An open-label, dose escalating Phase Ib study for the assessment of safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple intravenous doses of GLPG0187 in subjects with solid tumors.

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Primary objective:To assess the safety and tolerability of GLPG0187 when administered intravenously (IV) as a continuous infusion in subjects with solid tumors in order to determine the Recommended Phase II Dose (RP2D).Secondary objectives:• To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36388

Source
ToetsingOnline

Brief title
Phase Ib study with GLPG0187 in subjects with solid tumors.

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
solid neoplasm, solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Galapagos SASU
Source(s) of monetary or material Support: Galapagos SASU

Intervention

Keyword: Dose escalating, GLPG0187, Phase Ib, Solid tumors

Outcome measures

Primary outcome

The incidence rate of DLTs at each dose level based on the following safety parameters: Adverse drug reactions (ADR) and serious ADRs, changes in hematology and chemistry values, including those associated with hepatic and renal function, and assessment of physical examinations, vital signs and cardiac function (i.e. repeated electrocardiograms). NCI-CTCAE version 4.03 will be used.

Secondary outcome

• Exposure to GLPG0187 in plasma;

• Effects of GLPG0187 on bone resorption biomarker;

• Preliminary efficacy: Antitumor effects of GLPG0187 according to RECIST 1.1.

Study description

Background summary

Integrins constitute a family of cell surface receptors that play an important role in cell adhesion, migration, invasion, proliferation, and survival. A subgroup of eight members of the integrin family is characterized by their ability to recognize and bind to an Arginine-Glycine-Aspartic acid (RGD) domain

on adhesion proteins present in extracellular matrices. Six RGD-integrin receptors have been reported to be involved in cancer and metastases processes. Recently, several inhibitors of specific integrins have been investigated in clinical studies for a number of different tumor types. Integrin antagonism appears to represent a promising mechanism for anti-cancer therapy. Galapagos SASU (Galapagos) has designed a non-peptide integrin antagonist (GLPG0187), with high affinity for these cancer related integrins, which has been shown to treat experimentally-induced bone metastases from human cancer cells when administered prophylactically or therapeutically to animals. Histomorphometric evaluation reveals strong bone sparing effects and a reduction in bone tumor burden, greater than or similar to clinically relevant doses of zoledronate. In addition, visceral metastases are also significantly reduced. Furthermore, GLPG0187 inhibits tumor growth of human breast tumor in a xenografted mouse model, independently of the bone microenvironment. Thus, by targeting multiple cancer-related integrins, GLPG0187 provides a new approach to inhibiting metastatic tumor growth and bone tumor burden by affecting multiple processes in tumor pathology. Based on the promising preclinical safety and efficacy studies for this novel pan-integrin inhibitor, clinical studies are warranted in order to evaluate its clinical potential in the treatment of bone and visceral metastases.

Study objective

Primary objective:
To assess the safety and tolerability of GLPG0187 when administered intravenously (IV) as a continuous infusion in subjects with solid tumors in order to determine the Recommended Phase II Dose (RP2D).

Secondary objectives:
• To characterize the Pharmacokinetics (PK) of GLPG0187 after intravenous infusion;
• To characterize the Pharmacodynamics (PD) of GLPG0187;
• To evaluate the preliminary efficacy of GLPG0187 in terms of clinical activity.

Study design

A *3+3* dose-escalation design will be used. However, the first two dose cohorts will include only two subjects per cohort instead of three. Via this accelerated dose escalation the number of subjects that are exposed to the two lowest dose levels is minimized, thereby reducing the number of subjects treated at potentially suboptimal dose concentrations. From the third dose cohort onwards, in each cohort at least 1 and preferably 2 subjects with bone metastases will be included.

The DLT observation period for a dose level will be treatment cycle 1 (day 1 to

28).

Enrollment into the first 2 dose level cohorts will start with 1 subject. The second subject will be enrolled at least 3 days after the first subject received the first dose of GLPG0187. From dose cohort 3 onwards enrollment of the first 3 subjects can be simultaneously. For details refer to section 3 of the protocol.

Intervention

Subjects eligible for the study will be assigned to a dose level cohort. Subjects in the first dose level cohort will receive the starting dose of 20 mg/day. The sequential dose escalations increments are 100%, 100%, 100%, 100% and 25%. Consequently it is anticipated that the doses for the sequential cohorts will be 20, 40, 80, 160, 320, 400 mg/day

Treatment cycle 1 consists of 28 days. On day 1 of this cycle a single dose of GLPG0187 will be administered IV at a constant rate for one hour. The subject will be followed for 24-hours to assess the PK profile. On day 8 of cycle 1 (if no safety issue related to GLPG0187 infusion have been reported) the subject will start continuous infusion of GLPG0187 (same daily dose as received on day 1) for 21 days with weekly renewals of the infusion bag.

If, according to the Investigator, a subject has a clinical benefit from treatment with GLPG0187, the subject may stay on treatment after treatment cycle 1 until disease progression, Dose Limiting Toxicity (DLT), or discontinuation for any other reason. These subsequent treatment cycles (cycle 2 and onwards) consist of 21 days. During these cycles the subject receives a continuous infusion of GLPG0187 with weekly renewals of the infusion bag.

