausea, cough and pyrexia. Diarrhea, pneumonia and dyspnea were most frequently reported as adverse events of grade 3 or higher. Laboratory abnormalities of grade 3 or higher were amongst others neutropenia and elevations in levels of serum alanine or aspartate aminotransferase. The most frequent serious adverse events were pyrexia, pneumonia, diarrhea, colitis, dehydration, febrile neutropenia, acute renal failure and pneumonitis. Adverse events leading to study-drug discontinuation were reported in 25 patients (20 %).

This single-group study showed that idelalisib has an antitumor activity and an acceptable safety profile in patients with pre-treated indolent non-Hodgkin's lymphoma.

Based on these study results European Commission granted marketing authorization for idelalisib monotherapy in patients with FL, which is refractory to two prior lines of treatment.

6. RESEARCH QUESTIONS AND OBJECTIVES

The objective of this non-interventional study is to evaluate the effectiveness and safety of up to 3 years of therapy with idelalisib per patient in real-life practice, routinely used for the management of chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). Results from several studies (see above) show that there is a high probability for patients to benefit from treatment with idelalisib.

But, due to the patient population in which idelalisib is currently licensed, there is a paucity of robust data on outcome and response as well as safety and there are no current data on the use of idelalisib in real-life clinical routine available.

Therefore, the main objective is to evaluate the effectiveness and safety in patients with CLL and NHL in a real-life setting.

The following issues will be addressed:

- Description of effectiveness and safety of idelalisib in clinical daily routine.
- Therapy evaluation (compound/duration of response/reason for discontinuation).
- ADRs of special interest (diarrhea/colitis, pneumonitis, transaminitis) and the clinical management of these toxicities will be evaluated to assess the safety management of these ADRs.
- Clinical outcome of patients treated with idelalisib.
- Reasons for treatment reduction, discontinuation or interruption.
- Physical and mental health-related quality of life and health status while on idelalisib.
- Resource utilization in patients treated with idelalisib.

To address these issues the following objectives have been chosen:

The primary objectives are to evaluate:

- Progression-Free Survival (PFS) (rate and time to progression)
- Overall Response Rate (ORR)
- Overall Survival (OS) (rate and survival duration)

The secondary objectives are to evaluate:

- Incidence of adverse drug reactions (ADRs) and serious ADRs as well as fatal events (regardless of causality) and cause of death
- Incidence, risk factors, management and outcome of diarrhea/colitis (ADR of special interest)
- Incidence, risk factors, management and outcome of pneumonitis (ADR of special interest)
- Incidence, risk factors, management and outcome of liver enzyme elevation (ADR of special interest)
- Patient Reported Outcome including physical and mental health-related quality of life and health status using standardized general and disease-specific questionnaires (EORTC QLQ-C30, EORTC QLQ-CLL16, SF-12)
- Health resource utilization including frequency and duration of hospitalization
- Type, incidence and outcome of Special Situation Reports (SSRs)

7. RESEARCH METHODS

7.1. Study Design

This is a multicenter, non-interventional, two cohort (CLL and NHL), prospective post authorization safety study (PASS) to evaluate the clinical effectiveness and safety of idelalisib for treatment of patients with CLL or NHL. This design was chosen to assess effectiveness and safety of therapy with idelalisib up to 3 years per patient in clinical routine.

Patients are assigned to a therapeutic strategy within current practice, not according to a trial protocol. The prescription of idelalisib is separated from the decision to include the patient in the study. Diagnostic or monitoring procedures are only those ordinarily applied to the therapeutic strategy.

There are no dose regimens or medical procedures defined within this study plan. Every medical decision and course of treatment with idelalisib will reflect exclusively the decision of the clinical investigator in a routine clinical situation. Recommendations regarding dose reduction and liver function monitoring are detailed in the Zydelig SmPC. The concept of this non-interventional study and its documentation procedure will not affect the routine treatment situation.

7.2. Study flow

This non-interventional study does not influence the therapeutic strategy of the clinical investigator. It is only requested to document medical decisions and procedures and data during this PASS in the eCRF according to the study plan as available from routine medical care.

The selection of diagnostic or monitoring procedures (e.g. laboratory parameters) follows the discretion of the investigator. Diagnostics and monitoring procedures are exclusively the decision of the clinical investigator.

The tables below show the schedule for study activities.

Table 1. Schedule for study activities

Assessment/Activity	At the start of treatment with idelalisib	Treatment phase (approx. every 3 months)	End of Treatment
Informed consent	x		
Inclusion/ exclusion criteria	x		
Patient questionnaires	x	x	x

No changes to patient management should be made for the purposes of this study. The following data should be entered in the CRF only if available from monitoring done as part of standard care. The CRF will collect treatment phase data at time points every 3 months (+/- 4 weeks) after treatment initiation. When a patient visit occurs within such a defined timeframe the data can be entered in the CRF.

