A Phase 1b Study Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GS-9820 Monotherapy and Combination Therapy in Subjects with Lymphoid Malignancies

Published: 14-08-2012
Last updated: 26-04-2024

To determine appropriate dosing regimens for use in future clinical trials of GS 9820 in subjects with lymphoid malignancies.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39586

Source
ToetsingOnline

Brief title
Study evaluating GS-9820 with patients with lymphoid malignancies.

Condition

- Other condition
- Lymphomas Hodgkin's disease

Synonym
B-cell related malignancy, Lymphoma

Health condition

Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia, indolent Hodgkin's Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences;Inc.

Intervention

Keyword: Clinical Activity, Pharmacodynamics, Pharmacokinetics, Safety

Outcome measures

Primary outcome

To determine the MTD within the tested GS-9820 dose range and regimens

Secondary outcome

To characterize the safety profile of GS-9820, determined overall safety profile of each study treatment regimen characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events or abnormalities of laboratory tests or ECGs. Enumeration and description of any DLTs, serious adverse events, or adverse events leading to discontinuation of study treatment.

To characterize the pharmacokinetic profile of GS-9820, based on blood sampling performed at GS-9820 initial dosing (Day 1) and at steady state (Day 29).

To assess the pharmacodynamic effects of GS-9820 on base of flow cytometry and ELISA.

Antitumor activity will be evaluated using standard response criteria for NHL or for CLL

Patient Well-Being will be determined by the Changes from baseline in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy:

Lymphoma (FACT-Lym).

Study description

Background summary

B-cell lymphoid malignancies comprise the most common hematological malignancies. These cancers arise from the accumulation of monoclonal B lymphocytes in lymph nodes and often in organs such as blood, bone marrow, lymph nodes, spleen, and liver. Among the variants of these cancers are non-Hodgkin lymphomas (NHL) * including diffuse large B-cell lymphoma (DLBCL), indolent non-Hodgkin lymphoma (iNHL), and mantle cell lymphoma (MCL) * chronic lymphocytic leukemia (CLL), and Hodgkin lymphoma (HL). The goal of therapy for these diseases is to induce tumor regression and delay tumor progression in order to control disease-related complications and potentially extend life. Patients who require treatment are commonly given chemotherapeutic and/or immunotherapeutic agents. For any of these cancers, further sequential therapies are given in an attempt to control disease manifestations. Despite use of agents with differing mechanisms of action, progressive resistance to treatment develops.
Patients with progressive disease have a poor prognosis; median survival for these groups of patients is generally *2 years. Novel mechanisms of action are needed to offer additional treatment options for patients with lymphoid malignancies who are experiencing progressive lymphadenopathy or symptoms due to disease progression. Knowledge of the critical importance of PI3K* in B-cell biology and neoplasia has encouraged a search for inhibitors of this enzyme that could provide new options in the therapy of lymphoid malignancies, including CLL. Gilead Sciences, Inc has developed novel drugs that can suppress tumor growth through targeting of PI3K activity. High-throughput screening was the basis for the discovery of novel agents that selectively inhibit PI3K isoform function. These efforts initially led to identification of GS-1101 (also known as CAL-101), a 415-Dalton, orally bio-available, investigational drug that represented a first-in-class selective inhibitor of PI3K*.The nonclinical and early clinical findings with GS-1101 have created the foundation on which second-generation agents, such as GS-9820, will be evaluated. The design and conduct of this study is supported by an understanding of the natural history and current therapies for patients with recurrent lymphoid cancers; knowledge of the safety and activity of the predecessor compound, GS-1101 in patients with NHL, HL, and CLL; and the nonclinical and clinical information regarding GS-9820.

Study objective

To determine appropriate dosing regimens for use in future clinical trials of

GS 9820 in subjects with lymphoid malignancies.

Study design

This clinical trial is a Phase 1b, open-label, dose-escalation and expansion study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of GS 9820.

Intervention

GS-9820 will be administered on a BID schedule starting on Day 1.
Treatment will persist until the earliest of subject withdrawal from study, disease progression, intolerable GS-9820-related toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation.

Dose escalation
Patients will be sequentially enrolled at progressively higher dose levels Dose escalation will be performed with cohort sizes of 3 to 6 subjects using a classic 3+3 design. First cohort will start at 50 mg/dose BID.
Any subject started at a lower dose level during the dose escalation phase should be increased to 400 mg BID. A lower dose level of 200 mg is provided if a subject requires a study drug dose modification.

