A Randomized, Controlled, Double-Blind Phase III Trial to Compare the Efficacy, Safety and Pharmacokinetics of GP2013 plus CVP vs. MabThera® plus Cyclophosphamide, Vincristine, Prednisone vs. MabThera® plus Cyclophosphamide, Vincristine, Prednisone, followed by GP2013 or MabThera® Maintenance Therapy in Patients with Previously Untreated, Advanced Stage Follicular Lymphoma

Published: 29-07-2011
Last updated: 01-05-2024

*To demonstrate comparability of the ORR in patients with previously untreated, advanced stage FL who receive GP2013-CVP combination treatment to patients who receive MabThera®-CVP treatment. ORR will be determined during the combination treatment...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON44911

Source
ToetsingOnline

Brief title
GP13-301

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Advanced Stage Follicular Lymphoma, Previously Untreated

Research involving
Human

Sponsors and support

Primary sponsor: Sandoz
Source(s) of monetary or material Support: sponsor/farmaceut

Intervention

Keyword: CVP, Follicular Lymphoma, GP2013, MabThera®

Outcome measures

Primary outcome

ORR at the end of combination treatment period should be comparable between two

treatment groups using modified response criteria for lymphoma.

Secondary outcome

- evaluate PR, CR, PFS and OS

- Percentage of patients with AE and laboratory test abnormalities

- Percentage of patients with ADA formation

- Pharmacokinetic variables (Cmax, Cmin)

- CD19+ B-cell count (AUEC0-21 days)

Study description

Background summary

In spite of cost-effectiveness in most of the pharmacoeconomic studies undertaken to date, MabThera® remains an expensive drug and patient access often remains restricted by cost. The introduction of biosimilar medicinal products is considered desirable to enhance patient access to these kind of medicines and potential to provide access to patients and make further investigation for comparable medicines possible for physicians.
CD20-positive FL is the most common of the indolent lymphomas and the intent of treatment is disease control. Therefore, it is feasible that patients and investigators would accept to participate in a trial with a biosimilar antibody in FL. The development program of GP2013
aims at a marketing authorization application for GP2013 as a *Similar Biological Medicinal Product* to MabThera® in the EU, complying with the guidelines and legal framework of the European Medicines Agency (EMA). The demonstration that GP2013 and MabThera® are highly comparable in terms of physicochemical and pharmaceutical properties, in vitro binding, biological function and pharmacokinetic and pharmacodynamic potency in animals, provide the basis for the clinical comparison of GP2013 and MabThera®.

Study objective

*To demonstrate comparability of the ORR in patients with previously untreated, advanced stage FL who receive GP2013-CVP combination treatment to patients who receive MabThera®-CVP treatment. ORR will be determined during the combination treatment period using Modified Response Criteria for Malignant Lymphoma.

*To evaluate CR rate during of combination treatment period;
*To evaluate PR rate during of combination treatment period;
*To evaluate PFS, which is defined as time from date of randomization to date of first documented progression of disease, or death due to any cause, with up to 3 years of follow up post randomization;
*To evaluate OS, which is defined as: time from date of randomization to date of death due to any cause, with up to 3 years of follow up post randomization.
*To describe safety of GP2013-CVP in comparison to MabThera® either as single agent or in combination with CVP;
*To evaluate the incidence of immunogenicity ADA formation against GP2013 and MabThera®.
*To evaluate the pharmacokinetics of GP2013 and MabThera®.
*To evaluate peripheral CD19+ B-cell count as a pharmacodynamic marker following treatment with GP2013-CVP and MabThera®-CVP.
* To explore the population pharmacokinetics of GP2013 and MabThera®.

Study design

A Randomized, Controlled, Double-Blind Phase III Trial

Intervention

Combination Treatment period (8 cycles of 21 Days):
GP2013 (375 mg/m² i.v.) or MabThera® (375 mg/m² i.v.) +
Cyclophosphamide (750 mg/m2 i.v.)
Vincristine (1.4 mg/m2 (max dose 2 mg) i.v.)
Prednisone (100 mg p.o.)