Data element	At the start of treatment with idelalisib	Treatment phase	End of Treatment/End of Documentation
Demographic data	x		
Vital signs	x	x	x
Physical Examination	x	x	x
Karnofsky Performance Status	x	x	x
Medical history	x		
Tumor staging	x		
Previous treatment	x		
Concomitant diseases	x	x	x
Concomitant medication	x	x	x
Safety laboratory	x	x	x
Liver function tests	x	x	x
(Serious) Adverse Drug Reactions and fatal events[a]		x	x
Tumor assessment/ response evaluation	x	x	x
Idelalisib dosing	x	x	x
Reason for treatment discontinuation		x (if applicable)	x (if applicable)
Resource utilization		x	x

a Timelines for reporting to Gilead are within 3 calendar days of knowledge of all fatal events and SADRs and within 30 calendar days of knowledge of the ADRs.

7.2.1.1. Documentation at baseline (i.e. treatment initiation with idelalisib)

During baseline (i.e. idelalisib therapy initiation) the following should be documented (as available from medical records):

- Inclusion/Exclusion criteria
- Demographic data
- Vital signs
- Physical examination
- Karnofsky Performance Status
- Prior anti-cancer therapies (compound/PFS/DOT/DOR/BR/Reason for discontinuation)
- Tumor staging
- Concomitant diseases
- Concomitant medication
- Safety laboratory
- Idelalisib therapy start
- Liver function tests
- Tumor assessment
- Patient questionnaires

7.2.1.2. Documentation at each visit

The treatment documentation period is aimed at three monthly intervals (with the exception of liver function tests, see section below) and will last up to a maximum of 36 months per patient until Progressive Disease, death, toxicity or other reasons for treatment discontinuation or study treatment end, whichever occurs first, except for adverse drug reaction data which should be collected for an additional 4 weeks after last dose of idelalisib.

During each visit the following should be documented (as available from medical records):

- Vital signs
- Physical Examination

- Karnofsky Performance Status
- Concomitant diseases
- Concomitant medication
- Liver function tests
- Safety laboratory
- (Serious) Adverse Drug Reactions, fatal events (including cause of death, causality assessment for relationship to idelalisib) and SSRs
- Tumor response evaluation
- Idelalisib dosing
- Reason for and date of treatment discontinuation
- Resource utilization
- Patient questionnaires

7.2.1.2.1. Liver function tests

According to Zydelig SmPC the liver function (e.g. ALT, AST, total bilirubin) should be closely monitored (2-weekly intervals recommended) for the first three months of treatment with idelalisib. Results from liver function monitoring can also be entered in the CRF.

7.2.1.3. Documentation at study completion

In case of **end of treatment** or at **end of documentation period** (36 months [+/- 4 weeks] after initiation of therapy with idelalisib) the following should be documented (as available from medical records):

- Vital signs
- Physical Examination
- Karnofsky Performance Status
- Concomitant diseases
- Concomitant medication
- Liver function tests

- Safety laboratory
- (Serious) Adverse Drug Reactions (plus any occurring within 4 weeks following end of treatment) and SSRs
- Tumor response evaluation
- Idelalisib dosing prior to end of treatment
- Reason for and date of treatment discontinuation
- Resource utilization
- Questionnaires should also be administered to the patient at end of treatment / end of documentation.

7.2.2. Study completion

In this non-interventional study the enrollment of patients will start approximately in Q3 2015 and will last approximately 24 months (LPFV Q3 2017). To be considered to have completed the study, a patient will have been observed for approximately a maximum of 36 months or until discontinuation of idelalisib, whichever occurs first. Considering an estimated recruitment phase of 24 months the study is expected to be completed in Q3 2020.

7.2.3. Premature study termination

However, patients' individual study participation may be terminated prematurely at any time point. For instance, the following reasons may lead to a premature discontinuation (including, but not limited to withdrawal of IC; non-compliance; toxicity). The reason for study termination has to be recorded in the eCRF.

7.2.4. Interim Analysis

Interim analyses (4 in total) are planned in approximately annual frequency. The 1st interim analysis is planned after 50 patients (independent of the treatment arm) have received 3 months antineoplastic treatment.

The other three interim analyses will be performed at approximately annual frequency.

The scopes of the interim analyses are full analysis of available data. Analyses will be done in a descriptive way.

7.2.5. Follow-up

Not applicable.

7.3. Setting

7.3.1. Patient population

Patient enrolment and identification logs have to be completed by the study site for each patient enrolled in the study.

The study population will include 300 adult patients (≥ 18 years) with CLL or NHL.

During this study therapy data from patients routinely treated with idelalisib will be prospectively documented. Patients have to give a written consent to capture and release data concerning their treatment with idelalisib in a pseudonymized form (using patient ID and birth year) before being documented in this non-interventional study.