Study burden and risks

The patient is subjected to investigations that would take place in their regular care, but in the beginning more frequently to be able to monitor any adverse reactions. This forces the patient to the hospital more often than regular care. During the first 12 weeks the study requires patients to come to the outpatient clinic for follow-up every two weeks. The next 12 weeks patients will have to come monthly for a follow up visit. After that time patients will have to come in for a follow-up every 6 weeks until week 48. The period that follows patients have to come in for follow up every 12 weeks. Prior to each visit to the outpatient clinic, a blood sample will be taken to check the blood values. With regular care the patient would come monthly for follow up and will get their blood levels checked. Additional blood draws will be as much as possible combined with regular care.
The 1st 3 months, the patients are requested to complete a monthly questionnaire. Then the questionnaire is completed at each clinic visit. Until week 24 there is a CT scan done every 8 weeks. Then every 3 months. The 1st year, this would involve 8 additional CT scans in CLL patients and 5 CT scans in Hodgkin and Non Hodgkin's patients.

Studies in rats and dogs that received daily very high doses, showed the following adverse reactions, reduction of lymphocyte, decrease in size of the thymus, spleen and lymph nodes, bowel inflammation, increases in liver size and

inflammation of the liver, reduced sperm production.
GS 9820 is also given to a group of male volunteers with a fixed dose. None of the subjects experienced serious side effects or adverse reactions were observed in animal studies.

GS 9820 has been given to 39 patients. The following side effects have been reported and might have been caused by GS-9820: diarrhea, fatigue, fluid retention or swelling of the arms or legs, pain, fever, lung infection, decreased appetite, back pain, cough, rash.
For these patients there are no curative options. There are no standard treatments for these people available. The expectation is that the drug under study is effective with acceptable toxicity.

Contacts

Public
Gilead Sciences

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Scientific
Gilead Sciences

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Seattle, WA 98109
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Male or female *18 years of age.
2) Diagnosis of B-cell iNHL, DLBCL, MCL, HL, or CLL as documented by medical records and with histology based on criteria established by the World Health Organization.
3) Prior treatment for lymphoid malignancy.
4) Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of *1 lesion that measures *2.0 cm in the longest dimension [LD] and *1.0 cm in the longest perpendicular dimension [LPD] as assessed by CT or MRI).
5) Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, systemic corticosteroids, or investigational therapy) for the treatment of cancer *3 weeks before
the start of study therapy.
6) All acute toxic effects of any prior antitumor therapy resolved to Grade *1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2
permitted], or bone marrow parameters [any of Grade 1, 2, or 3 permitted).
7) Karnofsky performance score of *60.
8) Required baseline laboratory data (within 4 weeks prior to start of study therapy) as shown in the table below.
9) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit (Visit 1) throughout the study treatment period and for 30 days following the
last dose of GS-9820.
10) For male subjects of childbearing potential having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of study therapy (Visit 2) throughout the study treatment period and for 90 days following the last dose of GS-9820 and to refrain from sperm donation from the start of study treatment (Visit 2) throughout the study treatment period and for 90
days following the last dose of GS-9820.
11) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject*s cancer.
12) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions.
13) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

Exclusion criteria

1) Known histological transformation to an aggressive form of NHL (ie, Richter transformation).
2) Known active central nervous system or leptomeningeal lymphoma.
3) Presence of intermediate- or high-grade myelodysplastic syndrome (ie, subjects are excluded who have *5 bone marrow blasts; karotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or *2 lineages of cytopenias).
4) History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer,
asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for *1 year prior to start of study therapy, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for *5 years.
5) Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of start of study therapy (Visit 2).
6) Ongoing liver injury, chronic active HCV, HBV, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
7) Ongoing drug-induced pneumonitis.
8) Ongoing inflammatory bowel disease.
9) Ongoing alcohol or drug addiction.
10) Pregnancy or breastfeeding.
11) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
12) History of prior therapy with any inhibitor of AKT, Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K) (including GS-1101), or spleen tyrosine kinase (SYK).
13) Ongoing immunosuppressive therapy, including systemic corticosteroids for treatment of lymphoid malignancy. Note: Subjects may use topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions and systemic steroids for autoimmune anemia and/or thrombocytopenia. Ongoing use of lowdose systemic corticosteroids (*5 mg/day of methylprednisolone or equivalent) for rheumatologic conditions is permitted. During study participation, subjects may receive systemic or other corticosteroids as pretreatment for rituximab infusions or as needed for treatment emergent comorbid conditions.
14) Concurrent participation in another therapeutic clinical trial.
15) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator*s opinion, could adversely affect the safety of the subject or impair the assessment of study results.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2012
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GS-9820
Generic name:	GS-9820

Ethics review

Approved WMO Date:	14-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2013
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2015
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-000360-19-NL
CCMO	NL40813.018.12