Study burden and risks

Study assessments will be performed at prescreening, baseline, C1D1, C1D2, C1D8, C1D15, C1D22, C1D28 and CXD1, CXD8, CxD15, CxD21 of every consecutive cycle. Treatment duration will continue until disease progression (defined by RECIST), unacceptable toxicity, inability or unwillingness of the subject to comply with study procedures, patient withdrawal, death, or discontinuation from the study for any other reason, whereupon all patients will complete the End of Treatment visit. The final Follow up Visit should be performed 30 days after end of study to collect safety and survival information.

Please refer to Table 6.2.1.

Potential Risks and Benefit of GLPG0187:

GLPG0187 is a small molecule and reversible antagonist of integrin receptors,

not a biological: it does not exhibit highly species-specific action and is not considered agonistic towards immune system targets.

GLPG0187 is not a cytotoxic or cytostatic agent, as confirmed by the absence of adverse effects in rapidly dividing tissues of mice and dogs in repeated dose toxicity studies.

The systemic toxicity seen in animal species was observed at high doses only and was usually preceded by changes in hematology or biochemistry parameters, in particular the increase of eosinophils. These parameters will be closely monitored in this clinical study to identify potential toxicity early on.

As there are no data available on teratogenicity and excretion in milk, the compound should not be administered to pregnant or lactating women or women of childbearing potential.

As the clinical experience with GLPG0187 is limited to single dose Phase I healthy volunteer study, the trial medication should not be administered to subjects with hepatic or renal impairment, pediatric subjects or elderly.

Trial medication should not be given to subjects with a known or suspected hypersensitivity to any of the formulation constituents.

No specific warnings or precautions are known at present. As with any new compound in early clinical development, cardiovascular safety, biochemistry, hematology, coagulation and other laboratory safety parameters, including platelet aggregation, should be monitored.

General measures to maintain or support the basic vital functions should be taken in case of deliberate or accidental overdosage. No experiments have been performed to determine a specific antidote to GLPG0187.

General risks:
• Reaction to the use of contrast fluid (used for CT scans)
• Side effects of blood sampling
• Injection site reactions
• Side effects VIT inplantation

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. Pathologically confirmed diagnosis of advanced, recurrent, or metastatic cancer who are refractory to standard therapy or for whom no standard therapy exist.
2. Age >= 18 years.
3. Measurable (according to RECIST 1.1) and evaluable disease as determined by the Investigator.
4. ECOG Performance Status <= 2.
5. Estimated life expectancy of at least 12 weeks.
6. Toxicities incurred as a result of previous anticancer therapy (radiation therapy, chemotherapy, or surgery) must be resolved to <= Grade 2.
7. Written informed consent according to local guidelines.

Exclusion criteria

Prior Treatment:
1. Less than 4 weeks since the last treatment with other cancer therapies, (i.e. endocrine therapy, immunotherapy, chemotherapy, etc.), and < 6 weeks for nitrosoureas and Mitomycin C.
2. Prior therapy with integrin receptor antagonists.;Current Treatment:

3. Chronic daily treatment with corticosteroids (dose of * 10 mg/day methylprednisolone or equivalent), with the exception of inhaled steroids.
4. Current or recent (within 30 days of first study treatment) treatment with another investigational drug or participation in another investigational study.;Hematology, coagulation and biochemistry:
5. Inadequate bone marrow function: Absolute Neutrophil Count (ANC): < 1.5 x 109/L, or platelet count <100 x 109/L or hemoglobin < 6 mmol/L.
6. Inadequate liver function, defined as:
• Serum (total) bilirubin > 2 x the Upper Limit of Normal (ULN) for the institution;
• Aspartate Amino Transferase (ASAT) or Alanine Amino Transferase (ALAT) > 2.5 x ULN (> 5 x ULN in subjects with liver metastases);
• Alkaline phosphatase levels > 2.5 x ULN (> 5 x ULN in subjects with liver metastases, or > 10 x ULN in subjects with bone metastases).
7. Inadequate renal function, defined as:
• Serum creatinine > 1.5 x ULN
• Urine dipstick for proteinuria > 2+.;Other:
8. Clinically symptomatic or progressive brain metastases
9. Clinical Leptomeningeal metastases
10. Pregnancy or lactation. Urine pregnancy test to be assessed within 7 days prior to study treatment start.
11. For women of childbearing potential (defined as <2 years after last menstruation and not surgically sterile): absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel).
12. Major surgical procedure (including open biopsy, excluding central line IV and portacath) within 28 days prior to the first study treatment, or anticipation of the need for major surgery during the course of the study treatment.
13. Congestive heart failure NYHA Class III and IV. Cardiac arrhythmias (except for atrioventricular block type I, Mobitz type, and II, Wenckebach type) signs and symptoms of relevant cardiovascular disease.
14. Known hypersensitivity to any of the study drugs or excipients.
15. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, physical examination or laboratory findings) that may interfere with the planned treatment, affect subject compliance or place the subject at high risk from treatment-related complications.

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):	22-03-2011
Enrollment:	19
Type:	Actual

Ethics review

Approved WMO Date:	24-12-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-03-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-05-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-05-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2010-021164-15-NL
CCMO	NL34529.041.10