Retrospective enrollment will not be allowed.

7.3.1.1. Inclusion / Exclusion Criteria CLL (Cohort A)

7.3.1.1.1. Inclusion Criteria CLL

1) Diagnosis of chronic lymphocytic leukemia (CLL) and decision for treatment with idelalisib

2) Understand and voluntarily sign an informed consent form

3) Male or female ≥18 years of age at the time of signing the informed consent form

7.3.1.1.2. Exclusion Criteria CLL

1) Patients with history of another primary malignancy that is currently clinically significant or currently requires active intervention

2) Pregnant or breast feeding women

3) Concurrent participation in another therapeutic clinical trial

7.3.1.2. Inclusion / Exclusion Criteria NHL (Cohort B)

7.3.1.2.1. Inclusion Criteria NHL

1) Patients must have histopathologically confirmed diagnosis of non-Hodgkin's lymphoma and decision for treatment with idelalisib must have been made

2) Understand and voluntarily sign an informed consent form

3) Male or female ≥18 years of age at the time of signing the informed consent form

7.3.1.2.2. Exclusion Criteria NHL

1) Patients with history of another primary malignancy that is currently clinically significant or currently requires active intervention

2) Patients must not have received autologous stem cell transplant at least within 12 weeks prior to study treatment. If patients received autologous stem cell transplant more than 12 weeks ago, they must be fully recovered from the side effects of such treatment

3) Pregnant or breast feeding women

4) Concurrent participation in another therapeutic clinical trial

7.3.2. Specification of sites and number of patients

The study will be conducted in approximately 100 medical centers distributed over all states of Germany, the centers being hospitals and private practitioners willing to participate in this study. The study will include 300 adult patients with CLL or NHL.

150 patients will be enrolled per cohort based on their actual treatment situation:

- Cohort A: Initiating idelalisib regime in CLL patients, n=150
- Cohort B: Initiating idelalisib regime in NHL patients, n=150

As soon as a cohort is fully enrolled (150 treated patients) recruitment of this cohort will be stopped. Precision estimates for CLL endpoints are included in section 7.6.

7.3.3. Treatment setting

Since this is a non-interventional study, the administered dose and the numbers of cycles administered is at the investigator's discretion.

Treatment with idelalisib in CLL patients and will be documented via Cohort A, whereas the treatment with idelalisib in NHL patients and will be documented via Cohort B.

Detailed information on dosing, preparation, handling, storage and disposal of idelalisib are described in the Zydelig SmPC. All information on dosing will be collected accordingly in the eCRF.

Idelalisib is prescribed individually for each patient.

7.3.3.1. Special warnings and precautions for use

Please refer to the Zydelig SmPC for detailed information on warnings, precautions and undesirable effects.

7.3.3.2. Concomitant therapy

All medications ongoing at the start of this non-interventional study or started during the study and different from idelalisib must be documented in the eCRF.

7.4. Variables

The following variables will be captured as as available from medical records.

7.4.1. Demographic data

Age (year of birth), ethnicity, sex, height in centimeters (cm) and body weight (kg) will be documented. . Weight measurement will be repeated at each visit according to the clinical routine, at the discretion of the investigator.

7.4.2. Performance status

Will be assessed by the local investigator according to the Karnofsky performance score{22654}.

7.4.3. Concomitant diseases

Relevant co-morbidities (i.e. autoimmune disease, inflammatory bowel disease, cardiovascular, asthmatic disease, COPD, hypertension, hyperlipidemia, neuropsychiatric disorder, osteopathic disorder, diabetes mellitus, nephropathy) will be documented capturing the start and end date (if applicable).

7.4.4. Medical history related to specific ADRs

If Diarrhea appears, relevant parameters should be evaluated:

- Onset of diarrhea
- Description of number of stool and stool composition (e.g. watery, bloody, nocturnal)
- Duration of diarrhea (measured in weeks and days)
- When diarrhea resolved
- Dose at the time of diarrhea/ When discontinued
- Dose at reintroduction (if applicable)
- Travel history (up to 3 months before the onset of diarrhea)
- Medication history
- History of inflammatory bowel disease (IBD)

- Status of the disease at the time of idelalisib initiation, if available (remission or active)
- Lab results: including stool cultures and results, bowel colonoscopy results including biopsies
- Additional treatments tried, including steroids (iv and oral)
- Any other relevant medical history

If Pneumonitis appears, relevant parameters should be evaluated:

- Onset of pneumonitis
- Duration of pneumonitis (measured in weeks and days)
- When pneumonitis resolved
- Dose at the time of pneumonitis/ when discontinued
- Dose at reintroduction (should only be 1X reintroduction)
- Medication history, including mTOR inhibitors
- Lab results, pulmonary function and imaging studies reports: including sputum cultures and results, BAL results including biopsies, DLCO, chest CT and/or CXR reports
- Pneumocystis carinii isolated?
- Additional treatments tried, including antibiotics, steroids (iv and oral), oxygen
- Any other relevant medical history