Maintenance Treatment period (2 years, every 3 Months):
GP2013 (375 mg/m² i.v.) or MabThera® (375 mg/m² i.v.)

Study burden and risks

Summary of procedures:
1x bone marrow biopsy
1x tumor biopsy
19x pregnancy test (blood of urine)
13x CT /MRI scan
13x B-symptoms
1x 2d-Echo / MUGA
3x immunogenicityblood test

For GP2013 the same side-effects as for MabThera® can be expected. MabThera® can have the following side-effects:
* Infusion reactions: During or within the first 2 hours of the first infusion the patient may develop fever, chills and shivering. Lessfrequently, some patients may experience blisters, itching, sickness, tiredness, headache, breathing difficulties, tongue or throat swelling, itchy or runny nose, vomiting, flushing or palpitations. If the patient has a heart disease or angina, these reactions might get worse.
* Tumor Lysis Syndrome (TLS): It is caused by the fast breakdown of cancer cells. TLS can cause: kidney failure and the need for dialysis treatment, abnormal heart rhythm.
* Infections: Often these are colds, but there have been cases of pneumonia, urinary infections, herpes infections or reactivation of hepatitis B or hepatitis C infection.
* Other potential side effects including: pain in the tummy, back, chest, muscles and/or joints, at the infusion site (where the drip is put into your vein), feeling unwell, changes in blood pressure, changes in heart rate, diarrhea, indigestion, cramp, dizziness, tingling or numbness, anxiety or nervousness, cough, watery or itchy eyes, runny or itchy nose, sweating, sinusitis. Heart disorders are also possible such as changes in blood pressure, heart attack, irregular heart rate, abnormally fast heart rate; some patients also have some changes to blood tests including a fall in the number of red cells, white cells or both.
* Progressive Multifocal Leukoencephalopathy (PML): PML is a serious brain infection that can be fatal. Symptoms include memory loss, trouble thinking, difficulty in walking and/or loss of vision.

* Skin Reactions: Very rarely, severe blistering skin conditions that can be life-threatening may occur. Redness, often associated with blisters, may appear on the skin or on mucous membranes, such as inside the mouth, the genital areas or the eyelids, and fever may be present.
* Gastrointestinal Disorders: Very rarely, patients could experience damage to the intestinal wall such as perforation, causing an experience of severe stomach/abdominal pain, nausea, vomiting, chills, and fever.

Contacts

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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. Patient with previously untreated advanced stage, CD20-positive FL:
a. Ann Arbor classification stage III/IV;
b. WHO histologic grade 1, 2 or 3a, as confirmed by central pathological testing; and

c. Require therapy for FL as per local guidelines or in the opinion of the treating physician.
2. Patient age * 18 years.
3. Patient with at least one measurable lesion (accurately measureable in at least 2 perpendicular dimensions);
a. at least 1 measurable nodal lesion > 20 mm in the long axis; OR
b. at least 1 measurable extranodal lesion with both long and short axes * 10 mm.
4. Patient with ECOG performance status 0, 1 or 2.
5. Patient with adequate cardiac function defined as cardiac ejection fraction * 45% as measured by 2D-ECHO or MUGA, without clinically significant abnormalities.
6. Patient with the following laboratory values obtained during Screening (up to 28 days before randomization):
a. hemoglobin * 10g/dL (unless abnormalities are due to histologically proven bone marrow involvement by lymphoma);
b. absolute neutrophil count (ANC) * 1.5 x 109/L (unless abnormalities are due to histologically proven bone marrow involvement by lymphoma);
c. platelet count * 100 x 109/L (unless abnormalities are due to histologically proven bone marrow involvement by lymphoma);
d. total bilirubin < 1.5 x ULN (upper limit of normal) (if Gilbert-Meulengracht syndrome is present, up to 2.0 x ULN is allowed);
e. transaminases < 2.5 x ULN;
f. serum creatinine level < 2 x ULN or calculated creatinine clearance > 50 mL/min;
g. negative serologic or virologic markers for active of latent hepatitis B and hepatitis C infections.