If liver enzyme elevations/transaminitis appear(s), relevant parameters should be evaluated:

- Onset of ALT or AST elevation
- Duration of ALT or AST elevation (measured in weeks and days)
- When ALT/AST elevation resolved
- Dose at the time of ALT/AST elevation / When discontinued
- Dose at reintroduction (should only be 1X reintroduction)
- Medication history at the time of ALT/AST elevation

- Lab results: including ALT/AST/total bilirubin/alkaline phosphatase profiles during the period of liver enzyme elevation/transaminitis, any liver biopsy results

- Any other relevant medical history

7.4.5. Tumor history

Documentation of the date of first diagnosis, prior anti-cancer therapies (substances) including outcome and date of the last relapse of disease / reason for discontinuation of last therapy will be performed. Furthermore non-systemic treatment (e.g. surgery, radiotherapy) and stem cell transplantation (SCT) will be documented, if applicable.

7.4.6. Staging and prognostic factors

7.4.6.1. CLL

7.4.6.1.1. Binet Staging {20352}

7.4.6.1.2. Disease activity

Assessment of active/symptomatic disease in terms of significant B-symptoms, cytopenia not caused by autoimmune phenomena, symptoms or complications from lymphadenopathy, splenomegaly or hepatomegaly, lymphocyte doubling time of < 6 months, autoimmune anemia and/or thrombocytopenia.

7.4.6.2. NHL

7.4.6.2.1. Grading FL (1-3A) {24051}

7.4.6.2.2. Ann-Arbor classification (+ modifiers XEAB)

7.4.6.2.3. FLIPI {22475} or IPI

7.4.6.2.4. Disease activity

Assessment of active/symptomatic disease in terms of significant B-symptoms, hematopoetic insufficiency, rapid lymphoma progression, bulky disease, vital organ affection, ascites, pleural effusion

7.4.7. Concomitant medication

Intake of prior (within the last 4 weeks) and ongoing concomitant medication will be documented, capturing start and end date.

7.4.8. Vital signs

Routine vital signs measurements include systolic and diastolic blood pressure and pulse measurement. Assessment of vital signs follows the clinical routine and will be documented accordingly.

7.4.9. Safety and tolerability assessments

Safety will be monitored by assessing the below described examinations and by collecting of the adverse drug reactions at every visit. For details on ADR collection and reporting, refer to Section 9.

7.4.9.1. Laboratory safety evaluations

7.4.9.1.1. Clinical chemistry

Sodium, potassium, chloride, glucose, urea, creatinine, creatinine clearance [Cockcroft and Gault: CrCl = (140-age) * (weight in kg) * (0.85 if female) / (72 * serum creatinine)], calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, serum protein electrophoresis, cholesterol, triglycerides will be measured according to the clinical routine.

7.4.9.1.2. Coagulation panel

(a)PTT, PT-INR will be measured according to the clinical routine.

7.4.9.2. Tolerability

Tolerability will be measured by continuous adverse drug reaction reporting (ADR, SADR) as well as monitoring of dose modification, treatment interruption and discontinuation. For further details refer to section 9.

7.4.10. Tumor assessments

7.4.10.1. Subtype specification

7.4.10.1.1. CLL

Number of circulating clonal B-Lymphocytes (confirmed by flow cytometry (FCM) Y/N).

7.4.10.1.2. NHL

Subtype specification of NHL according to WHO definition from 2008 {24051}.

7.4.10.2. Laboratory hematologic measurements

- Complete blood count: hemoglobin, hematocrit, erythrocytes; leucocytes, neutrophils (absolute), lymphocytes (absolute), platelets, reticulocytes.

- Differential blood count
- Blood smear
- Flow cytometry (FCM)

7.4.10.3. Imaging studies

Radiologic evaluations (e.g. serial computed tomography (CT), PET-CT, X-ray) will be performed according to the clinical routine. Type and frequency of evaluations will be documented.

7.4.10.4. Clinical assessment of lymphadenopathy

Documentation of affected lymphnode areas (cervical, axillary, supraclavicular, inguinal, femoral, popliteal, hilar, mediastinal, paraaortic, iliac, mesenteric, celiac, portal) and matter of distribution (unilateral and/or bilateral) and matter of assessment (palpable enlarged/imaging method).

Assessment of organomegaly (hepatomegaly, splenomegaly)

7.4.10.5. Immunophenotyping

Assessment of e.g. CD5, CD10, CD19, CD20, CD22, CD23, CD79a, Bcl2, Bcl6, CD38, ZAP-70 will be documented if available.

7.4.10.6. Cytogenetics

Results of molecular FISH/PCR analyses will be documented.

7.4.10.6.1. CLL

- TP53 mutation
- Del 17p, Del 13q, Del 11q, Del 6q
- IGHV mutation (DNA sequencing)

7.4.10.6.2. NHL

- Translocation t(14;18)

7.4.10.7. Bone marrow assessment

Results of marrow aspirate and biopsy will be captured as available from the medical records (lymphocyte infiltration by %)

7.4.10.8. Serum markers

Results of serum marker analyses will be documented.

- Beta2 microglobuline
- Light chains
- Thymidine kinase

7.4.10.9. Minimal residual disease (MRD)

Results will be captured as available.

7.4.11. Idelalisib dosing

Idelalisib administration will be captured in the eCRF according to the medical records. The following dosing details will be documented in the eCRF:

Documentation of treatment start date, daily dose, treatment duration, dose modifications, treatment interruptions, reason for modification, interruption and permanent discontinuation (e.g. disease progression, adverse drug reactions, other) will be performed.

Other antineoplastic agents and/or antibodies will be documented as concomitant medication.

7.4.11.1. End of Treatment

At the end of idelalisib therapy reason for and date of end of treatment will be documented.

7.4.12. Effectiveness assessment

Response will be determined and categorized (CR, PR, SD, PD) by the local investigator according to local practice and be documented according to the medical records.

7.4.12.1. Progression free survival (PFS)

Progression free survival is defined as time from start of idelalisib (+/- other combination partner) therapy to progression or death of any cause.

7.4.12.2. Overall Response Rate (ORR)

Overall response rate (ORR) is the portion of patients with a tumor size reduction for a minimum time period, i.e. the sum of PR plus CR.

7.4.12.3. Overall Survival (OS)

For Overall Survival (OS) the rate, i.e. the portion of patients who are still alive three years from start of idelalisib (+/- other combination partner) therapy and the survival duration are evaluated.

7.4.13. Patient reported outcome

The following standardized general and disease-specific questionnaires will be used:

Cohort A (CLL patients): EORTC QLQ-C30 and CLL16, SF-12

Cohort B (NHL patients): EORTC QLQ-C30 and SF-12

To assess the quality of life under idelalisib therapy, all patients will be asked to complete validated questionnaires every three months. The first questionnaire will be handed out to the patient at the study site after signature of informed consent and prior to first intake of idelalisib.

The center must provide a quiet place where the patient has sufficient time and space to concentrate on the questions and to complete the questionnaire. No checks for completeness have to be done. Patient's refusal to complete all or any part of a questionnaire should be accepted.

7.4.13.1. EORTC QLQ-C30

The EORTC validated Quality of Life Core Questionnaire EORTC QLQ-C30 is used to measure cancer-related quality of life. The measure incorporates five functional scales (physical, role, cognitive, emotional, social), three symptom scales (pain, fatigue, nausea/vomiting), a global health and a global quality-of-life scale, and several single items for the assessment of additional symptoms commonly reported by cancer patients (e.g. appetite loss, sleep disturbance) as well as the perceived financial impact of the disease and treatment.

The EORTC QLQ-C30 consists of 30 items that are scored on 4-point Likert scales, ranging from 1 ("not at all") to 4 ("very much").

Two items in the global health and quality-of-life sub-scale are scored on a 7- point linear analogue scale. All functional scales and individual item scores are transformed to a 0–100 scale. Higher scores in the five functional scales and global health status scale represent better functioning, whereas higher scores in symptom scales reflect a greater extent of symptom distress.

7.4.13.2. EORTC CLL 16

The EORTC CLL 16 module is designed for patients with stage 0 to stage 4 chronic lymphocytic leukemia. It incorporates sixteen questions which address five domains of health related quality of life important in CLL. There are three multi item scales on: - Fatigue (2 items), treatment side effects (4 items) and disease symptoms (4 items), infection (4 items) and two single item scales on social activities and future health worries.

7.4.13.3. SF-12

The SF-12 health survey is a 12-item short form designed to provide a health related quality of life profile. The questionnaire is brief (only 12 questions), while yielding scores are directly comparable to the eight scores produced by the standard SF-36 questionnaire.

7.4.14. Resource utilization

The measures of healthcare resource utilization investigate frequency and duration of hospitalization (e.g. number of hospital days) starting after start of therapy with idelalisib.

7.5. Data Sources

Routine visit data as documented in the medical record will be entered in the eCRF and questionnaires completed by the patients will be collected.

7.6. Study Size

Due to the character of this non-interventional study no formal sample size calculation was done.

The target number of 150 patients per cohort enrolled in approximately 100 study sites distributed throughout Germany was chosen based on the expected number of patients starting treatment with idelalisib per site and year (2-3 patients per site per year). It is expected that the patient number of 150 per arm will also enable evaluations of subpopulations of CLL/NHL patients.