Exclusion criteria

1. Patient with Grade 3b (aggressive) FL or any histology other than FL grade 1, 2 or 3a.
2. Patient with histological evidence of transformation to high grade or diffuse large B-cell lymphoma.
3. Patient who has previously received any prior therapy for lymphoma, e.g. cytostatic or cytotoxic agents, antibodies, anti-lymphoma vaccination, experimental treatments and radiotherapy, except who received involved field radiation 4 weeks prior to Cycle 1 Day 1, of up to
two lesions that will not be used to evaluate disease progression.
4. Evidence of significant leukemic disease defined as >10 x 109 /L circulating CD20+ lymphoma cells.
5. Patient with clinical evidence of central nervous system (CNS) involvement by lymphoma or any evidence of spinal cord compression by lymphoma.
6. Patient with evidence of any uncontrolled, acute or chronic active infection (viral, bacterial, including tuberculosis, or fungal).
7. Patient receiving chronic (>3 months), high dose (> 20 mg of prednisone or > approximately 3 mg of dexamethasone per day or equivalent doses of other steroid medications) of systemic corticosteroids.
8. Patient with any malignancy within 5 years prior to date of randomization, with the exception of adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell

carcinoma or non-melanomatous skin cancer.
9. Patient with a known hypersensitivity to any of the study treatment ingredients e.g. to recombinant human antibodies.
10. Patient with concurrent serious illnesses, uncontrolled medical conditions, or other medical history including clinically relevant abnormal laboratory results, which in the investigator*s opinion would be likely to interfere with a patient*s participation in the study, or with the interpretation of study results:
a. uncontrolled neurological disease (e.g. recurrent seizures despite existing anticonvulsant therapy);
b. neuropathy * grade 1, neuromuscular disease;
c. severe disturbance of liver function;
d. severe constipation;
e. cystitis or other ongoing infections;
f. disturbance of micturition;
g. severe chronic obstructive pulmonary disease with clinically manifest hypoxemia (dyspnea > grade 1);
h. uncontrolled hypertension (defined as systolic BP > 160 mm Hg or diastolic > 100 mm Hg);
i. history of stroke or cerebral ischemia (within 6 months prior to randomization);
j. history of myocardial infarction or other clinically significant myocardial disease (within 6 months prior to screening) or unstable angina (* NYHA Grade II);
k. inadequate cardiac function defined as cardiac ejection fraction < 45% as measured by 2D-ECHO or MUGA;
l. known infection with HIV or any other severe immune-compromised state according to patient history (if required by local regulations or clinical practice guidelines, patient may be tested during the screening period to confirm HIV status);
m. evidence of ongoing drug or alcohol abuse within the last 6 months before screening;
n. Active tuberculosis. Patients with evidence of latent tuberculosis as per results of the tuberculosis screening test and further follow-up may enter the study after evaluation by an appropriate specialist and after sufficient treatment has been initiated according to local medical practice.
11. Patient has had major surgery, open biopsy or trauma within 4 weeks prior to date of screening (lymph node biopsy is not regarded as major surgery), or expects the need for major surgery during the course of study treatment.
12. Patient plans to receive live vaccines during the study or has received live vaccines 4 weeks prior to date of screening. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.
13. Patient is using growth factors or transfusions to meet study eligibility requirements during Screening period. (The use of growth factors and transfusions during screening is permissible, if there is suspicion of bone marrow involvement by lymphoma and patient is deemed not to be growth factor-dependent or transfusion-dependent)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2012
Enrollment:	31
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GP2013
Generic name:	Rituximab
Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-07-2011
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	07-10-2011
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-10-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	23-12-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Not approved Date:	28-12-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-02-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	21-03-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	18-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	06-06-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	07-06-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	15-06-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	26-07-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	04-09-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	19-12-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	18-04-2013
Application type:	Amendment
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Date:	12-08-2013
Application type:	Amendment
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Approved WMO

Date:	23-08-2013
Application type:	Amendment
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Approved WMO

Date:	29-08-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-12-2013
Application type:	Amendment
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Date:	19-12-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	24-12-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	07-08-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	17-03-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	27-11-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	28-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-08-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	31-08-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2010-019522-13-NL
ClinicalTrials.gov	NCT01419665
CCMO	NL36966.098.11