We estimated the margin of error (precision) for incidence of ADRs of special interest, progression–free survival, overall response rate, and overall survival, provided that 150 CLL patients and 150 NHL patients will be recruited into the study (Table 2). Because the sample incidence of the primary outcome measures in CLL/NHL is unknown, the incidence proportions from our trial for CLL and, for a sensitivity analysis, 30% increase in the proportion for ADRs, PFS and OS (10% increase for ORR) were used.

Table 2. Estimated precision of incidence proportion of ADRs of special interest, progression-free survival, overall response rate, and overall survival in CLL patients (n=150)

Outcome measures	Assumed sample incidence proportion in CLL (1)[a]	Precision (±width) (1)	Assumed sample incidence proportion in CLL (2)[b]	Precision (±width) (2)
Diarrhea	29.1%	± 7.06%	37.8%	± 7.59%
Colitis	7.27%	± 3.92%	9.45%	± 4.38%
Pneumonitis	5.45%	± 3.39%	7.09%	± 3.92%
ALT or AST elevation (G≥3)	9.10%	± 4.38%	11.8%	± 4.80%
PFS (progression events)	22.7%	± 6.50%	29.5%	± 7.06%
ORR	83.6%	± 5.88%	92.0%	± 3.92%
OS	15.5%	± 5.54%	20.2%	± 6.19%

a incidence proportion from study 116.
b 30% increase in the proportion (from 116) for ADRs, PFS and OS (10% increase for ORR).

7.7. Data Management

The data management for this non-interventional study will be performed by Gilead or a CRO.

For data capturing and data management of this PASS, a web-based eCRF will be employed.

The Electronic Case Report Forms (eCRFs) for data capturing include online validation of CRFs during data capturing, e.g. check on range, plausibility, typing errors. In addition to the system based plausibility checks, a formal query process will be implemented to solve inconsistencies in documented data.

Electronic data queries will be created for discrepancies and missing values and displayed to the investigational site via the eCRF system. Designated site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using WHO Drug.

Adverse drug reactions (ADR) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

7.8. Data Analysis

7.8.1. General

The statistical analysis of the data will be primarily descriptive. SAS version 9.4 or higher will be used for the analysis.

Summary statistics will be presented by cohort (CLL or NHL) and will include:

- nominal variables: frequencies and percentages.
- ordinal variables: frequencies, percentages, median, minimum and maximum.
- continuous variables: number (N) of observations, mean, standard deviation, 25th percentile, median, 75th percentile, minimum and maximum.

All data listings will be sorted by cohort, center ID and patient ID.

Missing values will not be imputed. All assessments will be analyzed with all available data.

For ADR events, in addition to frequencies and percentages, incidence rate in person-time will be calculated by dividing number of new cases by the total number of person-time at risk to account for varying length of follow-up.

If not otherwise specified, p-values will be presented as two-sided and the level of significance is set to 5% (two-sided). Additionally, corresponding 95%-confidence intervals will be provided, where applicable.

Descriptive analysis in pre-defined subgroups (e.g. age, gender, types of NHL, number of prior regimens, p17 deletion/TP 53 mutation status, etc.) will also be reported.

7.8.2. Demography and Baseline Characteristics

Characteristics of the patients at baseline will be presented according to section 7.2.1.1.

7.8.3. Primary Endpoints

All results will be presented by cohort and time interval (e.g. at 6 months, 12 months, etc.), if applicable.

7.8.3.1. Effectiveness

Frequency tables for tumor response evaluation, progression-free status and overall survival status will be provided.

Kaplan-Meier plots (estimates) of progression-free survival, overall response rate, and overall survival will be produced. The median duration of progression-free survival, overall response rate, and overall survival will be determined.

7.8.4. Secondary Endpoints

All results will be presented by cohort and time interval, if applicable.

7.8.4.1. Safety

Descriptive statistics will be provided for safety and associated endpoints (e.g. incidence of ADRs, serious ADRs, SSR, key laboratory abnormalities; vital signs and laboratory test results over time, frequency of comorbidities of interest and concomitant medications, detail of description of ADRs of special interest and SSR, death and cause of death).

Patients enter the study at different times and some may leave before the end of the study (e.g. withdraw, death, etc.). For ADR events, in addition to frequencies and percentages, incidence rate in person-time will be calculated by dividing number of new cases by the total number of person-time at risk to account for varying length of follow-up.

7.8.4.2. Patient Reported Outcome (PRO)

Descriptive statistics will be provided for Karnofsky Performance status.

Questionnaires will be analyzed according to their manuals.

7.8.4.3. Resource utilization

Descriptive statistics will be provided for number and duration of hospitalization periods.

7.8.4.4. Special situations report

Special situation reports will be summarized by type and whether associated with an adverse event/reaction or not.

7.9. Quality Control

Study initiation will be performed by online webinar or via telephone prior to start of recruitment at the site. During the study, CRO might perform site visits for source data verification (SDV). Monitoring visits will be performed according to the study-specific monitoring plan.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep a signed informed consent form, and give a signed copy to the patient.

Details of on-site monitoring will be described in the monitoring plan. The investigator should also ensure that the monitor and, when indicated also an auditor or regulatory inspector, is given direct access to source documents of the patient which support data recorded in the eCRF. The patient will be informed of this process and has to give authorization to it in the signed informed consent form.

Regular central manual data review and medical data review will be performed to discuss study status as well as any potential problems with data completeness or study conduct (details will be defined in the data management plan).

The investigator will be provided with an investigator site file upon initiation of the study. This file will contain all documents necessary for the conduction of the study and will be updated and completed throughout the study. It must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the sponsor) after the end of the study. The documents to be thus archived include the patient identification list and the signed patient informed consent forms. If archiving of the investigator site file is no longer possible at the site, the investigator must notify the sponsor.

7.10. Other Aspects

7.10.1. Joint Investigator/Sponsor Responsibilities

7.10.1.1. Access to Information for Monitoring

The investigator will provide the study monitor with access to any patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

7.10.1.2. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate institutions. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

8. PROTECTION OF STUDY PATIENTS

8.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The investigator will ensure that this study is conducted in accordance with the principles of the International Conference on Harmonization (ICH) Pharmacovigilance Planning E2E guidelines, and with the laws and regulations of the country in which the research is conducted.

The investigator will conduct this study in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

8.2. Independent Ethics Committee (IEC) Review

The investigator (or sponsor) will submit this protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an IEC. The investigator will not begin any study activities until approval from the IEC has been documented and provided as a letter to the investigator.

Any subsequent modifications made to the protocol or any accompanying material to be provided to the patient after initial IEC approval will also be submitted for IEC approval prior to use, with the exception of those necessary to reduce immediate risk to study patients.

8.2.1. Notification of the competent authority and other relevant institutions

This is a voluntarily conducted non-interventional post-authorisation safety study according to section 4 (34) and section 63f German Medicinal Law (AMG). The competent authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung; KBV), the Statutory Health Insurance Funds (GKV-Spitzenverband) and the Association of private Health Insurances (PKV) will be notified by sponsor or CRO of this study according to article and 63 f German Medicinal Law.

8.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual patient participating in this study after adequate explanation of the aims, methods and objectives of the study prior to study participation and before performing any study-related activities (i.e. completion of baseline patient questionnaire set or starting documentation in the eCRF). The investigator must utilize the most current IEC approved consent form for documenting written informed consent. The investigator should allow enough time for the patient to inquire about the details of the study. Each informed consent form will be appropriately signed and dated by the patient and the physician conducting the consent discussion. The patient should receive a copy of the signed informed consent form and any other written information provided to the patients prior to participation in this non-interventional study.

8.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document. Signed informed consent forms and patient identification list must be kept strictly confidential to enable patient identification at the site.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, eCRFs, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

In this study all fatal events (regardless of causality), Special Situation Reports (SSRs), all Adverse Drug Reactions (ADRs) and all Serious Adverse Drug Reactions (SADRs) occurring after the patient consents to participate in the study (i.e., signing informed consent) until study completion, loss of follow-up, withdrawal of consent, death, or 4 weeks after discontinuation of idelalisib, whichever comes first, will be collected.

The collection of ADRs, SADRs and SSRs reflects the real-life situation in which the treating physician with best knowledge of his patient assesses whether an observed event could be related to idelalisib. In this way, the study will collect safety data that is reflective of the real-life setting in which it is conducted. Adverse Events (AEs) and Serious Adverse Events (SAEs), with the exception of fatal cases, that have been assessed as Not Related to idelalisib, are not reportable for this study. Special situations (i.e. pregnancy) apply and should be reported as outlined below.

9.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of effectiveness, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.

- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

9.1.1. Adverse Drug Reactions

An ADR is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

9.1.2. Serious Adverse Drug Reactions

A SADR is defined as any SAE that is considered causally related to a medicinal product at any dose administered.

9.1.3. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and patient to expedited reporting requirements.

9.2. Assessment of Adverse Drug Reactions and Serious Adverse Drug Reactions

The investigator or qualified sub-investigator is responsible for assessing ADRs and SADRs for causality and for final review and confirmation of accuracy of event information and assessments.

9.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is a reasonable possibility that the event may have been caused by the medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

9.3. Special Situations Reports

9.3.1. Definitions of Special Situations

Special situation reports include reports of pregnancy; medication error, abuse, misuse, or overdose; lack of effect; adverse reactions in infants following exposure from breastfeeding; and adverse reactions associated with product complaints and occupational exposure.

A pregnancy report form is used to report any pregnancy that occurs during the study, whether or not maternal or paternal exposure to the product occurred.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, patient, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a patient.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the patient in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the patient has taken the excess dose(s). Overdose cannot be established when the patient cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the patient has taken the additional dose(s).

Lack of effect is defined as the failure of the expected or intended pharmacologic action or therapeutic effect as described in the pharmacology and/or indications section of the current product labelling.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one’s professional or non-professional occupation.

9.3.2. Instructions for Reporting Special Situations

9.3.2.1. Instructions for Reporting Pregnancies

All pregnancies (including partner pregnancies) that occur while exposed to the drug and the outcome of the pregnancy are to be reported to Gilead DSPH (Foster City) using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g. a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE via fax or email. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 9.5. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The outcome should be reported to Gilead DSPH using the pregnancy outcome report form.

9.4. Investigator Requirements and Instructions for Reporting Adverse Drug Reactions (ADRs) and Serious Adverse Drug Reactions (SADRs) to Gilead

All fatal events (regardless of causality) and all serious and non-serious adverse drug reactions (SADRs/ADRs) occurring after the patient consents to participate in the study (i.e., signing informed consent) until study completion, loss of follow-up, withdrawal of consent, death, or 4 weeks after discontinuation of idelalisib, whichever comes first, will be reported on the Non-interventional AE/SAE report form. Special Situation Reports (SSRs) will be recorded on the Gilead Special Situation Report (SSR) Form. Pregnancy reports will be recorded on the pregnancy eCRF/CRF.

Timelines for reporting ADRs and SADRs to Gilead are as follows:

- Within 3 calendar days of knowledge of all fatal events and SADRs
- Within 30 calendar days of knowledge of the ADRs

Special Situations will be reported to Gilead DSPH within 30 calendar days of knowledge of the event.

Details of the methods for reporting ADRs, SADRs, and SSRs to Gilead DSPH will be described in the CRF completion Guidelines. If reporting of events is by electronic submission via eCRF, this method must always be used unless the eCRF system is not functioning. Alternatively, details of the ADR, SADR, or SSR should be recorded on the appropriate paper reporting form (and submitted by fax or e-mail, within the timelines given above, to:

Gilead DSPH contact information is as follows:

Email: Safety_FC@gilead.com

Fax: +1 (650) 522-5477

9.5. Gilead Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all ADRs and SADRs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs) as determined by country-specific legislation or regulations.

Assessment of expectedness for ADRs, SADRs and SSRs will be determined by Gilead using reference safety information specified in the relevant local label.

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs).

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report is based on the standards set out in the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII. Note that an abbreviated report may be prepared in certain cases. The final CSR will be submitted within 12 months of study completion.

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

Gilead shall communicate to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

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12. APPENDICES

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
NA			

Appendix 2. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Prospective non-interventional post authorization safety study (PASS) of idelalisib in Germany

Study reference number:
tbd

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	14
1.1.2 End of data collection[2]	☒	☐	☐	14
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	14
1.1.5 Registration in the EU PAS register	☒	☐	☐	14
1.1.6 Final report of study results.	☒	☐	☐	14

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	15
2.1.2 The objective(s) of the study?	☒	☐	☐	20/21
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	27
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	22
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	38/39
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	37/38

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	27
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	27
4.2.2 Age and sex?	☒	☐	☐	27/28
4.2.3 Country of origin?	☐	☐	☒	
4.2.4 Disease/indication?	☒	☐	☐	27/28
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population?	☒	☐	☐	27/28

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
(e.g. event or inclusion/exclusion criteria)				

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	28
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	28
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	38/39
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	28/34
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	38/39
8.1.3 Covariates?	☒	☐	☐	36
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	34
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	38/39
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	35
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	37
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	37
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	37/38

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	35/38
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	39
11.3 Are methods of quality assurance described?	☒	☐	☐	39
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	39
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☒	☐	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	36
12.3 Does the protocol address other limitations?	☐	☐	☒	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been	☒	☐	☐	41

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
described?				
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	42

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	13

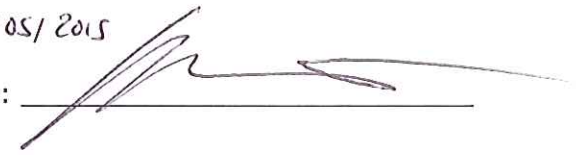
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	41
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	48

Comments:

Name of the main author of the protocol: Holger Krönig

Date 05/05/2015

Signature: 

Appendix 3. Study Acknowledgement

GILEAD SCIENCES GMBH
FRAUNHOFERSTR 17, 82152 MARTINSRIED, GERMANY

Prospective non-interventional post authorization safety study (PASS) of idelalisib in Germany

Final, 27 April 2015

This protocol has been approved by Gilead Sciences, Inc. The following signatures document this approval.

Holger Krönig

Gilead Study Director (Printed)
Author

Signature

Date

Anne-Ruth van Troostenburg de Bruyn

Gilead EU QPPV (Printed)

Signature

30 Apr 2015

Date

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